UCL SCHOOL OF PHARMACY

A HEXA-HERBAL CHINESE FORMULA FOR TREATMENT OF ATOPIC DERMATITIS: PHYTOCHEMICAL ANALYSIS AND SELECTED ANTI-INFLAMMATORY ACTIVITIES

Thesis submitted by

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DECLARATION

"I, Jennifer Bay Chang Chen, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Jennifer Bay Chang Chen

ABSTRACT

Diverse pharmacological activities and the solid clinical performance of Chinese herbal medicines have attracted worldwide attention in terms of its modernization. Here, a hexa-herbal Chinese formula (HHCF) for treating atopic dermatitis (AD) topically has been studied from chemical and biological perspectives. The HHCF comprises the rootstock of *Scutellaria baicalensis* Georgi (SCU), *Rheum tanguticum* Maxim. Ex Balf. (RHE), *Sophora flavescens* Aiton (SOP); the root bark of *Dictamnus dasycarpus* Turcz. (DIC); the bark of *Phellodendron chinense* C.K. Schneid. (PHE) and the fruit of *Kochia scoparia* (L.) Schrad. (KOC).

In this thesis the chemical composition of the HHCF has been profiled and characterized using liquid-chromatography (LC) coupled with triple quadruple mass spectrometry (MS). 68 chemical compounds including alkaloids, anthraquinones, coumarins, flavonoids, naphthalene derivatives, phenylbutanone glucosides, phenolic acids, pterocarpans, stilbenes and tannins were putatively identified in the LC-MS profile of the HHCF based on mass measurement and characteristic fragment ions. The source(s) of these chemical compounds has been analyzed using the developed EXCEL template and PHE, RHE and SOP contributed the largest number of chemical compounds identified in the HHCF, while KOC seems to contribute very little.

To evaluate the anti-inflammatory effects of the HHCF for treating AD/skin inflammation, the thymus and activation-regulated chemokine (CCL17), Prostaglandin E2 (PGE_2), IL-8, IL-6 and hyaluronidase inhibitory effects were studies *in vitro*. Results showed that the HHCF inhibited hyaluronidase activity, TNF-α- plus IFN-□-induced CCL17 production in spontaneously immortalized human epidermal keratinocytes (HaCaT) and IL-1β-induced PGE_2 in human fibroblasts with no effects on IL-8 and IL-6. Among the chemical compounds characterized in LC-MS profile of the HHCF, multivariate regression models indicated the major contributor to the CCL17 inhibition were berberine, catechin dimers, gallic acid, galloylglucose, 4-(4'-hydroxylphenyl)-2-butanone 4'-O-β-D-glucoside, pyrogallol and resveratrol 4'-O-β-D-(6''-O-galloyl) glucoside.

The effects of the HHCF against other pathogenesis-related targets need to be further study to ascertain its therapeutic efficacy against AD.

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ABBREVIATIONS

AD	Atopic dermatitis
A_{DIC}	Abundance of ions in DIC
A_{KOC}	Abundance of ions in KOC
APCI	Atmospheric pressure chemical ionization
A_{PHE}	Abundance of ions in PHE
A_{SCU}	Abundance of ions in SCU
A_{SOP}	Abundance of ions in SOP
BS	*Bacillus subtilis*
CCL	Chemokine (C-C motif) ligand
CCL2	Monocyte chemoattract protein-1 (MCP-1)
CCL3	Macrophage inflammatory protein-1α (MIP-1α)
CCL5	Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES)
CCL7	Monocyte-chemotatic protein (MCP-3)
CCL11	Eotaxin
CCL17	Thymus and activation-regulated chemokine (TARC)
CCL20	Macrophage inflammatory protein-3alpha (MIP-3α)
CCL22	Macrophage-derived chemokine (MDC)
CCL26	Eotaxin-3
CCL27	Cutaneous T cell-attracting chemokine (CTACK)
CCR	Chemokine receptor
CER	Ceramides
CF(s)	Chemotactic factor(s)
CHM(s)	Chinese herbal medicine(s)
CLA	Cutaneous lymphocyte-associated antigen
COX	Cyclooxygenase
CTAB	Cetyltrimethylammonium bromide
CXCL9	Monokine induced by interferon-gamma (Mig)
CXCL10	Interferon gamma-induced protein 10 (IP-10)
CXCL11	Interferon-inducible T-cell alpha-chemoattractant (I-TAC)
DC(s)	Dendritic cell(s)
dDC(s)	Dermal dendritic cell(s)
DIC	The root bark of *Dictamnus dasycarpus* Turcz.
DMEM	Dulbecco's modified Eagle medium
DNCB	2,4-Dinitrochlorobenzene
DNFB	1-fluoro-2,4,dinitrofluorobenzene
DNP	Dintrophenyl
DSS	Dextran sulfate sodium
EC	*Escherichia coli*
EIA	Enzyme immunoassay
ELISA	Enzyme-linked immunosorbent assay
Et	End time
EMSA	Electrophoretic mobility shift assay
ERK	Extracellular signal-regulated kinases
ELAM-1	Endothelial leukocyte adhesion molecule 1
EO-CER	Ester linked ω-hydroxy ceramides
ESI	Electrospray ionization
FasL	Fas ligand

FasR	Fas receptor
Fc epsilon RI	High affinity receptor for the Fc fragment of IgE
FFA	Free fatty acids
FLG	Filaggrin
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HaCaT	Spontaneously immortalized human epidermal keratinocytes
H&E	Hematoxylin and eosin
HHCF	Hexa-herbal Chinese formula
HLA-DR	Human histocompatibility leukocyte antigen-DR
HPLC	High performance liquid chromatography
HMC-1	Human mast cells
Hydro.	Hydrocortisone
hr(s)	hour(s)
HA	Hyaluronic acid
ICAM-1	Intercellular adhesion molecules-1
IDEC	Inflammatory dendritic epidermal cells
IDEC-DC(s)	Inflammatory dendritic epidermal cell-like dendritic cell(s)
IFN-γ	Interferon-gamma
Ig	Immunoglobulin
IκBα	Nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor, alpha
IL	Interleukin
Ion_{HHCF} *m/z*	*m/z* value of ions detected in the HHCF decoction
Ion_{HHCF} Rt	Retention time of ions detected in the HHCF decoction
Ion_{SBD} Et	End time of ions detected in the single botanical drug decoction
Ion_{SBD} *m/z*	*m/z* value of ions detected in the single botanical drug decoction
Ion_{SBD} St	Start time of ions detected in the single botanical drug decoction
IP-10	IFN-gamma-inducible protein 10
iNOS	Inducible nitric oxide synthase
IT-TOF	Ion trap time-of-flight
JNK	c-Jun N-terminal kinase
KC(s)	Keratinocyte(s)
KOC	The fruit of *Kochia scoparia* (L.) Schrad.
LC	Liquid chromatography
LCs	Langerhans cells
LCs-DC(s)	Langerhans cells-like dendritic cell(s)
LC-MS	Liquid chromatography-mass spectrometry
LC-Q-TOP-MS	Liquid chromatography quadrupole time-of-flight mass spectrometry
LPS	Lipopolysaccharide
LT	Leukotriene
LTQ-Orbitrap	Linear trap quadrupole orbitrap
LV	Latent variable
MAPK(s)	Mitogen-activated protein kinase(s)
MCP	Monocyte chemoattractant protein
MIC	Minimum inhibitory conccentration
MIG	Monokine induced by gamma interferon
MPO	Myeloperoxidase
MR	Mannose receptor

MTT	3-(4,5-dimethylthizaol-2-yl)-2,5-diphenyltetrazolium bromide
mRNA	Messenger RNA
mAbs	Monoclonal antibodies
mDC(s)	Myeloid dendritic cell(s)
NC/Nga	Nishiki-nezumi Cinnamon/Nagoya
NDIC	Knock-DIC-out HHCF
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NKOC	Knock-KOC-out HHCF
NO	Nitric oxide
NPHE	Knock-PHE-out HHCF
NRHE	Knock-RHE-out HHCF
NSCU	Knock-SCU-out HHCF
NSOP	Knock-SOP-out HHCF
OVA	Ovalbumin
SBD	Single botanical drug
PA	*Pseudomonus aeruginosa*
PBMC(s)	Peripheral blood mononuclear cell(s)
PBS	Ca2+ and Mg2+ -free phosphate buffer saline
PC-R	Principal component regression
PCR	Polymerase chain reaction
pDC(s)	Plasmacytoid dendritic cell(s)
PHE	The bark of *Phellodendron chinensis* C.K. Schneid.
PLS-R	Partial least-squares regression
PMA	Phorbol 12-myristate 13-acetate
qPCR	Quantitative polymerase reaction
QqQ	Triple quadrupole
Q-TOF	Quadrupole time-of-flight
RC	Regression coefficient
RMSEC	Root mean square error of calibration
RMSECV	Root mean square error of cross validation
PGE2	Prostaglandin E_2
RANTES	Regulated upon activation, normal T cell expressed and secreted
RHE	The rootstock of *Rheum tanguticum* Maxim. ex Balf.
Rt	Retention time
RT-PCR:	Reverse transcription polymerase chain reaction
Rx	Prescription
S	Streptomycin
SA	*Staphylococcus aureus*
SBD	Single botanical drug
SC	Stratum corneum
SCU	The rootstock of *Scutellaria baicalensis* Georgi
SD	Sprague-Dawley
SOP	The rootstock of *Sophora flavescens* Aiton
St	Start time
TIC	Total ion chromatograms
Th	T helper
Th0	Naïve T helper
Th1	T helper type-1
Th2	T helper type-*2*
TCM	Traditional Chinese medicine
THP-1	Human monocytic cells

TIC(s)	Total ion chromatogram(s)
TNBS	2,4,6-trinitrobenzene sulfonic acid
TNF	Tumor necrosis factor
TOF	Time-of-flight
TPA	12-O-tetradecanoylphorbol-13 acetate
TSLP	Thymic stromal lymphopoietin
TWEL	Transepidermal water loss
UPLC	Ultra performance liquid chromatography
VCAM-1	Vascular endothelial cell adhesion molecule 1
VEGF	Vascular endothelial growth factor
VLA-4	Very late Antigen-4

1 INTRODUCTION

1.1 PATHOPHYSIOLOGY, DIAGNOSIS AND TREATMENTS OF ATOPIC DERMATITIS/ECZEMA FROM A WESTERN MEDICINE POINT OF VIEW

Atopic dermatitis (AD), also known as atopic eczema, is a chronic/chronically relapsing, genetically predisposed and highly pruritic inflammatory skin disease that commonly occurs at early infancy and childhood, but can persist or start in adulthood. (Johansson et al., 2004, Leung and Bieber, 2003) Clinically, AD presents as eczematous skin lesions on distinct areas of the body that usually varying with age [e.g. on the cheeks and scalp in infancy and on flexures, nape and limbs in childhood]. (Kawakami et al., 2009) Lesions in the acute phase are characterized by erythematous papules associated with serious exudate and excoriation while lesions in the chronic phase are recognized as excoriation and lichenification [i.e. thickening of the skin with accentuated skin markings]. This is a disorder that can adversely affect the quality of life. [e.g. sleep disturbance due to intense itchiness sensation and social stigma of visible skin lesions] (McKenna and Doward, 2008, Watson and Kapur, 2011) It is the most common inflammatory skin disease in children; affecting about 15-30% in children and 2-10% in adults; and has incased in prevalence around the world in the last few decades, particularly in developed nations. (Bieber, 2010, Ring, 1999) About 60% of affected individuals show an onset during the first year of life and ~60% of cases have a spontaneous remission before adolescence, but the condition may run a course of remissions and exacerbations. (Kay et al., 1994, Bieber, 2008, Williams, 2000) A study carried out by Kissling and Wüthrich (Kissling and Wüthrich, 1993) showed that in about two thirds of children with AD, there is no remission or AD will develop with progression to adulthood. (Ring, 1999)

The term ‘atopy’ identifies disease that is associated with an elevated serum immunoglobulin (Ig) E levels, the presence of specific IgE antibodies in serum or a positive skin prick test. (Johansson et al., 2004, Bieber, 2010) However, a subgroup of individuals with AD has a normal serum IgE levels with no sign of IgE-mediated sensitization and absence of immediate-type hypersensitivity skin reactions that is defined as intrinsic AD. (Bieber, 2010, Novak and Bieber, 2003, Kagi et al., 1994) Therefore, the word ‘atopic’ in atopic dermatitis describes the association of this form

of dermatitis with asthma and allergic rhinitis. (Williams, 2000, Spergel and Paller, 2003) In fact, AD often represents the beginning of an atopic march that is followed by the development of asthma/allergic rhinitis. This phenomenon may be due to epicutaneous sensitization and the subsequent migration of activated T-cells into the nose and airways, causing airway disease. (Spergel and Paller, 2003, Watson and Kapur, 2011, Akdis et al., 2006)

1.1.1 Pathophysiology of AD

The pathophysiology of AD is not fully understood, yet, various aspects of the pathophysiological mechanisms have been researched such as genetic predisposition, skin barrier dysfunction, altered immunological function, microbial colonization and psychological and environmental influences. (Leung, 2000, Ring, 1999)

The immunological basis of AD pathogenesis has been demnostrated in various studies. These include the appearance of eczematous skin lesions in patients with underlying immunological disorders (Table 1.1a) and the observation of altered systemic (Table 1.1b) and cutaneous immune response (Table 1.1c) in patients with AD. The nature of the cutaneous inflammatory response in AD appears to be orchestrated by the local cytokine milieu that results from the interplay between resident/infiltrated mononuclear cells [e.g. T lymphocytes, dendritic cells, keratinocytes, mast cells, macrophages and eosinophils] in response to the inflammatory stimulus. (Akdis et al., 2006, Hamid et al., 1994) This has been shown by the distinct pattern of inflammatory mediators and resident cells [i.e. atopic milieu] underlying the characteristic clinical manifestations in acute and chronic AD skin lesions.

Histologically, acute AD skin lesions are characterized by mild epidermal hyperplasia and intercellular edema of the epidermis and some vesiculation. Chronic AD lesions are characterized by additional increase in epidermal thickness (lichenification) (Rupec et al., 1996). Other skin abnormalities in AD include down-regulated expression of skin barrier proteins [e.g. filaggrin; section 1.1.1.4.1], altered skin lipid composition [e.g. ceramides; section 1.1.1.4.2] and down-regulated expression of anti-microbial peptides [section 1.1.1.5] that contribute to the increased susceptibility of the skin to pathogen invasion. Skin barrier is also secondarily affected by the local expression of Th2- [i.e. IL-4 and IL-13 down-regulate expression of filaggrin (Howell et al., 2009) and anti-

microbial peptides (Nomura et al., 2003, Howell et al., 2006).], Th22- [i.e. IL-22 mediates epidermal hyperplasia (Nograles et al., 2009) and down-regulates expression of profilaggrin/filaggrin (Gutowska-Owsiak et al., 2011).] and Th1- [i.e. IFN-γ induces apoptosis of keratinocytes (Trautmann et al., 2000, Rebane et al., 2012)] type cytokines. Fig.1.1 shows the schematic overview of major pathophysiological alterations in skin of patients with AD.

Table 1.1 Underlying immunological abnormalities in AD patients.

1.1a AD-like eczematous skin lesions as symptoms in patients with immunological disorders:

- Ø Appearance of AD-like eczematous skin lesions and increased (é) serum immunoglobulin E (IgE) levels in patients with primary T-cell immunodeficiency disorders. (Buckley and Fiscus, 1975)
- Ø Bone marrow transplants from atopic donors resulted in atopic symptoms and positive immediate skin test. (Agosti et al., 1988)

1.1b Systemic immune response in AD patients:

- Ø é serum levels of IgE, eosinophil cationic protein, interleukin (IL)-2 receptor (Czech et al., 1992), eosinophils (Antunez et al., 2004), soluble intercellular adhesion (iCAM-1) and soluble E-selectin. (Hirai et al., 1996, Yamashita et al., 1997, Wolkerstorfer et al., 1998) [i.e. serum levels of eosinophil cationic protein, soluble iCAM1 and soluble E-selectin were correlated to disease severity in AD patients]
- Ø é peripheral blood T lymphocyte activation i.e. é expression of HLA-DR and CD24 in both extrinsic and intrinsic AD. (Akdis et al., 1999a)
- Ø é number of peripheral blood CD 23^{+} [i.e. IgE Fc receptor II] B cells in extrinsic AD, but not intrinsic AD. (Akdis et al., 1999a)
  Peripheral blood B cells spontaneously produce high levels of IgE; indirect evidences hypothesized that this phenomenon may be associated with the increased secretion of IgE-inducing IL-4 [i.e. anti-IL-4 inhibited spontaneous IgE synthesis in lymphocytes isolated from AD patients and levels of IL-4-induced soluble CD23 is increased in sera of AD patients]. (Rousset et al., 1991, Vollenweider et al., 1991, Leung, 1995)

1.1c Cutaneous immune response in biopsies from lesional skin of AD patients:

Protein expression in both extrinsic and intrinsic AD skin lesions:

- Ø Detectable: IL-2, interferon (IFN)- γ, IL-5 and IL-13. Undetectable: IL-4. (Akdis et al., 1999a)

mRNA expression in extrinsic/intrinsic AD skin lesions v.s. normal skin:

- Ø é expression of IL-5, IL-13 and IL-1β in extrinsic AD > intrinsic AD. (Neis et al., 2006)
- Ø é expression of IL-4, IL-10, IL-12, IFN-γ and granulocyte macrophage colony-stimulating factor (GM-CSF) in extrinsic AD ≈ intrinsic AD. (Jeong et al., 2003)
- Ø é expression of IL-31 is associated with IL-4 and IL-13 expression. (Neis et al., 2006)

Table 1.1 Underlying immunological abnormalities in AD patients.

- Decreased (ê) expression of tumour necrosis factor (TNF)-α in extrinsic AD ≈ intrinsic. (Jeong et al., 2003)
- IL-6 and transforming growth factor (TGF)-β expression levels are similar to healthy control (Jeong et al., 2003)

mRNA expression in both acute and chronic AD skin lesions v.s. normal skin:

- é expression of IL-4 and IL-13 in acute AD > chronic AD. (Hamid et al., 1994)
- é expression of IL-5 in chronic AD > acute AD. (Hamid et al., 1994)
- é expression of GM-CSF and IL-12 p40 subunit in chronic AD >acute AD. (Hamid et al., 1996, Bratton et al., 1995)

Cytokine receptors mRNA expression in acute and chronic v.s. normal skin:

- é expression of alpha subunit of IL-5 and GM-CSF receptor in chronic AD > acute AD. (Taha et al., 1998)
- é expression of alpha subunit of IL-4 receptor. only in acute AD. (Taha et al., 1998)

Immunohistology:

Mononuclear cell infiltration consists mainly of:

- $CD4^+$ T helper lymphocytes or memory $CD45RO^+$ T lymphocytes expressing cutaneous lymphocyte-associated antigen (CLA) in the epidermis and dermis. (Bos et al., 1989, Picker et al., 1990a, Chan, 2008, Wakita et al., 1994, Jeong et al., 2003, Rho et al., 2004, Akdis et al., 1999a, Leung et al., 1983a),
- Eosinophils/eosinophils cationic protein [i.e. é in extrinsic > intrinsic AD (Jeong et al., 2003, Rho et al., 2004, Akdis et al., 1999a) and é in both acute/spongiosis and chronic/epidermal hyperplasia AD lesional skin (Kiehl et al., 2001)],
- $CD1a^+$ epidermal Langerhans cells (Rho et al., 2004, Leung et al., 1983a),
- Few macrophages in some cases (Jeong et al., 2003) e.g. in acute AD lesions and prominent macrophages in chronic AD lesions. (Leung et al., 1983a)

Sparse perivascular T-cell infiltrate in unaffected/asymptomatic skin of individuals with AD. (Leung et al., 1983a, Mihm et al., 1976)

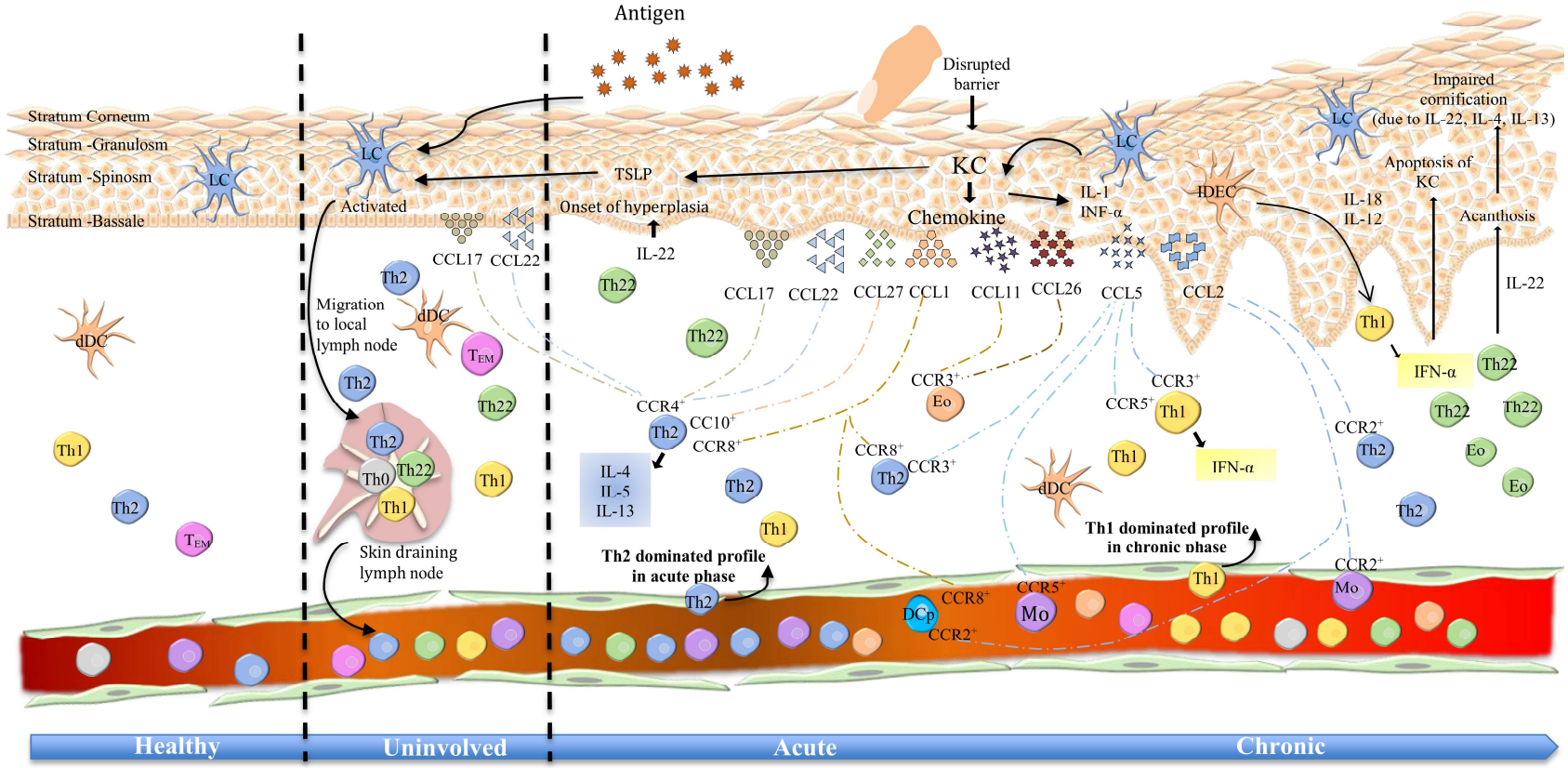

Fig.1.1 Schematic overview of major pathophysiological alterations in skin of patients with AD.

Uninvolved, acute and chronic AD skin lesions feature skin barrier and immune abnormalities that are linked to the interplay between genetic and environmental factors. Uninvolved skin of AD patients shows an increased expression of Th2-type [i.e. IL-4, IL-5 and IL-13] and Th22-type [i.e. IL-22] cytokines when compared with healthy non-atopic skin (Gittler et al., 2012, Hamid et al., 1996, Hamid et al., 1994). Antigens (via impaired skin barrier) come into contact with resident dendritic cells [e.g. Langerhans cells and dermal dendritic cells] that subsequently prime T cells (Novak, 2012). Antigens penetration or mechanical injury [i.e. scratching] also trigger keratinocytes to release inflammatory cytokines [e.g. IL-1, TNF-α and TSLP] and chemokines that contribute to the recruitment of immune cells and the perpetuation of AD (Esche et al., 2004, Homey et al., 2006). Expression of Th2-type [e.g. IL-4, IL-5 and IL-13] and Th22-type [i.e. IL-22] cytokines are further increased in acute and chronic AD skin lesions when compared with uninvolved skin of AD patients. Chronic AD skin lesions show higher expression of Th-1 type cytokines [e.g. IFN-□ and IL-12] and lower IL-4 expression when compared with acute AD skin lesions (Gittler et al., 2012, Hamid et al., 1996, Hamid et al., 1994). CCL, chemokine (C-C motif) ligand; CLA, cutaneous lymphocyte-associated antigen; DC, dendritic cell; dDC, dermal dendritic cell; DCp, dendrictic cell precursor; Eo, eosinophil; IDEC, inflammatory dendritic epidermal cell; IL, interleukin; KC, keratinocyte; LC, Langerhans cell; Mo, monocyte; T_{EM}= effector memory T cell; Th, T-helper; TSLP, thymic stromal lymphopoietin.

1.1.1.1 T helper type-1 (Th1)/T helper type-2 (Th2) paradigm

Lesional AD skin is characterized by the predominant infiltration of T lymphocytes, eosinophils, cells of dendritic cell lineage [i.e. inflammatory dendritic epidermal cells and Langerhans cells] and macrophages and the increased *in situ* expression of both Th1- and Th2- cytokines. (Grewe et al., 1994, Ohmen et al., 1995, Jeong et al., 2003, Hamid et al., 1994, Akdis et al., 1999a, Hamid et al., 1996) Thus, distinct cytokines secreted by activated skin-homing T lymphocytes appear to play a central regulatory role in AD. (Akdis et al., 2000a) They induce hyper-IgE production [i.e. interleukin (IL)-13], eosinophila [i.e. IL-5] (Akdis et al., 1999b, Akdis et al., 1999a) and keratinocyte apoptosis [i.e. interferon gamma (IFN-γ)] (Trautmann et al., 2000), as summarized in Appendix I. Various factors have been shown to trigger/exacerbate AD via activating T lymphocytes; these include aeroallergens, food allergen, autologous proteins and toxins secreted from *Staphylococcus aureus*; as summarized in Table 1.2.

The atopy patch-test [i.e. epicutaneous application of aeroallergens] has been used as a model to evaluate the pathogenesis of AD due to

1) its ability to induce eczematous skin lesions that resemble lesional AD skin both clinically [i.e. erythema, induration, papules and/or vesicles] and histologically [i.e. acanthosis, spongiosis and dermal infiltration of mainly $CD1^+$ and $CD4^+$ T lymphocytes and activated eosinophils] in sensitized patients (Langeveld Wildschut et al., 1995, Langeveld Wildschut et al., 1996, Bruynzeel Koomen et al., 1988, Bruijnzeel et al., 1993),

2) its specificity as a positive response does not occur in normal nonatopic patients and only occur in ~50% of aeroallergen-sensitized patients with AD (Langeveld Wildschut et al., 1995, Langeveld Wildschut et al., 1996),

3) its positive correlation with total serum IgE levels,

4) the presence of IgE-bearing epidermal Langerhans cells (Langeveld Wildschut et al., 1995),

5) its allergen specificity as there is induction of allergen-specific T lymphocytes at atopy patch-test skin sites in aeroallergen-sensitized patients with AD. (Sager et al., 1992, van Reijsen et al., 1992).

The atopy patch-test reaction has been proposed to result from the binding of aeroallergens with the high affinity receptor for the Fc fragment of IgE (Fc epsilon RI) on Langerhans cells that present antigens to T lymphocytes. (Langeveld Wildschut et al., 1995)

Based on the sequential analysis of cytokines expression in atopy patch-test skin lesions of AD patients, it has been proposed that Th1- and Th2- cytokines contribute to the development of AD skin lesions at different stages. A biphasic expression pattern has been observed during the development of atopy patch-test lesions, in which IL-4-dominated production by Th2 and naïve T helper (Th0) lymphocytes was seen within 24 hrs after allergen application, followed by a decline of IL-4 production [i.e. to background levels] and an IFN-γ-dominated production by Th1 and Th0 lymphocytes at late phase [i.e. 48 hrs] and chronic phase [i.e. 72 hrs]. (Thepen et al., 1996) Similarly, biopsies of AD skin lesions also demonstrated an IL-4 and IL-13 dominated mRNA expression at the acute phase and an IFN-γ, IL-5- and GM-CSF-dominated mRNA expression at the chronic phase. (Hamid et al., 1994, Bratton et al., 1995, Hamid et al., 1996) In addition, allergen-specific T lymphocytes clones derived from the early atopy patch-test skin lesions exhibited a Th2-cytokine profile while those taken from the later phase [i.e. 48-72 hrs] exhibited a Th1- or Th0-cytokine profile; secreting IFN-γ with a concentration matching the range found in chronic AD skin lesions. This phenotype switching of T helper lymphocytes has been linked to the substantial influx of macrophages at the atopy-patch test site and AD skins lesions. (Thepen et al., 1996) IL-12 produced by macrophages has been able to induce Th1 development *in vitro* (Hsieh et al., 1993) and IL-12 expression remained elevated in the 48 and 72 hrs patch-test lesions and chronic AD skin lesions. (Hamid et al., 1996, Grewe et al., 1998a)

Aside from macrophages, dendritic cells, eosinophils and keratinocytes may also be the source of IL-12 that promotes a switch from a Th2- to a Th1-like immune response in AD and induces IFN-γ production. (Kang et al., 1996, Muller et al., 1994, Grewe et al., 1998b) In terms of dendritic cells, it is postulated that resident Langerhans cells (LCs) stimulated with antigen via their overexpressed surface receptors [i.e. the high affinity receptor for the Fc fragment of IgE (Fc epsilon RI)] would migrate to lymphoid organs, preferentially primed Th0 lymphocytes to release Th2-cytokines [e.g. IL-4] and increase the release of chemokines [e.g. macrophage chemoattractant protein-1 (MCP-1/CCL2) and IL-16] that promote the recruitment of monocytes, namely inflammatory dendritic epidermal cells (IDEC) and/or T lymphocytes into the epidermis from the peripheral blood. (Novak et al., 2004c, Reich et al., 2001, Kaser et al., 1999, Klechevsky et al., 2008) Recruited IDEC may equip Fc epsilon RI on their surface at the cutaneous site of inflammation and hence, up-regulated the uptake of antigen and amplified inflammatory

response [e.g. augment the amount of inflammatory mediators and enhanced T cells proliferation as observed *in vitro*] (Novak et al., 2004c). In contrast to LCs, Fc epsilon RI-stimulated IDEC release IL-12 and IL-18 that may promote Th1 differentiation, characterized by an increased IFN-γ production as seen in the chronic eczematous phase. (Novak et al., 2004c, Langenkamp et al., 2000) In addition, blood-derived eosinophils, in response to Th2-type cytokines [e.g. IL-4 and GM-CSF], are able to secrete IL-12 that may also underline the biphasic nature of AD. (Grewe et al., 1998b) Moreover, it has been demonstrated *in vitro* that keratinocytes are more sensitive to Th1- than to Th2- cytokines in term of chemokine release and have a propensity to attract Th1 lymphocytes over Th2 lymphocytes. This interaction between T lymphocytes and keratinocytes maybe another factor that contribute to the accumulation of Th1 lymphocytes in AD skin lesions. (Albanesi et al., 2001)

The major roles of these resident cells [i.e. T lymphocytes (Appendix Ia), dendritic cells (Appendix Ic) and keratinocytes (Appendix Ie)] in the pathogenesis of AD are summarized in Appendix I.

Table 1.2 Triggering factors of Atopic dermatitis (AD).
***Staphylococcus aureus* (*S. aureus*)** colonization [80- 100%] in lesional AD skins (Leyden et al., 1974, Hauser et al., 1985, Friedman and Goldman, 2011) and trigger skin inflammation (Strange et al., 1996, Herz et al., 1998) via secretion of toxins. Toxins acts as superantigens that: · stimulated T lymphocytes to proliferate and secrete cytokines [i.e. stimulation of $CD4^+/CD8^+$ CLA^+ T lymphocytes from peripheral blood and skin biopsies of AD patients with *Staphylococcal* enterotoxin B resulted in the secretion of high levels of IL-5 and IL-13, relatively lower levels of IL-4 and very little IFN-γ], (Akdis et al., 1999b, Akdis et al., 1999a) · activated T lymphocytes via interaction with class II major histocompatibility complex products on antigen-presenting cells, follow by different regions on the β chain of T lymphocytes receptor complex, (Schlievert, 1993) · elicited skin inflammation after patch test in AD patients, (Strange et al., 1996) · up-regulated T lymphocytes expression of CLA; via induction of IL-12 production and hence, facilitated cutaneous infiltration of T lymphocytes, (Leung et al., 1995, Akdis et al., 2000b) · induced the production of IgE antibodies to toxins e.g. S*taphylococcal* enterotoxins A, B and toxic shock syndrome toxin-1 in ~50% AD patients and may subsequently trigger the release of histamine from basophils. (Leung et al., 1993)
Aeroallergen may induce T lymphocytes activations; as demonstrated by the presence of allergen-specific T lymphocytes in aeroallergen-induced patch test lesions in AD patients. (Werfel et al., 1996, Sager et al., 1992, van Reijsen et al., 1992)
Food may induce T lymphocytes activations; as demonstrated by the increased expression of CLA on T lymphocytes derived from patients with milk-induced eczema when cultured with casein *in vitro*. (Abernathy Carver et al., 1995)
Autologous proteins may elicit autoimmune response as shown by the presence of IgE antibodies against epidermal autologous proteins in serum of AD patients. (Natter et al., 1998, Valenta et al., 2000, Valenta et al., 1996)
Barrier disruption may induce pro-inflammatory cytokines; as shown by the elevated mRNA expression of TNF-α, IL-1α, IL-1β and GM-CSF, but not IL-6 or IFN-γ in murine epidermis with acute barrier disruption [i.e. treated with acetone or tape stripping] or with chronic barrier disruption [i.e. essential fatty acid deficient mice]. (Wood et al., 1992)

Table 1.2 Triggering factors of Atopic dermatitis (AD).
Genetic predisposition · Loss-of-function or missense mutations in the gene encoding filaggrin (FLG), a structural protein that is important for maintaining the integrity of skin barrier; (Palmer et al., 2006, Sandilands et al., 2007) clinically correlated with scaling (Dubrac et al., 2010) or may promote the ingress of foreign environmental substance that triggers/exaggerates aberrant immune response as seen in mouse models. (Fallon et al., 2009, Oyoshi et al., 2009, Scharschmidt et al., 2009, Moniaga et al., 2010) · Polymorphisims in chemokines, cytokines and cytokine receptors. (Morar et al., 2006)

1.1.1.2 Mechanisms controlling the infiltration of inflammatory cells into AD skin

Expression of cytokines in the skin of AD patients can play an important role in dictating the type of inflammatory response, as well as its intensity and chronicity. (Lukacs et al., 1997) These events may depend on the accumulation of particular set of cell types that are recruited to the site of inflammation by the actions of local chemotactic factors, together with the assistance of endothelial cell adhesion molecules to bypass the blood vessels. (Schon et al., 2003, Chan, 2008, Steinhoff et al., 2006)

In AD patients, four endothelial cell adhesion molecules [i.e. vascular cell adhesion molecule- 1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), E-selectin and P-selectin] expressed in the dermal microvasculature were increased when compared with the non-atopic control. (Jung et al., 1996) Tumour necrosis factor-alpha (TNF-α) may be responsible for this increased expression of adhesion molecules in the skin of AD patients since the number of TNF-α containing cells is correlated with the extent of adhesion molecule expression in skin of AD patients. (de Vries et al., 1998, Sigurdsson et al., 2000) Cutaneous-lymphocyte-associated antigen (CLA), an antigen that is predominantly expressed at inflammatory cutaneous lesions [i.e. 80-90%] and less likely to be present in circulating T lymphocytes [i.e. 10-15%] or lymphocytes at non-cutaneous sites of inflammation [i.e. <5%] (Picker et al., 1990b), may play an important role in stimulating T lymphocytes to migrate across activated endothelium and selectively to the cutaneous site of inflammation using CLA-E-selectin, very late antigen-4 (VLA-4)-VCAM-1 and lymphocyte function-associated antigen-1 (LFA-1)-ICAM interactions. (Santamaria Babi et al., 1995, Homey et al., 2002)

In addition, expression of specific chemokine receptors on inflammatory cells is also required for cell trafficking to the cutaneous site of inflammation. Chemokines interact with their corresponding receptors expressed on inflammatory cells, and this leads to their adhesion to the endothelium, followed by transendothelial migration from the blood vessel and chemotaxis within the skin to sites of inflammation. (Homey et al., 2006) For example, the majority of Th2 cells in peripheral blood selectively express chemokine receptors (CCR) 4 that are receptors for CC chemokines [i.e. CCL17 and CCL22]. In response to the production of these chemokines by monocytes, macrophages, dendritic cells or keratinocytes, Th2 cells migrate across vascular endothelium and to the sites of inflammation. (Imai et al., 1999, Homey et al., 2006) Keratinocytes are the major cell component of the epidermis and contribute to the

pathogenesis of AD by producing various chemokines, examples are summarized in Table 1.3 and illustrated in Fig.1.1. (Girolomoni et al., 2006, Homey et al., 2006) Other than trafficking of inflammatory cells to site of inflammation, chemokines may also take part in dictating the inflammatory response via activating T lymphocytes and directing lymphokine production from these cells. (Lukacs et al., 1997, Taub et al., 1996, Zhou et al., 1993)

Table 1.3 Atopic dermatitis (AD)-associated chemotactic factors (CFs) generated by keratinocytes (KCs).				
CF	**Levels in skin/plasma/serum**	**Target receptor**	**Target cell**	***In vitro* expression**
CCL1/ I-309	**In lesional AD skin:** CCL1 mRNA was expressed in the basal epidermal layer, dermal endothelial cells and in cells with dendritic morphology. **In normal or nonlesional AD skin:** Not detected. **In serum:** Increased levels of CCL1. (Gombert et al., 2005)	**CCR8** [i.e. Increased amount of CCR8+ infiltrating cells with.a subset exhibiting dendritic morphology in lesional AD skin.] (Gombert et al., 2005)	Subset of circulating CLA^+/CLA^- $CD4^+$ and $CD8^+$ T lymphocytes [i.e. Th2, not Th1] and Langerhans cells (LCs) precursors. (Gombert et al., 2005, Sebastiani et al., 2001)	**In human dermal fibroblasts and KCs:** CCL1 mRNA expression was not inducible by TNF-α, IL-1β, IFN-γ, IL-4 or left unstilmulated. (Gombert et al., 2005)
				In immortalized human epidermal KCs (HaCaT): CCL1 was secreted by HaCaT when treated with Trichophyton rubrum conidia. (Li et al., 2011b)
				In dermal endothelial cells: CCL1 mRNA was highly expressed in the resting state; up-regulated upon stimulation with TNF- α/IL-1β.
				In monocyte-derived LCs: CCL1 mRNA and protein were expressed in the resting state; up-regulated when treated with *Escherichia coli*-derived LPS and *Staphylococcus. aureus*-derived PGN. (Gombert et al., 2005)
				In monocyte-derived interstitial DCs and monocytes: CCL1 mRNA and protein were not expressed in the resting state; inducible by *Staphylococcus. aureus*-derived peptidoglycan. (Gombert et al., 2005)

Table 1.3 Atopic dermatitis (AD)-associated chemotactic factors (CFs) generated by keratinocytes (KCs).				
CF	**Levels in skin/plasma/serum**	**Target receptor**	**Target cell**	***In vitro* expression**
CCL2/ MCP-1	**In lesional AD skin:** CCL2 mRNA was expressed in basal epidermal KCs. (Vestergaard et al., 2004) **In serum:** Increased levels of CCL2 may (Kaburagi et al., 2001) or may not (Gluck and Rogala, 1999) correlated with disease severity. (Vestergaard et al., 2004)	**CCR2** [i.e. Increased amount of $CCR2^+$ monocytes.in peripheral blood of AD patients.] (Vestergaard et al., 2004)	$CD163^+$ monocytes/ macrophages, dendritic cells (DCs), DCs precursors, both Th1 and Th2 lymphocytes (Vestergaard et al., 2004, Vanbervliet et al., 2002, Nakamura et al., 1995, Sebastiani et al., 2001)	**In human primary epidermal KCs form normal or lesional AD skin:** CCL2 mRNA and protein were not expressed in the resting state and were induced by IFN-γ or phorbol myristate 13-acetate (PMA), but not by IL-4 and TNF- α. (Giustizieri et al., 2001) In other studies, CCL2 mRNA and protein expression were induced in normal human epidermal keratinocytes (NHEK) by IFN-γ or TNF-α or synergistically by IFN γ plus TNF- α. (Li et al., 2000b, Barker et al., 1991, Vestergaard et al., 2004) **In HaCaT**: CCL2, together with IL-1β, IL-6 and IL-8 were secreted by HaCaT when treated with substance P. (Liu et al., 2007)

Table 1.3 Atopic dermatitis (AD)-associated chemotactic factors (CFs) generated by keratinocytes (KCs).				
CF	**Levels in skin/plasma/serum**	**Target receptor**	**Target cell**	***In vitro* expression**
CCL5/ RANTES	**In lesional AD skin:** CCL5 was immunologically stained in lesional AD skin, (Park et al., 2005) mRNA expression was down-regulated (Gaspar et al., 2013) and expressed in basal epidermal KCs (Kaburagi et al., 2001). **In normal skin:** Not detected. (Kaburagi et al., 2001) **In serum:** Increased levels of CCL2 were correlated with disease severity, total serum IgE levels, eosinophil counts and serum lactate dehydrogenase levels. (Kaburagi et al., 2001) (Yamada et al., 1996)	**CCR1, CCR3, CCR5**	Monocytes, DCs, Th1 lymphocytes [via CCR5], eosinophils and Th2 lymphocytes [via CCR3]. (Sallusto et al., 2000, Shinkai et al., 1999, Kameyoshi et al., 1992)	**In human primary epidermal KCs from normal or lesional AD skin:** CCL5 mRNA and protein were not expressed in the resting state and were induced by IL-4, IFN-γ, TNF-α and PMA. (Giustizieri et al., 2001) **In HaCaT**: CCL5 mRNA and protein expression were induced by treatment with IFN-γ plus TNF-α. (Wang et al., 2011b)
CCL11/ eotaxin	**In lesional and nonlesional AD skin:** CCL11 mRNA was expressed and	**CCR3**	Eosinophils (Jose et al., 1994,	**In foreskin-derived fibroblasts:** CCL11 mRNA expression was induced by IL-4, but not induced in human

Table 1.3 Atopic dermatitis (AD)-associated chemotactic factors (CFs) generated by keratinocytes (KCs).				
CF	**Levels in skin/plasma/serum**	**Target receptor**	**Target cell**	***In vitro* expression**
	immunologically stained in lesional AD skin. Only mRNA expression, but not protein expression was up-regulated in nonlesional AD skin. (Park et al., 2005, Yawalkar et al., 1999, Taha et al., 2000, Gaspar et al., 2013) **In normal skin:** May (Taha et al., 2000) or may not be expressed. (Yawalkar et al., 1999) **In serum:** Increased levels of CCL11, but not correlated with disease severity (Kaburagi et al., 2001, Jahnz Rozyk et al., 2005, Hossny et al., 2001)	[i.e. Up-regulated CCLR3 mRNA expression in lesional AD skin and immunologically stained in lesional and nonlesional AD skin, but not detected in non-atopic controls.] (Yawalkar et al., 1999)	Mochizuki et al., 1998, Ponath et al., 1996), basophils (Uguccioni et al., 1997), Th2 lymphocytes (Sallusto et al., 2000, Gerber et al., 1997)	umbilical vein endothelial cells or KCs. (Mochizuki et al., 1998)
CCL17/ TARC	**In lesional AD skin:** Immunologically stained in epidermal KCs, vascular endothelium of cutaneous venules and dermal infiltrating cells [i.e. $CD3^+$ lymphocytes and $CD1a^+$ DCs] in	**CCR4** [i.e. Increased amount of CCR4+ memory (CD45RO+) CD4+ T	Th2 type memory T lymphocytes [i.e. since CCR4 receptor were selectively	**In human epidermal KCs.** CCL17 mRNA expression was induced by IFN-γ with no secreting CCL17. (Horikawa et al., 2002) In another study, secreted CCL17 was induced by IFN-γ or TNF- α or

Table 1.3 Atopic dermatitis (AD)-associated chemotactic factors (CFs) generated by keratinocytes (KCs).				
CF	**Levels in skin/plasma/serum**	**Target receptor**	**Target cell**	***In vitro* expression**
	lesional AD skin. (Vestergaard et al., 2000, Kakinuma et al., 2001, Horikawa et al., 2002, Campbell et al., 1999, D'Ambrosio et al., 2002) **In normal or nonlesional AD skin:** Not detected. (D'Ambrosio et al., 2002, Vestergaard et al., 2000) **In serum/plasma:** Increased levels of CCL17 were correlated with disease severity, serum levels of lactate dehydrogenase, soluble E-selectin, soluble IL-2 receptor, total IgE, eosinophils counts, and platelet counts. (Kakinuma et al., 2001, Fujisawa et al., 2002, Horikawa et al., 2002, Hijnen et al., 2004, Hon et al., 2004)	lymphocytes in blood and lesional skin (Vestergaard et al., 2000, Yamamoto et al., 2000, Kakinuma et al., 2001) that was positively correlated with disease severity, number of infiltrated T lymphocytes, total serum levels of IgE, lactic dehydrogenase, eosinophil number, eruption score and IL-4 and IL-13 secretion.] (Nakatani et al., 2001, Wakugawa et al.,	expressed by Th2 cells] and/or those expressing cutaneous lymphocyte antigen (CLA). (Bonecchi et al., 1998, Campbell et al., 1999, Yamamoto et al., 2000, Imai et al., 1999)	synergistically by IFN-γ plus TNF- α. (Vestergaard et al., 2000) **In peripheral blood mononuclear cells:** Produced by peripheral blood mononuclear cells [i.e. stimulated with IL-3, IL-4 or GM-CSF or synergistically by IL-3 plus IL-4 or GM-CSF plus IL-4], monocytes [i.e. stimulated with IL-3 or GM-CSF] and monocyte-derived DCs. [i.e. monocyte cultured with IL-4 and GM-CSF]. (Imai et al., 1999) **In HaCaT:** CCL17 protein expression was induced by IFN-γ or TNF-α or synergistically by IFN-γ plus TNF-α. (Vestergaard et al., 2000, Horikawa et al., 2002)

Table 1.3 Atopic dermatitis (AD)-associated chemotactic factors (CFs) generated by keratinocytes (KCs).				
CF	**Levels in skin/plasma/serum**	**Target receptor**	**Target cell**	***In vitro* expression**
		2001, Okazaki et al., 2002)		
CCL20/ MIP-3α	**In lesional AD skin:** Immunologically stained in epidermal keratinocytes. **In plasma:** Increased levels of CCL20. **In normal skin:** Weak/negligible. (Nakayama et al., 2001)	**CCR6**	Immature DCs and memory/effector T lymphocytes. (Nakayama et al., 2001, Liao et al., 1999)	**In human neonatal dermal KCs:** CCL20 mRNA and protein expression levels were induced by IL-1α, IFN-γ and TNF-α or synergistically by IL-1α plus IFN-γ plus TNF-α. (Nakayama et al., 2001)
				In HaCaT: CCL20 protein expression was induced by TNF-α, IL-1β or IL-17A. (Karakawa et al., 2010, Kim et al., 2011b)
CCL22/ MDC	**In lesional AD skin:** Immunologically stained in epidermal KCs, dermal infiltrating cells [i.e. T cells and DCs]; but not in nonlesional skin. (Galli et al., 2000, Horikawa et al., 2002) **In nonlesional AD skin:** Not detected. (Horikawa et al., 2002)	**CCR4**	TH2 type lymphocytes. (Andrew et al., 1998, Imai et al., 1999)	**In human epidermal KCs:** CCL22 mRNA and protein expressions were induced by IFN-γ. (Horikawa et al., 2002)
				In monocyte-derived DCs: CCL22 protein expression was detected in culture medium of LCs-like DCs and IDEC-DCs; derived from peripheral blood monocytes of AD patients. (Novak et al., 2004c)
				In human peripheral blood-derived cells: Secreted constitutively by DCs, B cells and macrophages. Produced by natural killer cells and monocytes upon stimulation with various cytokines [e.g. strong stimulants: IL-4 and IL-13

Table 1.3 Atopic dermatitis (AD)-associated chemotactic factors (CFs) generated by keratinocytes (KCs).				
CF	**Levels in skin/plasma/serum**	**Target receptor**	**Target cell**	***In vitro* expression**
	In serum/plasma: Increased levels of CCL22 were correlated with the disease severity, serum levels of lactate dehydrogenase, total IgE, eosinophil counts and CTACK. (Galli et al., 2000, Hon et al., 2004, Horikawa et al., 2002)			and weak stimulants: GM-CSF]. CCL22 production in monocytes, DCs and natural killer cells and B cells were inhibited by IL-10. (Andrew et al., 1998) **In Th1- and Th2-type cells:** Produced by *in vitro*-polarized Th-1 or Th-2 type cells; dominantly in Th2-type cells. (Galli et al., 2000) **In HaCaT:** CCL22 protein expression was induced by IFN- γ. (Horikawa et al., 2002)
CCL26/ eotaxin-3	**In lesional and nonlesional AD skin:** CC26 mRNA was expressed in lesional AD skin at 150 fold higher levels than nonlesional AD and normal skin and was immunologically stained in epidermal KCs. (Owczarek et al., 2010, Gaspar et al., 2013) **In serum:** Increased levels of CCL26 were correlated with disease severity,	**CCR3**	Eosinophils but not neutrophils. (Shinkai et al., 1999)	**In human umblical vein endothelial cells:** CCL26 mRNA expression was induced by IL-4, but not by TNF- α, IL-1β, IFN- γ or IFN-γ plus TNF-α. (Shinkai et al., 1999) **In human dermal fibroblasts:** CCL26 mRNA expression was induced by IL-4, IL-13 or synergistically by IL-4 plus TNF-α or IL-13 plus TNF-α. Not induced by IL-1β or TNF-α. (Banwell et al., 2002) **In human KCs:** CCL26 production was not induced by IL-4 and TNF-α. **In HaCaT**: CCL26 mRNA and protein expression were induced by IL-4 or IL-13 or synergistically by IL-4 plus

Table 1.3 Atopic dermatitis (AD)-associated chemotactic factors (CFs) generated by keratinocytes (KCs).				
CF	**Levels in skin/plasma/serum**	**Target receptor**	**Target cell**	***In vitro* expression**
	serum levels of CCL17, CCL22 and eosinophil counts. (Kagami et al., 2003)			TNF- α, but not induced by TNF-α or IFN-γ. (Kagami et al., 2005)
CCL27/ CTACK	**In lesional AD and normal skin:** Immunologically stained in epidermal basal keratinocytes in normal [i.e. low amount at suprabasal layers] or lesional AD skin [i.e. increased amount in suprabasal layers], immobilized on dermal extracellular matrix, fibroblasts and surface dermal endothelial cells. (Homey et al., 2000, Homey et al., 2002) **In serum:** Increased levels of CCL27 were correlated with disease severity, serum levels of soluble IL-2 receptor, soluble E-selectin, TARC and MDC. (Kakinuma et al., 2003, Hijnen et al., 2004)	**CCR10** [i.e. In lesional AD skin, strongly expressed in skin dermal leukocytes and intra-epidermal lymphocytes. In normal skin, expressed in cells within the superficial dermal plexus, but not in the epidermis.] (Homey et al., 2002)	CLA^+ memory T cells, but not naïve T cells, CLA^- T cells, B cells, monocytes or neturophils. (Morales et al., 1999)	**In human KCs:** CCL27 mRNA was expressed in untreated KCs and up-regulated by TNF-α plus IL-1β (Morales et al., 1999); not up-regulated by IL-4 or IFN-γ and suppressed by IL-10. (Homey et al., 2002) **In HaCaT:** CCL27 protein expression was induced by TNF-α. (Karakawa et al., 2010)

Table 1.3 Atopic dermatitis (AD)-associated chemotactic factors (CFs) generated by keratinocytes (KCs).				
CF	**Levels in skin/plasma/serum**	**Target receptor**	**Target cell**	***In vitro* expression**
ICAM	**In nonlesional AD skin:** Increased levels of ICAM in nonlesional AD skin when compared with normal non-atopic skin. (Jung et al., 1996) **In serum:** Increased levels of ICAM were correlated with disease severity. (Kojima et al., 1994)	Lymphocyte function-associated antigen 1 (LAF-1) (Dustin et al., 1988)	T Lymphocytes (Dustin et al., 1988)	**In HaCaT**: ICAM protein and mRNA expressions were induced by IFN-γ. (Bito et al., 2002)

1.1.1.3 Dysregulated apoptosis

Increased survival/dysregulated apoptosis of cells resident at skin tissue such as eosinophils (Akdis et al., 1999b), T lymphocytes (Akdis et al., 2000c) and keratinocytes (Trautmann et al., 2000) may also contribute to the pathology of AD. Cutaneous lymphocyte-associated antigen plus (CLA^+) T lymphocytes derived from lesional AD skin were resistant to Fas-mediated apoptosis and apoptosis was possibly inhibited by the local cytokines milieu [e.g. IL-2, IL-4 and IL-15] and extracellular-matrix components [e.g fibronectin/transferrin] (Akdis et al., 2000c, Akdis et al., 2000a). Infiltrated T lymphocytes also affect the survival of other localized cells at the site of inflammation. IL-5 released from CLA^+ $CD4^+$/$CD8^+$ T cells may contribute to the increase of eosinophil survival. (Akdis et al., 1999b) In addition, infiltration of T lymphocytes could affect the morphology of keratinocytes, induce or increase their susceptibility to apoptosis via Fas ligation [i.e. binding its surface Fas ligand to the Fas receptor on keratinocytes] and increase expression of Fas receptor on keratinocytes by IFN-γ. Subsequently, dysregulated apoptosis of keratinocytes may lead to acantholysis and spongiosis of the epidermis as seen in eczematous skin lesions. (Trautmann et al., 2000)

1.1.1.4 Defective epidermal barrier in AD

The integrity of the skin barrier, measured by transepidermal water loss (TEWL), is disrupted in both lesional and nonlesional skin of patients with AD and is correlated with disease severity and serum IgE levels. (Hon et al., 2008, Gupta et al., 2008, Lee et al., 2006) Inherited or acquired defects in the skin barrier lead to an increased susceptibility to pathogen invasion that subsequently trigger the epidermal-driven Th2 response and initiate the onset of AD. (Elias and Steinhoff, 2008) Thus, an impaired epidermal barrier plays an important role in the pathogenesis of AD.

The uppermost, cornified layer of the skin epidermis, known as the stratum corneum (SC), serves as a protective skin barrier that restrict water loss from the body and prevent the infiltration of foreign substances (e.g. pathogens and allergens) from the environment. The SC is the end product of the epidermal differentiation. The keratinocytes proliferate in the basal cell layer of the epidermis and progress upwards through the spinous and granular layers, ultimately forming the impenetrable, multilayer SC consisting of flat anucleated corneocytes embedded in a lipid-riched extracellular

matrix before being shed from the outer layer of the skin [i.e. desquamation]. (Sandilands et al., 2009, McAleer and Irvine, 2013)

1.1.1.4.1 Role of filaggrin (FLG)

During epidermal differentiation, different proteins are expressed. Among these proteins, a major structural protein is present in the SC, known as filaggrin (FLG), has caught much attention in recent research due to its importance in maintaining the integrity of the skin barrier. FLG is a class of structural protein, isolated from the SC of mammalian epidermis. (Steinert et al., 1981) It is synthesized as a precursor protein, profilaggrin, that is encoded by the *FLG* gene located within the epidermal differentiation complex on chromosome 1q21 (a cluster of genes encoding proteins involved in epidermal differentiation/homeostasis). (Mischke et al., 1996) In the granular layer of the epidermis, profilaggrin is stored as an inactive form within the keratohyalin granules. In response to an increased Ca^{2+} levels, profilaggrin is degranulated from the keratohyalin granules, dephosphorylated and cleaved by several proteases (such as serine proteases matriptase (List et al., 2003), prostatin (Leyvraz et al., 2005) and kallikrein 5 (Deraison et al., 2007) to active/functional FLG monomers. These active FLG monomers bind to the keratin intermediate filaments, to aggregate and align them into tightly packed, parallel arrays of macrofibrils. (Dale et al., 1985) This leads to condensation of the cytoskeleton of keratinocytes and the subsequent crosslinking by transglutaminases and modification by peptidylarginine deiminase ultimately results in the formation of an insoluble keratin matrix. The insoluble keratin matrix acts as a protein scaffold for the attachment of other proteins and lipids in the SC, together providing the mechanical strength and integrity of the skin barrier. (Sandilands et al., 2009, McAleer and Irvine, 2013) Moreover, FLG monomers are degraded into hygroscopic amino acids by different proteases at the desquamation step. These free amino acids and their derivatives [e.g. pyrrolidone carboxylic acid (Rawlings and Harding, 2004) and trans-urocanic acid (Suchi et al., 1993)], together with lactate and urea; acting as natural moisturizing factors that regulate the levels of hydration in the SC and modulate pH gradient in the epidermis. Carrier with null-mutation of FLG has lower amounts of natural moisturizing factors (O'Regan et al., 2010), higher levels of transepidermal water loss (Nemoto Hasebe et al., 2009) and highervalues of skin pH. (Jungersted et al., 2010). Increased pH of the epidermis can subsequently disrupt the structural integrity and anti-microbial activity of the skin, and facilitate pathogens invasion. (Rawlings and Harding, 2004, Kamata et al., 2009, Brown and McLean, 2012)

Loss-of-function mutations in the FLG gene (e.g. two well characterized FLG mutation: R501X and 2282del4 are carried by 9% of people of European origin) have now been established in a series of studies as an important causative factor for a defective skin barrier; predisposing individuals to AD. (Marenholz et al., 2006, Palmer et al., 2006, Weidinger et al., 2006, Irvine, 2007, Sandilands et al., 2007, Henderson et al., 2008) Although mutations of the FLG gene only occur in about 20-30% of patients with AD (Palmer et al., 2006, Weidinger et al., 2006, Rodriguez et al., 2009, Van den Oord and Sheikh, 2009, Otsuka et al., 2014) and differ between population groups [e.g. both FLG mutations: R501X and 2282del4 are absent in non-European; such as African and Asian (Palmer et al., 2006)], down-regulated expression of FLG is seen in nearly all individuals suffering from moderate-to-severe AD (Howell et al., 2009) and in both lesional and nonlesional skin (Seguchi et al., 1996, Jensen et al., 2004, Henderson et al., 2008) regardless of FLG genotype. Moreover, FLG expression is lower in lesional skin, compared to nonlesional skin in AD. (Howell et al., 2009) Thus, FLG gene mutations alone do not account for the down regulation of FLG expression in AD skin. It is postulated that defect in FLG expression could be acquired due to the atopic cytokine milieu (e.g. overexpression of IL-4 and IL-13) during the inflammatory response. (Howell et al., 2009, Gutowska Owsiak et al., 2011, Hvid et al., 2011a, Hvid et al., 2011b) This phenomenon is reflected *in vitro* as keratinocytes that differentiated in the presence of IL-4 and IL-13 cytokines or post-exposure to these cytokines exhibited reduced FLG mRNA and protein expressions. (Howell et al., 2009) In addition, gene mutations induced-down-regulation of proteases that are involved in the processing of profilaggrin to active filaggrin within the SC may also cause filaggrin deficiency. (Brown and McLean, 2012)

Collectively, FLG deficiency in AD patients might lead to a defective skin barrier and subsequently, promote the ingress of foreign environmental substance that trigger/exaggerate aberrant immune response. This phenomenon is also observed in the FLG-deficient flaky tail (gene symbol ft) mouse model that is induced by mutation of the FLG-gene. (Fallon et al., 2009, Moniaga et al., 2010, Scharschmidt et al., 2009, Oyoshi et al., 2009)

1.1.1.4.2 Role of ceramides (CER)

The highly organized, multilayered lipid matrix surrounding corneocytes embedded in the SC consists primary of ceramides, fatty acids and cholesterol. These lipids play a

vital role in maintaining skin barrier function. (Janssens et al., 2012) Changes in levels (Jungersted et al., 2010) and carbon chain length of ceramides (CER) and free fatty acids [i.e. reduced chain length of free fatty acids (FFA) and CER and increased levels of unsaturated FFA] lead to a less dense lipid organization and disturbed barrier function with increased levels of transepidermal water loss (Janssens et al., 2012, Van Smeden et al., 2014) in both lesional and non-lesional SC of patients individuals with AD. The atopic cytokine milieu at the site of inflammation has been linked to the alteration of the levels and chain length of CER in the skin. For example, interferon-γ and Th2 cytokines [i.e. IL-4, IL-6] decrease the expression of ceramide-producing enzymes that are responsible for the synthesis of the long carbon chain in CER, resulting in decreased levels of long-chain CER in the epidermis. (Hatano et al., 2005, Sawada et al., 2012, Tawada et al., 2014)

1.1.1.5 Innate immune deficiency

Individuals with AD are prone to recurrent bacterial or viral skin infection and colonization with *Staphylococcus aureus* (see Table 1.2) that could be due to the defective skin barrier and the down-regulation of the sensing and responding mechanism in the skin such as the down-regulated expression of antimicrobial peptides [i.e. cathelicidins (LL-37), human β-defensins (hBD)-2, 3, dermicidin, sphingosine] (Rieg et al., 2005, Ong et al., 2002, Nomura et al., 2003, Arikawa et al., 2002), macrophage inflammatory peptide-3 (Kim et al., 2007) and gene polymorphisms of toll-like receptor 2 (Ahmad-Nejad et al., 2004) and nucleotide-binding oligomerization domain 1 (NOD1). (Weidinger et al., 2005)

1.1.2 Diagnosis

There is no specific test for the diagnosis of AD; diagnosis is based on clinical history [e.g. personal or family history of atopy/skin creases/general dry skin in the past year] and physical examination [e.g. pruritus, age-specific morphology and location of lesions and chronicity of the disorder]. Skin biopsies are rarely carried out due to the non-specific histology of AD that usually only show sparse lymphocytes in the dermis and epidermis. However, when clinical manifestations are incompatible with AD, skin biopsies will be carried out to rule out systemic diseases with AD-like features such as nutritional deficiencies, immunodeficiency syndromes and cutaneous T-cell lymphoma. (Williams et al., 1994a, Williams et al., 1994c, Williams et al., 1994b, Watson and

Kapur, 2011, Blauvelt et al., 2003) Clinical manifestations of AD usually vary with age. During early infancy (from birth to 2 years old), lesions are generally more acute and are characterized by pruritic erythematous papules, vesicles, weeping and oedema; typically these lesions emerge on the cheeks, forehead or scalp and might extend to the trunk or the outer surface of the extremities as scattered, poorly defined and often symmetrical patches. Lesions in children from 2 years of age to puberty are less likely to be exudative, usually appear as lichenified papules or plaques; and typically affect the neck, wrist, ankles and flexural area of the extremities [i.e. elbow or back of the knee]. Lesions developing during adolescence and adulthood are usually in the chronic phase are characterized by dry scaling erythematous papules and large lichenified plaques and typically affect the flexural area of the extremities, hand and feet. Regardless of age, pruritus associated with AD can persist throughout the day and worsen at night. Also, post-inflammatory hypopigmentation or hyperpigmentation may be observed. The later is predominantly noted at the site of lichenification and pigmentary changes resulting from AD are reversible when the underlying inflammation is controlled. (Spergel and Paller, 2003, Leung and Bieber, 2003, Watson and Kapur, 2011)

The severity of AD can be assessed by scoring systems such as the scoring atopic dermatitis (SCORAD) index and eczema area and severity index (EASI). (SCORAD, 1993, Housman et al., 2002, Hanifin et al., 2001) Allergological diagnostics e.g. skin test and laboratory investigations may also be carried out to identify provocative factors e.g. food and environmental allergen. (Bieber, 2010)

1.1.3 Treatments

There is no 100% life-long cure for AD, so management of AD is primarily focused on symptomatic relief and prevention of recurrence/exacerbation. This involves regular and continuous usage of emollient and skin barrier repairing agents to improve the appearance of the skin, prevent dryness and pruritus and limit the need for pharmacological intervention. In cases of flare-ups of AD and bacterial/viral colonization, anti-inflammatory, anti-bacterial or anti-viral agents will be required. In addition, AD is a chronic disease that requires continuous compliance to skin care and the appropriate use of topical/systemic treatments. Thus, education of patients and/or their caregivers on various aspects of the disease and the correct use of medication

forms a vital part in the management of AD. (Akdis et al., 2006, Ellis et al., 2003)

1.1.3.1 Maintenance of skin hydration

The skin of individuals with AD is characterized by dryness due to the impaired skin barrier fuction. This issue is managed by the regular and continuous use (i.e. even in the absence of any signs of disease) of moisturizers and emollients to prevent moisture loss, drying and itching of the skin. (Ellis et al., 2003) In clinical studies, ceramide-rich emollients have been shown to be useful in improving AD conditions, by restoring the extracellular lamellar membranes of the stratum corneum and by reducing transepidermal water loss. (Chamlin et al., 2002)

1.1.3.2 Anti-inflammatory therapy

1.1.3.2.1 Topical corticosteroids

Topical glucocorticoid forms the first-line of treatment for acute flare-ups of AD. These products are applied on the affected areas before using an emollient. (Watson and Kapur, 2011, Ellis et al., 2003, Akdis et al., 2006) The mechanism of action of glucocorticoids includes suppressing of the expression of genes encoding cytokines via forming a complex with the cytoplasmic steroid receptor in all cells that is subsequently transported to the nucleus and opposes the activation of the transcription factors i.e. activator protein 1 (AP-1) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). This suppresses the expression of T cell growth factors [e.g. IL-2, IL4, IL-15, IL-17 and IFN-γ] and other inflammatory mediators [e.g. cyclooxygenase (COX)-2, inducible nitric oxide synthase and intracellular adhesion molecule-1) and increases expression of anti-inflammatory mediators [e.g. IL-10]. (Dinarello, 2010) Because of the concern of cutaneous side effects of glucocorticoids (e.g. skin atrophy, telangiectasia, petechiae, skin thinning, striae, steroid acne, rosacea-like eruption and increased hair growth) and systemic side effects (e.g. hypothalamic-pituitary-adrenal axis suppression, growth retardation, reduced bone density and increased risk of glaucoma cataract), the least potent preparation required to control AD is utilized intermittently in the short-term. Low potency preparations are also used for sensitive skin areas (e.g. face, neck, groin and underarms). (Watson and Kapur, 2011, Ellis et al., 2003, Akdis et al., 2006) Recent studies demonstrated that twice-weekly applications of topical fluticasone (0.05% cream or 0.0005% ointment) or methylprednisolone (0.1% cream) may reduce the risk of relapse. (Berth Jones et al., 2003, Glazenburg et al., 2009,

Hanifin et al., 2002, Peserico et al., 2008) This maybe due to the reduced sensitiveness/responsiveness of the skin to topical corticosteroids after long-term use. (Ring et al., 2008, du Vivier and Stoughton, 1975, du Vivier, 1976)

1.1.3.2.2 Topical calcineurin inhibitors

Topical calcineurin inhibitors [i.e. tacrolimus (0.03%) ointment and pimecrolimus (1%) cream] are used as second-line treatment for moderate-severe AD in patients aged 2 years and older. Their primary mechanism of action includes inhibiting the release of cytokines from activated T cells via inhibition of calcineurin; unlike corticosteroids, calcinuerin inhibitors neither reduce the number of T helper cells in the skin nor affect the Langerhans cells. (Carr, 2013, Ellis et al., 2003, Hoetzenecker et al., 2005) In addition, they inhibit the infiltration of cytokine expressing inflammatory cells in the dermis (Simon et al., 2004, Simon et al., 2005) and suppresse the expression of IL-5, chemokines [i.e. CCL5] and CC chemokine receptor 3 (CCR3) (Park et al., 2005). They are usually prescribed for non-immunocompromised patients on long-term usage of corticosteroids [i.e. persistent or frequently relapsing AD] or for treatment of lesions in sensitive skin areas [e.g. face, neck and genitals] when systemic or cutaneous side effects associated with corticosteroids are of particular concern (Akdis et al., 2006). The most common side effect observed with the use of topical calcineurin inhibitors is a transient burning sensation of the skin (Queille Roussel et al., 2001, Akdis et al., 2006, Watson and Kapur, 2011). However, the US Food and Drug Administration (FDA) has only approved their use as second-line agents for short-term and intermittent treatment of AD since safety information related to their long-term use is limited. In addition, a black box warning about potential cancer risks associated with their use e.g skin cancer and lymphoma has also been issued. (U.S. Food and Drug Administration, 2005, Ring et al., 2008)

1.1.3.3 Anti-microbial/viral treatment

Staphylococcus aureus (*S. aureus*) colonies can be isolated from 80-100% lesional skin of patients with AD even in the absence of any clinical signs of infection (Friedman and Goldman, 2011, Hauser et al., 1985). Toxins secreted by *S. aureus* behave as an antigen and can alter the course of AD. (Breuer et al., 2001, Breuer et al., 2002) Skin infection in AD is treated by short-term topical and/or oral antibiotic therapy. Mild and localized form of *S. aureus* infection can be managed by a short term application of topical

fusidic acid to avoid resistance. (Peeters et al., 2004) Widespread infection is treated by systemic antibiotic i.e. first- or second-generation cephalosporins or penicillins for 7 to 10 days. Clindamycin or oral fusidic acid are alternative for those allergic to cephalosporins or penicillins. (Akdis et al., 2006)

Individuals with AD are also prone to viral infection. For example, eczema herpeticum caused by herpes simplex virus is a life-threatening complication in AD. This condition requires systemic antiviral treatment e.g. acyclovir. (Akdis et al., 2006, Watson and Kapur, 2011)

1.1.3.4 Other treatments

For severe AD that is refractory to conventional topical treatments, systemic corticosteroids or immunosuppresants [i.e. cyclosporine and azathioprine] may be required for short-term use with close monitoring for side effects.

In addition, the sedative effect of first-generation antihistamines [e.g. chlorpheniramine and diphenhydramine] may benefit individuals having difficulties in sleeping due to pruritus. (Watson and Kapur, 2011, Akdis et al., 2006)

1.1.4 *In vitro* and *in vivo* models for AD

1.1.4.1 In vitro models

Abnormal phenomena observed in the pathogenesis of AD [i.e. pathogenesis-related targets] are mimiced and developed in *in vitro* models, actives that can correct the abnormal condition developed *in vitro* may be developed as a potential clinical therapy for AD. Some commonly used pathogenesis-related targets-based assays include up-regulated production of cytokines or chemokines by T cells or keratinocytes (Le et al., 2011), down-regulated expression of antimicrobial peptides and filaggrin by keratinocytes and release of mediators associated with pruritus [e.g. tryptase and histamine] from mast cells, as summarized in Table 1.3 and 1.4.

1.1.4.2 In vivo models

Murine models are commonly used in *in vivo* experiments for AD due to low cost, ease of handling and the ability to manipulate their genome. Various murine models have been developed to understand the pathogenesis of AD and to act as preclinical models for drug screening. There is no perfect model that can fully reproduce the complex condition of AD. Understanding the characteristics of each model is thus important for

researchers to select the suitable models that cover the hallmarks of AD in question. Generally, murine models of AD can be classified into three groups i.e. spontaneous, epicutaneous sensitization induced and genetically engineered mouse models of AD (Table 1.5) (Jin et al., 2009).

To conclude, increasing restrictions and ethical concerns arise from the use of animals and human skin for scientific experimentation promote the development of *in vitro* skin models. I*n vitro* skin models allow controlled manipulations of defined parameters and are more consistent when compared with *in vivo* models. There is an ongoing trend towards the development of 3D *in vitro* skin models that aim to mimic and recreate human skin *in vitro* (Flaten et al., 2015). The successful development of *in vitro* AD models require better understanding of the cellular communication involved in the pathogenesis of AD. And *in vivo* models provide a portal for understanding the signaling molecules involved in the pathogenesis of AD and subsequently aid the development of *in vitro* AD models and the identification of new drug targets. In addition, *in vivo* models allow the evaluation of a drug under a more complex biological system that may provide a better prediction of the efficacy and toxicity of the drug in human. No single *in vitro* or *in vivo* model is able to cover all pathogenic aspects of AD, a panel of models are required so that the efficacy and toxicity of a drug in human can be extrapolated from *in vitro* and/or *in vivo* data with a higher degree of confidence.

To summarize, the side effects and short-term usage of conventioanl therapies reflects the need for novel therapy. Despite AD has a multifactorial aetiology, pathogensis-related targets identified to date can be used as targets for for screening new drugs.

Table 1.4 *In vitro* models for AD.	
Pathogenesis-related targeted	**Methods**
Cytokines expression in T lymphocytes	Screening of active compounds that inhibit anti-CD3 monoclonal antibodies (mAbs)-induced cytokine production [i.e. TNF-α, IFN-Y, GM-CSF, IL-1β and IL-8] in peripheral blood mononuclear cells. (Winiski et al., 2007)
T lymphocytes proliferation	Screening of active compounds that inhibit anti-CD3 mAbs-induced proliferation of human peripheral blood mononuclear cells. (Winiski et al., 2007)
Antimicrobial peptides expression in keratinocytes	Screening of active compounds that up-regulate hBD-2, hBD-3 or cathelicidine expression in human keratinocytes for improving the impaired antimicrobial defense mechanisms in AD skin. (Buchau et al., 2008)
Filaggrin (FLG) expression in keratinocytes	Screening of active compounds that promote the expression of FLG mRNA and/or proteins expression using human immortalized keratinocytes (HaCaT) or normal human epidermal keratinocytes (NHEK) in a 3-dimensional human dermal model; in presence/absence of down-regulators of FLG i.e. IL-4 and IL-13. (Otsuka et al., 2014)
Defected epidermis barrier	Supplement the culture medium of Leiden epidermal models (LEMs) with atopic cytokines [i.e. IL-4, IL-13, IL-31 and TNF-α] to develop an *in vitro* epidermis with pathophysiological changes occurring in AD [i.e. 1) spongiosis; 2) increased TSLP levels in the medium; 3) reduced FLG mRNA and protein expression; 4) increased basal keratinocyte proliferation; 5) decreased level of long chain free fatty acids, altered ratio of CER:cholesterol and ester linked ω-hydroxy CER subclasses (EO CER):non-EO CER; 6) altered enzyme elongase 1 mRNA and protein expression; 7) reduced long periodicity phase (LPP) repeated distance] and evaluate the effectiveness of tested sample against these changes. (Danso et al., 2014)
Thymic Stromal Lymphopoietin (TSLP)	Screening of active compounds that inhibit flagellin-induced TSLP protein and mRNA expressions in primary human keratinocytes (Le et al., 2011)
	Screening of active compounds that inhibit double-stranded RNA-induced TSLP protein and mRNA expressions in primary human keratinocytes in an atopic cytokine milieu [i.e. in the presence of IL-4, IL-13 and TNF-α) (Le et al., 2010)

Table 1.4 *In vitro* models for AD.	
Pathogenesis-related targeted	**Methods**
Histamine and tryptase production in mast cells	Screening of active compounds that inhibit anti-IgE-induced histamine and tryptase production in human skin mast cell. (Zuberbier et al., 2001)
Chemostatic factors expression	Screening of active compounds that inhibit stimulant-induced release of chemostactic factors from cultured skin cells e.g. HaCaT or other inflammatory cells. (See Table 1.3)

Table 1.5 *In vivo* models for AD.				
Model type	**Mouse model**	**Age of onset**	**Local/systemic symptoms**	**References**
Spontaneous models	NC/Nga mice	8-17 weeks	Ø Scratching behaviour. Ø Erythema, edema, hemorrhage, erosion/ excoriation, scaling and dryness on the face, neck, ears and back. Ø Impaired skin barrier: epidermal hyperplasia, increased transepidermal water loss and decreased stratum corneum ceramide content. Ø Increased serum IgE levels. Ø Increased numbers of mast cells with degranulation and infiltration of $CD4^+$ and $CD8^+$ T lymphocytes, eosinophils and macrophages.	(Matsuda et al., 1997b, Aioi et al., 2001, Shiohara et al., 2004)
	DS-Nh mice	9-29 weeks	Ø Scratching behavior. Ø Eythema, edema, hemorrhage and erosion/ excoriation and dryness on the face, neck, chest and flexor surfaces. Ø Impaired skin barrier: epidermal hyperplasia, increased transepidermal water loss and intercellular edema of the epidermis. Ø Increased serum IgE levels. Ø Increased numbers of mast cells with degranulation and infiltration of $CD4^+$ and $CD8^+$ T lymphocytes and eosinophils. Ø Colonization of *S. aureus* in the skin lesions.	(Hikita et al., 2002)
Epicutaneous sensitization induced models	Repeated sensitization with hapten (e.g. TNCB and oxazolone)	3-4 weeks	Ø Scratching behavior. Ø Erythema, scaling and dryness. Ø Impaired skin barrier: epidermal hyperplasia, increased transepidermal water loss, decreased surface area of each corneocyte obtained from the inflamed skin, villus formation on the rear surface of corneocytes, decreased stratum corneum ceramide content, aberrant epidermal differentiation and impaired lamellar body secretion. Ø Increased serum IgE levels. Ø Increased numbers of mast cells with degranulation and infiltration of $CD4^+$ and $CD8^+$ T lymphocytes, eosinophils and neutrophils.	(Harada et al., 2005, Yamashita et al., 2005, Matsumoto et al., 2004, Man et al., 2008, Webb et al., 1998)
	Repeated sensitization with allergen (e.g. ovalbumin)	50 days	Ø Scratching behavior. Ø Impaired skin barrier: epidermal and dermal hyperplasia. Ø Increased serum ovalbumin-specific IgG1, IgE and IgG2a levels. Ø Infiltration of $CD4^+$ T lymphocytes, mast cells and eosinophils. Ø Up-regulated expression of Th2 cytokines [i.e. IL-4, IL-5 and IL-13] with little or no change in Th1 cytokines [i.e. IFN-□] and chemokines [i.e. CCL11 and CCL17].	(Spergel et al., 1999a)
Genetically engineered models	IL-4 transgenic mice	4 months	Ø Scratching behavior. Ø Xerosis, eczematous lesions occur around the eye, ear, neck, mouth, tail and leg. Ø Impaired skin barrier: epidermal hyperplasia.and mild spongiosis.	(Chan et al., 2001, Chen et al., 2004a)

Table 1.5 *In vivo* models for AD.				
Model type	**Mouse model**	**Age of onset**	**Local/systemic symptoms**	**References**
			Ø Increased serum IgE and IgG1 levels. Ø Infiltration of $CD3^+$, $CD4^+$ and $CD8^+$ T lymphocytes, mast cells, eosinophils and macrophage-like mononuclear cells. Ø Colonization of *S. aureus* in the skin lesions. Ø Up-regulated expression of both Th1 [i.e. IL-2, IL-12p40, IFN- □ and TNF-β] and Th2 [i.e. IL-3, IL-4, IL-5, IL-6, IL-10 and IL-13] cytokines.	
	IL-13 transgenic mice	2 months	Ø Scratching behavior. Ø Impaired skin barrier:. epidermal hyperplasia, spongiosis and increased collagen deposition in the skin. Ø Increased serum IgE and IgG1 levels. Ø Infiltration of $CD4^+$ T lymphocytes, mast cells, eosinophils, macrophages and Langerhans cells. Ø Up-regulated expression of cytokines [i.e. TSLP] and chemokines [i.e. CCL2, CCL5, CCL17, CCL22, CCL27].	(Zheng et al., 2009)
	IL-31 transgenic mice	2 months	Ø Scratching behavior. Ø Mild to moderate hair loss, conjunctivitis and swelling around the eye. Ø Impaired skin barrier: epidermal hyperplasia. Ø Normal serum IgE levels. Ø Increased numbers of mast cells and infiltration of inflammatory cells.	(Dillon et al., 2004)
	TSLP-transgenic mice	2-3 weeks after doxycycline treatment	Ø Erythema, xerosis, erosions. Ø Impaired skin barrier: epidermal hyperplasia and spongiosis. Ø Increased serum IgE and IgG1 levels. Ø Infiltration of lymphocytes, mast cells, eosinophils and macrophages.	(Yoo et al., 2005)
	Capase-1 transgenic mice	8 weeks	Ø Scratching behaviour. Ø Erosion, eczematous lesions and skin ulcers around the eye, face, ear, neck, trunk and leg. Ø Impaired skin barrier: epidermal hyperplasia and massive keratinocyte apoptosis. Ø Increased serum IL-1β and IL-18 levels. Ø Increased susceptibility to bacterial infection. Ø Infiltration of lymphocytes, mast cells and neutrophils.	(Yamanaka et al., 2000)
	Cathepsin E deficient mice	10 weeks	Ø Scratching behavior Ø Erythema, erosion and hair loss. Ø Impaired skin barrier: epidermal hyperplasia. Ø Increased serum IgE levels. Ø Infiltration of lymphocytes, mast cells, eosinophils and macrophages.	(Tsukuba et al., 2003)
	RelB deficient mice	4-10 weeks	Ø Scratching behaviour. Ø Reddened skin, scaling, hair loss and eczematous lesions occur on the ear, footpad, trunk and head.	(Barton et al., 2000)

Table 1.5 *In vivo* models for AD.				
Model type	**Mouse model**	**Age of onset**	**Local/systemic symptoms**	**References**
			Ø Impaired skin barrier: epidermal and dermal hyperplasia. Ø Increased serum IgE levels. Ø Infiltration of $CD4^+$ and $CD8^+$ T lymphocytes, eosinophils and neutrophils.	
	Stratum corneum chymotrptic enzyme transgenic mice	7-8 weeks	Ø Scratching behaviour. Ø Scaling and hair loss. Ø Impaired skin barrier: epidermal hyperplasia. Ø Increased numbers of mast cells and infiltration of inflammatory cells.	(Hansson et al., 2002)

1.2 PATHOPHYSIOLOGY, DIAGNOSIS AND TREATMENTS OF ATOPIC DERMATITIS/ECZEMA FROM A CHINESE MEDICINE POINT OF VIEW

In ancient Chinese medicinal books such as the Golden mirror of medicine-Key of Surgical Method [i.e. written by Wu Qian in 1742] (Chen et al., 2004b) and the Treatise on Causes and Symptoms of Diseases [i.e. written by Chao Yuangfang in 610 AD] (Nanjing Unversity of Chinese Medicine, 2009), different terminologies [e.g. $\binom{Si\ Wan\ Feng}{四\ 彎\ 風}$, $\binom{Xuan\ Er\ Chuang}{旋\ 耳\ 瘡}$, $\binom{Feng\ Xue\ Chuang}{風\ 血\ 瘡}$, $\binom{Huang\ Shui\ Chuang}{水\ 瘡}$, $\binom{Wo\ Chuang}{瘑\ 瘡}$, $\binom{Shi\ Xuan}{濕\ 癬}$ and $\binom{Jin\ Yin\ Chuang}{浸\ 淫\ 瘡}$] have been used to name skin conditions based on their appearance, location or etiology. Within these various terminologies, modern Chinese practitioners are able to determine some that were describing what is known as atopic dermatitis /eczema in today's medical field. These terminologies are collectively known as $\binom{Shi\ Chuang}{濕\ 瘡}$ in modern Chinese medicine. (Zheng, 2002) According to the Chinese medicine standard for disease diagnosis and treatment published by the State Administration of Traditional Chinese Medicine of the People's Republic of China in 1994 (Dai et al., 2001), Shi Chuang is defined as relapsing skin rash that manifests in different forms and locations, usually symmetrically distributed. The condition is commonly seen in the head, face, distal part of limbs, scrotum and may be evident all over the body.

1.2.1 Pathology of AD in Chinese medicine

From a Chinese medicine point of view, AD is mainly caused by pathogenic factors i.e. wind, dampness and heat. These pathogenic factors are generated internally or originated from the external environment.

1.2.1.1 Endogenous pathogenic factors

Endogenous pathogenic factors are generated due to disharmonies of the internal organs that maybe an innate problem or are induced by diet or psychological status.

1.2.1.1.1 Spleen deficiency, accumulation of heat and dampness $\binom{Pi\ Xu\ Shi\ Re}{脾\quad 濕\ 熱}$

The spleen assists the stomach in digesting ingested food and drink, and transform them into an essence, known as essence of water and grains $\binom{Shui\ Gu\ Jing\ Wei}{水\ 谷\ 精\ 微}$. The spleen then

further transforms the essence into Qi $\binom{Qi}{氣}$, nutritive body fluid $\binom{Jing\ Ye}{津\ \ 液}$, essence $\binom{Jing}{精}$ and blood $\binom{Xue}{血}$ for transporting nutrients all over the body and maintaining normal body function. During this process, the essence of water and grains is transported upward by the spleen to the lung and heart where it is transformed into Qi and blood; nourishing the whole body. If the essence loses its upward transportation by the Qi of spleen, one will suffer from tiredness, dizziness, bloating and diarrhoea. The spleen is also responsible for the transformation and distribution of fluid. If spleen function is impaired, fluid will not be transformed or distributed properly and thus, will accumulate to form endogenous pathogenic dampness, phlegm or oedema. Moreover, spleen controls blood flow within the vessels. Therefore, symptoms such as blood in faeces and subcutaneous bleeding may occur when one is suffering from spleen-qi deficiency. Other symptoms reflecting problem of spleen include loss of appetite, abnormal taste of food, pale lip, muscle wastage and weakness of limbs. (Lin, 2008, Maciocia, 2005)

Spleen deficiency may be an innate problem or may be triggered by the consumption of wind-instigating food e.g. spicy/sweet/oily/cold food, wine, chicken etc. This leads to accumulation of endogenous pathogenic dampness in the body. Long-term accumulation of dampness will lead to heat in blood. Heat is also generated due to diet and psychological status. The accumulated dampness and heat in the body interact with the external pathogenic wind, heat and dampness at the skin interphase, resulting in AD (Bai et al., 1999, Zeng, 2007, Chen et al., 2014a, Song and Wen, 2012).

1.2.1.1.2 Heat in blood $\binom{Xue\ Re}{血\ \ 熱}$

Heart governs blood and blood vessel. Qi of the heart pushes blood to circulate in the blood vessels. Qi of the heart also transports food essences to nourish the skin. In addition, the heart governs the status of the mind that includes spirit, thinking, consciousness and psychological health (Maciocia, 2005). When one's state of mind is not at ease e.g. worry/sadness or excessive consumption of hot-energy foods [e.g. spicy and oily food], endogenous pathogenic fire is induced in the heart $\binom{Xin\ Huo}{心\ \ 火}$ that causes heat in the blood. Heat in the blood leads to the generation of endogenous pathogenic wind; over-production of wind in turn triggers the production of dryness $\binom{Zao}{燥}$. These endogenous pathogenic factors; together with exogenous pathogenic heat, dampness and wind result in AD. (Zeng, 2007, Chen et al., 2014a)

1.2.1.1.3 Wind-dryness due to deficiency of blood $\binom{Xue\ Xu\ Feng\ Zao}{血\quad 風\ 燥}$

When one suffers from severe/chronic illness e.g. stasis of dampness and heat or defects of spleen [i.e. block the formation of qi and blood from essence of food and water] it can lead to blood deficiency. Deficiency of blood results in the generation of itch-causing pathogenic wind-dryness and malnourishment of the internal organs and skin; reflected as dry, pigmented, thickened, itchy and flaky skin. Blood deficiency also affects the normal function of wei qi $\binom{Wei\ Qi}{衛\ 氣}$ that is responsible for protecting the skin from externalpathogenic factors, and subsequently, further exacerbates the skin condition. (Qin, 2014, Liu, 2012, Wang and Yue, 1997, Kim and Zhou, 2000)

1.2.1.2 External pathogenic factors

Among the six external pathogenic factors, heat, dampness and wind are the main ones involved in inducing AD. These pathogenic factors are closely associated with climates; for example, heat, dampness and wind are more prevalent during summer, late summer and spring, respectively. When the body is weak or encounters excessive or abrupt changes of weather conditions, the equilibrium between the body and the environment is disturbed. Extermal pathogenic factors are then able to attack the body causing diseases. (Zeng, 2007, Maciocia, 2005)

1.2.1.2.1 Heat $\binom{Re}{熱}$

Upon reaching certain levels, heat is transformed into fire or toxins. People working under intense sunlight or hot environments are prone to be attacked by external pathogenic heat. Clinical manifestations of skin arising from invasion of external pathogenic heat include red papules and burning sensation that are of rapid onset and spread quickly. When heat is transformed into toxin, pain, swelling or blistering may develop. (Zeng, 2007) Other non-skin related signs include fever, sweating, over-flowing-rapid pulse and a red tongue with yellow fur. (Maciocia, 2005)

1.2.1.2.2 Dampness $\binom{Shi}{濕}$

People living in an environment with high humidity are prone to invasion by external pathogenic dampness. External pathogenic dampness penetrates muscles and sinews, resulting in a feeling of heaviness in limbs. (Maciocia, 2005) Skin lesions due to dampness are more likely to be located in the lower parts of the body and may be accompanied by blistering, weeping and swelling. (Zeng, 2007, Song and Wen, 2012)

1.2.1.2.3 Wind $\binom{Feng}{風}$

The risk of external pathogenic wind invasion increases during spring. When wei qi $\binom{Wei\ Qi}{衛\ 氣}$ fails to protect the body, wind invades the space between the skin and muscles. Wind, dampness and heat can stay at the skin interphase and affect the normal function of wei qi and ying qi (also known as nutritive qi) in blood. This leads to malnourishment of the skin, manifested as dryness, cracking and peeling of skin. Also, skin lesions due to wind are accompanied by itching. (Zeng, 2007, Maciocia, 2005)

1.2.2 Diagnosis and treatment of AD in Chinese medicine

In Chinese medicine, botanical drugs are prescribed as single- or multi-herbal formulae. It is generally believed that multi-herbal formulae have been developed based on centuries of clinical experiences, with the gradual addition of one or more botanical drugs into single-herbal formulae or the combination of two pre-existing multi-herbal formulae (Yi and Chang, 2004). The combination use of botanical drugs is designed to bring about a higher therapeutic efficiency. For example, for certain formulae, no single botanical drug comprising a multi-herbal formula could achieve the biological activity as that of using the complete combination of all the botanical drugs forming the formula (Kiyohara et al., 2004, Phillipson, 1995). Therefore, the therapeutic efficacy of a Chinese herbal medicine formula is expected to be an integral effects of multiple ingredients. The phytochemical complexity and variation [i.e. which is linked to the source, processing and extraction methods] of Chinese herbal medicine have hinders its modernization. In this regard, ongoing efforts have been focused on the quality control of Chinese herbal medicine based on the fingerprint techniques so as to assure its efficacy, safety and consistency (Zhong et al., 2009, Yang et al., 2016).

The treatment of eczema in Chinese medicine is determined according to the patterns $\binom{Zheng}{証}$ of disharmony, diagnosed based on clinical manifestations $\binom{Zheng}{症}$ e.g. location and appearance of skin lesions, pulse and tongue appearance. (Maciocia, 2005) Patients with AD may manifest with different patterns. Based on the diagnosed patterns, patient-specific treatments are feasible. (Maciocia, 2005) The main patterns that are diagnosed and the corresponding clinical manifestations and internal treatments are summarized in Table 1.6. Corresponding to western medicine, patterns of accumulation of heat and dampness $\binom{Shi\ Re\ Nei\ Yun}{濕\ 熱\quad 緼}$, accumulation of dampness due to deficiency of spleen

(脾 濕 *Pi Xu Shi Yun*) and wind-dryness due to deficiency of blood (血 風 燥 *Xue Xu Feng Zao*) are usually diagnosed in patients with acute, sub-acute and chronic AD, respectively. (Xu, 1994)

It can be seen from Table 1.6, for the internal treatment of AD, botanical drugs that bear the properties to target a diagnosed pattern are formulated together as a formula. For example, formulae used to treat the pattern of "wind-dryness due to deficiency of blood" usually consist of botanical drugs that bear the properties to dispel wind, replenish the blood and to promote blood circulation. Botanical drugs that are commonly used to replenish the blood and promote blood circulation include the root of *Angelica sinensis* (Oliv.) Diels, *Ligusticum striatum* DC and *Paeonia lactiflora* Pall.. And the root of *Glycyrrhiza uralensis* Fisch. and *Scutellaria baicalensis* Georg are commonly used for clearing pathogenic heat and toxins.

External treatment of AD is designed based on recognizing patterns of disharmony as with internal treatment. During the acute phase of AD, the skin is usually characterized by redness, papules, swelling, blistering, burning sensation and weeping. These symptoms indicate penetration of pathogenic heat into blood and accumulation of pathogenic dampness and heat in the body. Herbal medicines with clearing heat and dampness properties (清 熱 利 濕 *Qing Re Li Shi*) [e.g. *Sophora flavenscens* Aiton (苦 參 *Ku Shen*), *Scutellaria baicalensis* Georgi (岑 *Huang Qin*), *Phellodendron chinense* C. K. Schneid. (柏 *Huang Bo*), *Artemisia capilllaris* Thunb. (茵 陳 *Yin Chen*) and *Gentiana scabra* Bge. (龍 膽 草 *Long Dan Cao*)] or with clearing heat and toxin properties (清 熱 解 毒 *Qing Re Jie Du*) [e.g. *Lonicera japonica* Thumb. (金 銀 花 *Jin Yin Hua*), *Chrysanthemum indicum* L. (野菊花 *Ye Ju Hua*), *Portulaca oleracea* L. (馬 齒 莧 *Ma Chi Xian*) and *Taraxacum officinale* (蒲 公 英 *Pu Gong Ying*)] can be used to treat these patterns. If weeping is severe, the skin is commonly treated by washing the lesions with decoction or masking the lesions with muslin cloth that has been soaked with the decoction [e.g. *Portulaca oleracea* L. (馬 齒 莧 *Ma Chi Xian*) decoction, 10% *Phellodendron chinense* C.K. Schneid. decoction (柏 溶 液 *Huang Bo Rong Ye*) and (三 洗 劑 *San Huang Xi Ji*)]. If weeping is not severe, treatment would usually be in a dosage form of a decoction or thickened paste [i.e. mixing herbal medicines with honey/oils] that are directly applied on skin lesions. Examples are (三 洗 劑 *San Huang Xi Ji*) [i.e. 5-6 times per day during the acute phase and 3 times per day during the sub-acute phase], (青 黛 散 油 調 *Qing Dia San You Diao*) [i.e. 4-5 times per day during the acute phase and 3 times per day during the sub-acute phase]. (Hoessel et al., 1999) During the

chronic phase of AD, skin lesions are thickened, harden and appeared to be dark red in colour; Chinese herbal medicines with properties that promote blood circulation, dissolve stasis and stop itch are used e.g. (*Qing Dia Gao* 青 黛 膏) [i.e. 3 times per day], (*Hei Dou Liu You Ruan Gao* 黑 豆 餾 油 軟 膏) [i.e. 3 times per day]. (Kim and Zhou, 2000, Wei, 2007, Song and Wen, 2012, Xu, 1994)

Table 1.6 Diagnosis and internal treatment of AD in Chinese Medicine.				
Pattern	**Symptoms for Pattern Diagnosis**	**Treatment aim**	**Internal treatment formula, component [action]**	**Reference**
Accumulation of dampness and heat (*Shi Re Nei Yun* 濕 熱 縕)	· Rapid-onset and short course. · Skin lesion appears red with papules, ceaseless burning and itching sensation. · Weeping of yellow fluid from scratch-induced broken skin. · Feeling thirsty. · Feeling feverish; but skin is not hot to touch. · Dry stool, darkened urine and decreased urine output. · Tongue appears red with thin white fur. · Rapid and smooth pulse.	Clearing of heat and dampness.	**Formula:** (*Long Dan Xie Gam Tang* 龍 膽 瀉 肝 湯) **comprising of 10 components:** · The root of *Gentiana scabra* Bunge [Clear pathogenic heat and dry-dampness.] · The fruit of *Gardenia jasminoides* J.Ellis [Clear pathogenic heat, dampness and toxin.] · The root of *Scutellaria baicalensis* Georgi [Clear pathogenic heat, dampness and toxin.] · The root of *Bupleurm chinense* DC. [Clear pathogenic heat.] · The root of *Rehmannia glutinosa* (Gaertn.) DC. [Eliminate pathogenic heat from the blood.] · The stem of *Alisma plantago-aquatica* subsp. *Orientale* (Sam.) Sam. [Clear pathogenic dampness and heat.] · The root of *Angelica sinensis* (Oliv.) Diels [Replenish blood and promote blood cirmulation.] · The seed of *Plantago asiatica* L. [Clear pathogenic dampness.] · The stem of *Aristolochia manshuriensis* Kom. [Clear pathogenic heat and dampness.]	(Wei, 2007, Lin and Tang, 2002, Kim and Zhou, 2000)

Table 1.6 Diagnosis and internal treatment of AD in Chinese Medicine.				
Pattern	**Symptoms for Pattern Diagnosis**	**Treatment aim**	**Internal treatment formula, component [action]**	**Reference**
			· The root of *Glycyrrhiza uralensis* Fisch.[Clear pathogenic heat and toxin.]	
Heat in blood (*Xue Re* 血 熱)	· Papules. · Bleeding and not much fluid from scratch-induced broken skin. · Intense itching sensation, especially during the night. · Tongue appears red with thin white or yellow fur. · Rapid and string-like pulse	Cooling of blood, dispelling wind.	**Formula:** (*Pi Xuan Tang* 皮 癬 湯) **comprising of 9 components:** · The root of *Rehmannia glutinosa* (Gaertn.) DC. [Eliminate pathogenic heat from the blood.] · The root of *Angelica sinensis* (Oliv.) Diels [Replenish blood and promote blood cirmulation.] · The root of *Paeonia lactiflora* Pall. [Nouish the blood.] · The root of *Scutellaria baicalensis* Georgi [Clear pathogenic heat, dampness and toxin.] · The root of *Sophora flavenscens* Aiton [Clear pathogenic heat and dampness.] · The fruit of *Xanthium sibiricum* Patrin ex Widder [Clear pathogenic dampness and dispel wind.] · The root bark of *Dictamnus dasycarpus* Turcz. [Clear pathogenic heat and toxin and dispel wind.] · The fruit of *Kochia scoparia* (L.) Schrad.[Dispel wind.] · The root of *Glycyrrhiza uralensis* Fisch.[Clear pathogenic heat and toxin.]	(Lin and Tang, 2002)

Table 1.6 Diagnosis and internal treatment of AD in Chinese Medicine.				
Pattern	**Symptoms for Pattern Diagnosis**	**Treatment aim**	**Internal treatment formula, component [action]**	**Reference**
Accumulation of dampness due to deficiency of spleen (*Pi Xu Shi Yun* 脾 濕)	· Gradual-onset. · Skin lesion appears red with papules. · Scratch-induced erosion and exudation. · Scaly flakes. · Abdominal bloating, loose stool. · Always feeling tired. · Tongue appears pale and swollen [i.e. teeth mark at the border] with white and greasy fur. · Slow and string-like pulse.	Strengthening the spleen and removing dampness.	**Formula:** (*Chu Shi Wei Ling Tang* 除 濕 胃 苓 湯) **comprising of 14 components:** · The root of *Saposhnikovia divaricata* (Trucz.) Schischk. [Dispel pathogenic wind.] · The root of *Atractylodes lancea* (Thunb.) DC. [Clear pathogenic dry-dampness, invigorate the spleen and dispel wind.] · The root of *Atractylodes macrocephala* Koidz. [Clear pathogenic dry dampness and invigorate the spleen.] · The inner part of *Poria cocos* (Schw.) Wolf [Clear pathogenic dampness and invigorate the spleen.] · The peel of *Citrus reticulata* Blanco [Clear pathogenic dry-dampness and invigorate the spleen.] · The bark of *Magnolia officinalis* Rehder & E.H.Wilson [Clear pathogenic dry-dampness.] · The *Polyporus umbellatus* (Pers.) Fries [Clear pathogenic dampness.] · The fruit of *Gardenia jasminoides* J.Ellis [Clear pathogenic heat, dampness and toxin.]	(Wei, 2007, Lin and Tang, 2002, Kim and Zhou, 2000)

Table 1.6 Diagnosis and internal treatment of AD in Chinese Medicine.				
Pattern	**Symptoms for Pattern Diagnosis**	**Treatment aim**	**Internal treatment formula, component [action]**	**Reference**
			· The stem of *Aristolochia manshuriensis* Kom. [Clear pathogenic heat and dampness.] · The stem of *Alisma plantago-aquatica* subsp. *Orientale* (Sam.) Sam. [Clear pathogenic dampness and heat.] · Talc (Magnesium silicate hydroxide) [Clear pathogenic heat and dampness.] · The root of *Glycyrrhiza uralensis* Fisch.[Clear pathogenic heat and toxin.] · The stem and leaf of *Mentha alaica* Boriss [Dispel pathogenic heat and wind.] · The bark of *Cinnamomum cassia* (L.) J.Presl [Promote Qi to activate the blood.]	
Wind-dryness due to deficiency of blood (*Xue Xu Feng Zao* 血 風 燥)	· Chronic and relapsing. · Skin lesion appears dark/pigmented/rough/thickened. · Intense itching sensation; exacerbated upon contacting hot or soapy water. · Thirsty but not desire to drink. · Loss of appetite.	Replenishing blood and skin, expelling wind to stop itchiness.	**Formula:** (*Dang Gui Yin Zi* 當 歸 飲 子) **comprising of 10 components:** · The root of *Angelica sinensis* (Oliv.) Diels [Replenish blood and promote blood cirmulation.] · The root of *Ligusticum striatum* DC.[Promote Qi to promote blood circulation and dispel pathogenic wind.] · The root of *Paeonia lactiflora* Pall. [Nouish the blood.]	(Wei, 2007, Kim and Zhou, 2000)

Table 1.6 Diagnosis and internal treatment of AD in Chinese Medicine.				
Pattern	**Symptoms for Pattern Diagnosis**	**Treatment aim**	**Internal treatment formula, component [action]**	**Reference**
	· Abdominal bloating. · Tongue appears pale with white fur. · Fine and slow pulse.		· The root of *Rehmannia glutinosa* (Gaertn.) DC. [Eliminate pathogenic heat from the blood.] · The fruit of *Tribulus terrestris* L. [Dispel pathogenic wind.] · The root of *Saposhnikovia divaricata* (Trucz.) Schischk. [Dipel pathogenic wind.] · The aerial part of *Schizonepeta tenuifolia* Briq. [Dispel pathogenic wind.] · The root of *Polygonum multiflorum* Thunb. [Noursih the blood.] · The root of *Astragalus propinquus* Schischkin [Invigorate Wei Qi to protect the skin from external pathogenic factors.] · The root of *Glycyrrhiza uralensis* Fisch.[Clear pathogenic heat and toxin.] **Formula:** *Si Wu Xiao Feng Yin* 四 物 消 風 飲 **comprising of 10 components:** · The root of *Rehmannia glutinosa* (Gaertn.) DC. [Eliminate pathogenic heat from the blood.]	

Table 1.6 Diagnosis and internal treatment of AD in Chinese Medicine.				
Pattern	**Symptoms for Pattern Diagnosis**	**Treatment aim**	**Internal treatment formula, component [action]**	**Reference**
			· The root of *Angelica sinensis* (Oliv.) Diels [Replenish the blood and promote blood cirmulation.] · The root of *Paeonia lactiflora* Pall. [Nouish the blood.] · The aerial part of *Schizonepeta tenuifolia* Briq. [Dispel pathogenic wind.] · The stem and leaf of *Mentha alaica* Boriss [Dispel pathogenic heat and wind.] · The slough of Cryptotympana pustulata Fabricius [Dispel pathogenic heat and wind.] · The root of *Bupleurm chinense* DC. [Clear pathogenic heat.] · The root of *Ligusticum striatum* DC.[Promote Qi to promote blood circulation and dispel pathogenic wind.] · The root of *Scutellaria baicalensis* Georgi [Clear pathogenic heat, dampness and toxin.] · The root of *Glycyrrhiza uralensis* Fisch.[Clear pathogenic heat and toxin.]	
			Formula: *Yang Xie Ding Feng Tang* 養 血 定 風 湯 **comprising of 9 components:**	

Table 1.6 Diagnosis and internal treatment of AD in Chinese Medicine.				
Pattern	**Symptoms for Pattern Diagnosis**	**Treatment aim**	**Internal treatment formula, component [action]**	**Reference**
			· The root of *Rehmannia glutinosa* (Gaertn.) DC. [Eliminate pathogenic heat from the blood.] · The root of *Angelica sinensis* (Oliv.) Diels [Replenish the blood and promote blood cirmulation.] · The root of *Paeonia lactiflora* Pall. [Nouish the blood.] · The root of *Ligusticum striatum* DC.[Promote Qi to activate the blood and dispel pathogenic wind.] · The root of *Asparagus cochinchinensis* (Lour.) Merr.[Clear pathogenic heat and toxin.] · The root of *Ophiopogon japonicas* (Thunb.) Ker Gawl. [Clear pathogenic heat and moisten dryness.] · Batryicated silkworm · The root of *Polygonum multiflorum* Thunb. [Noursih the blood.] · The root bark *Paeonia suffructicosa* Andrews [Eliminate pathogenic heat from the blood and promote blood cirmulation.]	

1.2.3 The hexa-herbal Chinese formula (HHCF)

1.2.3.1 Clinical uses

The hexa-herbal Chinese formula (HHCF) studied in this project is composed of $\binom{Bai\ Xian\ Pi}{白\ \ 癬\ \ 皮}$ [Dried root bark of *Dictamnus dasycarpus* Turcz.], $\binom{Da\ Huang}{大}$ [Dried root and rhizome of *Rheum tanguticum* Maxim. ex Balf./ *Rheum palmatum* L./*Rheum officinale* Baill.], $\binom{Di\ \ Fu\ \ Zi}{地\ \ 膚\ 子}$ [Dried ripe fruit of *Kochia scoparia* (L.) Schrad.], $\binom{Huang\ Bo}{柏}$ [Dried bark of *Phellodendron chinensis C. K.* Schneid.], $\binom{Huang\ Qin}{芩}$ [Dried root of *Scutellaria baicalensis* Georgi] and $\binom{Ku\ Shen}{苦\ 參}$ [Dried root *of Sophora flavescens* Aiton]. The HHCF formula cosists of four botanical drugs that is used in the $\binom{San\ Huang\ Xi\ Ji}{三\ \ 黃\ \ \ 洗劑}$ formula. $\binom{San\ Huang\ Xi\ Ji}{三\ \ 黃\ \ \ 洗劑}$ is a skin wash indicated for AD and originates from the standard teaching material of Chinese medicine; written in the 1970s. (Guangdong College of Chinese Medicine, 1975) $\binom{San\ Huang\ Xi\ Ji}{三\ \ 黃\ \ \ 洗劑}$. The $\binom{San\ Huang\ Xi\ Ji}{三\ \ 黃\ \ \ 洗劑}$ is prepared from equal portion of powdered $\binom{Da\ Huang}{大}$, $\binom{Huang\ Bo}{柏}$, $\binom{Huang\ Qin}{芩}$ and $\binom{Ku\ Shen}{苦\ 參}$. The preparation method or composition of the formula may be modified slightly between different clinical practices. In clinical studies, $\binom{San\ Huang\ Xi\ Ji}{三\ \ 黃\ \ \ 洗劑}$ and its modifications have been used not only in the treatment of AD (Zhang, 1998, Yan et al., 2012, Fu et al., 2013, Zhou, 2013, Wang, 2014), but also used for managing other skin conditions such as prurigo gestationis (Cao, 2008), varicella zoster virus (Zhang, 2012, Li, 1996), dyshidrosis, seborrhoeic dermatitis, chicken pox, tinea pedis (Li, 1996), acne (Huang and He, 2013), anal fistula (Song et al., 2014) and bleeding of hemorrhoids (He, 2011). In the HHCF, $\binom{Bai\ Xian\ Pi}{白\ \ 癬\ \ 皮}$ and $\binom{Di\ \ Fu\ \ Zi}{地\ \ 膚\ 子}$ were added to the $\binom{San\ Huang\ Xi\ Ji}{三\ \ 黃\ \ \ 洗劑}$ formula that act as agonists to enhance the therapeutic effect.

1.2.3.2 Actions according to Traditional Chinese medicine concepts

The HHCF is formulated to clear pathogenic factors of AD [i.e. heat, wind, dryness and dampness], remove toxins, stop itchiness and acts as an astringent for weeping skin condition. The main actions of the individual constituent botanical drugs in the HHCF are summarized in Table 1.7.

$\binom{Huang\ Bo}{柏}$ and $\binom{Huang\ Qin}{芩}$ possess properties for clearing heat, dryness, dampness, fire and toxin. $\binom{Huang\ Bo}{柏}$ also has skin astringent function. Apart from being able to clear heat, dampness and dryness, $\binom{Ku\ Shen}{苦\ 參}$ removes wind [i.e. to stop itchiness] and kills

microbes, and is commonly used in treating scrotum eczema and vilvitis. *Di Fu Zi* clears heat, dampness and wind. (地 膚 子 *Di Fu Zi*) can combine with (苦 参 *Ku Shen*) *or* (白 癬 皮 *Bai Xian Pi*) to enhance its actions of clearing dampness and wind. When (地 膚 子 *Di Fu Zi*) combines with (芩 *Huang Qin*), the overall heat clearing effect will be enhanced. It also confers an additional action of removing wind. (白 癬 皮 *Bai Xian Pi*) clears heat, dampness, toxin and wind and is commonly used with (柏 *Huang Bo*), (芩 *Huang Qin*) or (苦 参 *Ku Shen*). For example, (白 癬 皮 *Bai Xian Pi*), (地 膚 子 *Di Fu Zi*), (苦 参 *Ku Shen*) and (柏 *Huang Bo*) are also used together as a washing liquid in treating eczema. (Song and Wen, 2012) (大 *Da Huang*) possesses functions of clearing heat, fire and toxin, cooling of blood and promoting blood flow to avoid stasis i.e. bruises and is used externally for healing wound with burning sensations, abscesses or ulcers. (大 *Da Huang*) combines with (柏 *Huang Bo*) to treat mouth ulcers and is used with (芩 *Huang Qin*) or (柏 *Huang Bo*) to treat bleeding or wounds with burning sensation and is used with (柏 *Huang Bo*) and (苦 参 *Ku Shen*) to treat eczema. (Chinese Pharmacopoeia Commission, 2010, Zhang, 2009)

Table 1.7 Main actions of botanical drugs in the HHCF.

Pattern	**Botnaical drugs in the HHCF**
Clearing heat and dry-dampness (清 熱 燥 濕 *Qing Re Zao Shi*)	Dried root of *Sophora flavescens* Aiton (苦 参 *Ku Shen*), Dried root of *Scutellaria baicalensis* Georgi (芩 *Huang Qin*), Dried bark of *Phellodendron chinensis* C. K. Schneid. (柏 *Huang Bo*)
Removing wind to stop itchiness (祛 風 止 癢 *Qu Feng Zhi Yang*)	Dried root bark of *Dictamnus dasycarpus* Turcz. (白 癬 皮 *Bai Xian Pi*), Dried fruit of *Kochia scoparia* (L.) Schrad. (地 膚 子 *Di Fu Zi*)
Clearing heat and toxin (清 熱 解 毒 *Qing Re Jie Du*)	Dried root and rhizome of *Rheum tanguticum* Maxim. Ex Balf. (大 *Da Huang*), Dried root of *Scutellaria baicalensis* Georgi (芩 *Huang Qin*), Dried bark *of Phellodendron chinensis* C. K. Schneid. (柏 *Huang Bo*), Dried root bark of *Dictamnus dasycarpus* Turcz. (白 癬 皮 *Bai Xian Pi*)

1.2.3.3 Traditional preparation and application of the HHCF

The six botanical drugs (dried) in the HHCF are used in equal portion and are cut into small pieces. They are prepared as a decoction i.e. first macerated in water [i.e. at a

volume of 5 fold the dry weight of all botanical drugs used) for one hour followed by boiling for 50 minutes. The HHCF decoction is used as an external treatment to alleviate itching sensation and inflammation in AD.

To summarize, the pathogenesis of AD from both Western and Chinese medicine point of view involves multi-factors. Chinese medicine treat AD by formulating botanical drugs that targets different diagnosed syndrome and aiming to restore the body to the normal physiological condition. The exploration on the action of the HHCF at molecular level may provide an insight on its mechanism in treatment of AD

1.3 PHYTOCHEMISTRY AND IMMUNOLOGICAL ACTIVITIES OF BOTANICAL DRUGS IN THE HHCF

1.3.1 The root and rhizome of *Rheum tanguticum* Maxim. ex Balf. (RHE)

Rheum tanguticum Maxim. ex Balf. (RHE) [Polygonaceae], also known as $\binom{Da\ Huang}{大}$ in Chinese, is one of the three botanical drugs recognized as $\binom{Da\ Huang}{大}$ in the Chinese Pharmacopoeia; the other two being *Rheum officinale* Baill. and *Rheum palmatum* L.. RHE is derived from a perennial herb distributed in the Sichuan and Gansu province of China and Qinghai-Tibet plateau (Wang and Ren, 2009). RHE is collected in late autumn when stems and leaves are withered or in the following spring before germination. After removing the remaining soil and rootlets, it is segmented or sliced as egg-shaped or cylindrical-shaped pieces before or after the drying step (Chinese Pharmacopoeia Commission, 2010).

In Chinese medicine, $\binom{Da\ Huang}{大}$ has the properties of relieving conditions associated with excess heat [e.g. constipation, hematemesis, red eyes, swollen throat or gum, boils, sores and abscess], damp-heat [e.g. jaundice] and blood stasis [e.g. amenorrhea]. It is also used topically for burns and scalds (Chinese Pharmacopoeia Commission, 2010).

Phytochemical studies have shown the presence of anthraquinones and their glycosides as the main secondary metabolites in RHE. Aloe-emodin, chrysophanol, emodin, physcion, and rhein are the major compounds employed to assess the quality of $\binom{Da\ Huang}{大}$ in the Chinese Pharmacopoeia (Chinese Pharmacopoeia Commission, 2010). Secondary metabolites isolated from RHE are listed in Appendix II.

Crude extracts of RHE have demonstrated various immunomodulatory activities *in vitro* and *in vivo* as listed in Appendix III. Compounds isolated from RHE have also demonstrated immunomodulatory activities in various studies e.g. Aloe-emodin (Hu et al., 2014, Park et al., 2009), Chrysophanol (Kim et al., 2010c), Emodin (Chang et al., 1996, Li et al., 2005, Choi et al., 2013), Rhein (Gao et al., 2014b), catechin (Abe et al., 2005, Nakanishi et al., 2010), cinnamic acid (Hadjipavlou Litina and Pontiki, 2015), gallic acid (Kim et al., 2006, Tsang et al., 2016), Resveratrol (de la Lastra and Villegas,

2005, Wadsworth and Koop, 1999)and β-Sitosterol. (Nath et al., 1980, Loizou et al., 2010)

1.3.2 The root of *Scutellaria baicalensis* Georgi (SCU)

The dried root of *Scutellaria baicalensis* Georgi (SCU) [Lamiaceae], also known as (*Huang Qin* 芩) in the Chinese Pharmacopoeia, is derived from a perennial herb distributed in the Hebei and Shanxi provinces of China and inner Mongolia. (Zhao and Xiao, 2007a) SCU is collected in spring or autumn and dried after removing the remaining soil, rootlets and outer cork.

In Chinese medicine, (*Huang Qin* 芩) relieves conditions associated with excess heat and dampness [e.g. discomfort in the chest, jaundice, diarrhoea] and excess heat [e.g. cough, sore throat, fever, swelling abscess and threatened abortion]. (Zhao and Xiao, 2007a, Chinese Pharmacopoeia Commission, 2010)

Phytochemical studies revealed the presence of flavonoids such as baicalin, baicalein, Wognoside, Wogonin, Scutellarin, Scutellarein, Oroxyloside and Oroxylin A (Wagner et al., 2011) as the major secondary metabolites in SCU. Baicalin is the major compound employed to assess the quality of (*Huang Qin* 芩) in the Chinese Pharmacopoeia. (Chinese Pharmacopoeia Commission, 2010) Other compounds isolated from SCU are listed in Appendix IV..

Crude extracts of SCU have demonstrated various immunomodulatory activities *in vitro* and *in vivo* as listed in Appemdix V. Compounds isolated from SCU have also demonstrated immunomodulatory activities in various studies e.g. baicalein (He et al., 2015, Mabalirajan et al., 2013, Zhang et al., 2013d, Kim et al., 2009d, Hsieh et al., 2007, Woo et al., 2006, Lee et al., 2011b),baicalin (Chu et al., 2015, Mir Palomo et al., 2016, Zhou et al., 2016b, Yang et al., 2013a, Li et al., 2012a, Zhu et al., 2007, Krakauer et al., 2001, Li et al., 2000a), chlorogenic aid (dos Santos et al., 2006, Krakauer, 2002), chrysin (Graus et al., 2005, Kim et al., 2004b), eriodictyol (Lee, 2011, Lee et al., 2013), ferulic acid (Sakai et al., 1997, Cheng et al., 2008), oroxylin A (Zhou et al., 2016a, Wang et al., 2013b), pinocembrin (Soromou et al., 2012), protocatechuic acid (Min et al., 2010), salidroside (Zhang et al., 2013b, Li et al., 2013a), scutellarein (Sung et al.,

2015), wogonin (Wei et al., 2016, Enomoto et al., 2007, Huang et al., 2006) and wogonoside (Gao et al., 2016, Yang et al., 2013b).

1.3.3 The root bark of *Dictamnus dasycarpus* Turcz. (DIC)

The dried root bark of *Dictamnus dasycarpus* Turcz. (DIC) [Rutaceae], also known as (白 癣 皮 *Bai Xian Pi*) in the Chinese Pharmacopoeia, is derived from a perennial herb distributed in the Liaoning, Hubei and Shandong provinces of China (Zhao and Xiao, 2007b). DIC is collected in spring and autumn, after removing the remaining soil and fibrous roots, the root's bark is stripped off and dried.

In Chinese medicine, (白 癣 皮 *Bai Xian Pi*) relieves conditions associated with excess heat and dampness [e.g. eczema, rubella, scabies, tinea, sore and jaundice] and wind [e.g. itchiness]. (Chinese Pharmacopoeia Commission, 2010)

Phytochemical studies revealed the presence of alkaloids [e.g. dictamnine] and limonoids [e.g. obacunone and fraxinellone] as the major secondary metabolites in DIC. Among them, obacunone and fraxinellone are the major compounds employed to assess the quality of (白 癣 皮 *Bai Xian Pi*) in the Chinese Pharmacopoeia (Chinese Pharmacopoeia Commission, 2010). DIC also contains other class of metabolites such as coumarins, flavones and sesquiterpenes as listed in Appendix VI.

Crude extracts of DIC have demonstrated various immunomodulatory activities *in vitro* and *in vivo* as listed in Appendix VII and anti-pruritogenic activity *in vivo*. (Jiang et al., 2008) Compounds isolated from DIC have also demonstrated immunomodulatory activities in various studies e.g. dictabretol A (Choi et al., 2016), dictabretols A-D (Kim et al., 2015), limonin (Matsuda et al., 1998), luteolin (Ueda et al., 2002, Seelinger et al., 2008), 8-methoxy-N-methylflindersine (Yoon et al., 2012), dictamnoside A (Chang et al., 2001), fraxinellone (Kim et al., 2009c, Sun et al., 2009b), 2-Methoxy-4-acetylphenol 1-O-α-rhmamnopyranosyl-(1" à 6')-β-glycoside, 2-Methoxy-4-(8-hydroxyethyl)-phenol 1-O-α-rhamnopyranosyl-(1" à 6')-β-glycoside (Chang et al., 2002), quercetin (Hämäläinen et al., 2007), rutin (Guardia et al., 2001b, Selloum et al., 2003), scopoletin (Kim et al., 2004a, Moon et al., 2007), skimmianine (Yoon et al., 2012, Ratheesh et al., 2013)and wogonin. (Lee et al., 2003)

1.3.4 The root of *Sophora flavescens* Aiton (SOP)

The dried root of *Sophora flavescens* Aiton (SOP) [Fabacae/Leguminosae], also known as $\binom{Ku\ Shen}{苦\ 参}$ in the Chinese Pharmacopoeia, is derived from a perennial shrub distributed in Shanxi, Hubei, Henan, Hebei province of China (Wagner et al., 2011). SOP is collected in spring or autumn; after removing the remaining rootlets and soil, it is washed and sliced before or after the drying step. (Chinese Pharmacopoeia Commission, 2010)

In Chinese medicine, $\binom{Ku\ Shen}{苦\ 参}$ relieves conditions associated with excess heat and dampness [e.g. eczema, scabies, tinea, leprosy, vaginal discharge and jaundice with anuria] and wind [e.g. itchiness]. (Chinese Pharmacopoeia Commission, 2010)

Phytochemical studies revealed the presence of quinolizidine alkaloids and prenylated/lavandulylated flavonoids as the major secondary metabolites in SOP. Matrine and oxymatrine are the dominant alkaloids in SOP and are employed as the marker compounds to assess the quality of $\binom{Ku\ Shen}{苦\ 参}$ in the Chinese Pharmacopoeia. Others alkaloids are stereoisomers and dehydroanalogs of matrine and quinolizidine alklaloids without the matridine skeleton. In addition, a series of flavonoids with chalcone, flavanone, flavanonol, flavonol, pterocarpan and isoflavone skeletons and prenyl or lavandulyl side chains at C-6 or C-8 position were isolated from SOP. (Appendix VIII)

Crude extracts of SOP have demonstrated various immunomodulatory activities *in vitro* and *in vivo* as listed in Appendix IX and anti-pruritogenic activity *in vivo* (Yamaguchi Miyamoto et al., 2003). Compounds isolated from SOP have also demonstrated immunomodulatory activities in various studies e.g. desmethylanhydroicaritin (Kim et al., 2009b), formononetin (Cavendish et al., 2015, Slotkin et al., 2011), lupeol (Saleem, 2009, Geetha and Varalakshmi, 2001), matrine (Liu et al., 2007), (2S)-2'-methoxykurarinone (Jeong et al., 2010), norkurarinol (Oh et al., 2012), oxymatrine (Zheng et al., 2005, Dong et al., 2011b), oxysophocarpine (Yang et al., 2015b), sophoraflavanone G (Kim et al., 2002, Wun et al., 2013), sophocarpine (Gao et al., 2012b, Gao et al., 2009), sophoridine (Huang et al., 2014), 7,9,2',4'-tetrahydroxy-8-isopentenyl-5-methoxychalcone (Choi et al., 2010), trifolirhizin (Zhou et al., 2009a), and umbellifrone (Rauf et al., 2014).

1.3.5 The fruit of *Kochia scoparia* (L.) Schrad. (KOC)

The dried fruit of *Kochia scoparia* (L.) Schrad. (KOC) [Chenopodiaceae], also known as $\binom{Di\ Fu\ Zi}{地\ 膚\ 子}$ in the Chinese Pharmacopoeia, is derived from an annual herb that is able to survive in harsh conditions; distributed in the Jiangsu, Shandong, Henan and Hebei province of China. KOC is collected in autumn when the fruits are ripen and dried under the sun. (Chinese Pharmacopoeia Commission, 2010, Zhao and Xiao, 2007b)

In Chinese medicine, $\binom{Di\ Fu\ Zi}{地\ 膚\ 子}$ relieves conditions associated with excess heat and dampness [e.g. slow and painful urination, rubella, eczema and vaginal discharge] and wind [e.g. itchiness]. (Chinese Pharmacopoeia Commission, 2010)

Phytochemical studies revealed the presence of triterpenoid saponins as the major secondary metabolites in KOC. Among them, momordin Ic is the major compounds employed to assess the quality of $\binom{Di\ Fu\ Zi}{地\ 膚\ 子}$ in the Chinese Pharmacopoeia. (Chinese Pharmacopoeia Commission, 2010) Secondary metabolites isolated from KOC are listed in Appendix X.

Crude extracts of KOC have demonstrated various immunomodulatory activities *in vitro* and *in vivo* as listed in Appendix XI and anti-pruritogenic activity *in vivo*. (Kubo et al., 1997) Compounds isolated from KOC have also demonstrated immunomodulatory activities in various studies e.g. hyperoside (Kim et al., 2011a), isorhamnetin (Hämäläinen et al., 2007, Boesch Saadatmandi et al., 2011), momordin Ic (Matsuda et al., 1997a, Choi et al., 2002), oleanolic acid. (Choi et al., 2002, Tsai and Yin, 2008), quercetin (Boesch Saadatmandi et al., 2011, Guardia et al., 2001a) and rutin. (Guardia et al., 2001a)

1.3.6 The bark of *Phellodendron chinensis* C. K. Schneid. (PHE)

The dried bark of Phellodendron chinensis Schneid. (PHE) [Rutaceae], also known as $\binom{Huang\ Bo}{柏}$ in the Chinese Pharmacopoeia, is derived from a shrub distributed in the Hunan, Hubei, Guizhou, Shaanxi and Sichuan province of China. (Zhao and Xiao, 2007a) PHE is collected in autumn, removed from coarse bark, and then dried. (Chinese Pharmacopoeia Commission, 2010)

In Chinese medicine, $\binom{Huang\ Bo}{柏}$ relieves conditions associated with excess heat and dampness [e.g. diarrhea, jaundice, vaginal discharge, tinea pedis, leg flaccidity, fever, ulcer and eczema]. (Chinese Pharmacopoeia Commission, 2010)

Phytochemical studies revealed the presence of alkaloids as the major secondary metabolites in PHE. Among them, berberine is the major compounds employed to assess the quality of $\binom{Huang\ Bo}{柏}$ in the Chinese Pharmacopoeia. (Chinese Pharmacopoeia Commission, 2010) Secondary metabolites isolated from PHE are listed in Appendix XII.

Crude extracts of PHE have demonstrated various immunomodulatory activities *in vivo* as listed in Appendix XIII. Compounds isolated from PHE have also demonstrated immunomodulatory activities in various studies e.g. berberine (Kuo et al., 2004, Kim et al., 2008), chlorogenic acid (dos Santos et al., 2006), ferulic acid (Sakai et al., 1997), magnoflorine (Mori et al., 1994), palmatine (Ma et al., 2016), phellodendrine (Mori et al., 1995), skimmianine (Ratheesh et al., 2013), syringing (Yin et al., 2012), tetrahydrocoptisine (Li et al., 2013b) and tetrahydropalmatine (Li et al., 2013b).

To summarize, the knowledge on the chemical compounds and anti-inflammatory activities of botanical drugs making up the HHCF facilitate the chemical characterization and understanding the mechanism of action of this CHM formula.

1.4 APPLICATION OF LIQUID CHROMATOGRAPHY (LC-MS)-BASED METABOLITE PROFILING IN THE RESEARCH OF CHINESE HERBAL MEDICINE

Chinese herbal medicines (CHM) are primarily prescribed as a formula consisting of more than one botanical drugs, managing the body system in a holistic manner based on the overall symptoms and sign of syndromes. It is generally expected that holistically, the effects of a CHM formula is attributed to the combined action of multiple constituents. (Wang et al., 2008, Zhang et al., 2011) The advancement in analytical techniques opens up the possibility of profiling a multitude of small molecule metabolites in the complex CHM extracts and living systems. Among them is LC-MS, and it is typically used to define the chemical constituents [i.e. the secondary metabolites] in a CHM extract and their pharmacokinetics in an organism [i.e. through tracking the absorbed constituents in biological samples such as plasma] and to assess the endogenous metabolite changes in biological samples of organisms in response to the CHM treatment. These offer a window for evaluating the therapeutic efficts of a CHM formula and for interrogating how chemical constituents of CHM relate to their therapeutic effects. For example, comparing the metabolite profile of biological samples from a normal control and a diseased model using multivariate statistical analysis allows the identification of perturbed metabolites [i.e. biomarkers of a disease condition] and several studies have demonstrated the ability of CHM to restore the perturbed metabolites towards normal levels after administration (Wang et al., 2010b, Liang et al., 2011). Through tracking the absorbed chemical constituents of a CHM in biological samples after administration could give an insight on which of these chemical constituents are the most likely to contribute to the therapeutic efficacy.(Wang et al., 2011c, Alolga et al., 2015, Zhang et al., 2015a, Cheng et al., 2016) Correlation analysis between the metabolite profiles and the corresponding biological activity of a CHM extract and its variants allows the prediction of core active metabolites. (Wang et al., 2014e, Liu et al., 2015)

During LC-MS, sample molecules are separated by the LC [e.g. high pressure liquid chromatography (HPLC) or ultra performance liquid chromatography (UPLC)] and are continuously analyzed by the mass analyzer(s). Before entering the high-vacuum mass analyzer, solvent is removed and metabolites are converted into ions under atmospheric pressure using an ion source. Electrospray ionization (ESI) and atmospheric pressure

chemical ionization (APCI) are the most commonly used soft type ionization sources, they tend to form intact molecular ions with minimal in-source fragmentation that aid initial identification. In general, ESI is more suitable for the analysis of polar and higher molecular mass compounds such as protein while APCI is more suitable for the ionization of non-polar, weakly polar and thermally stable low molecular mass compounds such as lipids. Ions from the atmospheric pressure ionization interphase are then resolved by the mass analyzer(s) and measured by the detector (Zhou et al., 2012, Qi et al., 2015).

High resolution hybrid tandem mass spectrometry such as quadrupole time-of-flight (Q-TOF) (Alolga et al., 2015, Liu et al., 2015), ion trap time-of-flight (IT-TOF) (Chen et al., 2011) and linear trap quadrupole orbitrap (LTQ-Orbitrap) (Peng et al., 2011) has been frequently used for detecting and identifying small molecule metabolites in CHM extracts and biological samples based on high resolution and accurate mass measurement of precursor and product ions. Time-of-flight (TOF) mass spectrometry is able to provide high resolution mass spectra with mass accuracy of the order of 5 ppm and its fast scanning speed is best for use with UPLC-based metabolite profiling studies in which chromatographic peak widths are particularly narrow. It is also able to provide accurate mass measurements of both precursor and product ions simultaneously [i.e. MSE] after coupling to the mass-resolving quadrupole and collision cell to form the Q-TOF mass spectrometry. When coupled with ion-trap mass spectrometry [i.e. IT-TOF-MS], it is able to provide accurate mass measurements of precursor ions and product ions in multiple fragmentation steps [i.e. MSn] (Li et al., 2013c, Want et al., 2010). In terms of quantification, the fast scanning speed of the high resolution mass spectrometry [e.g. TOF-based and Orbirtrap-based mass spectrometry] allows the acquisition of enough data points across a chromatographic peak and hence, compounds can be quantified simultaneously after a full scan using the extracted ion chromatograms (EICs) of the theoretical m/z value for the target compounds. This avoids the need to pre-select selected reaction monitoring (SRM) transition for compounds to be quantified as seen with triple quadrupole (QqQ) mass spectrometry. Orbitap-based mass spectrometry provides a better dynamic range and sensitivity than TOF-based mass spectrometry in carrying out the integrated qualitative and quantitative analysis of metabolites in the full scan mode. Orbitrap offers high mass accuracy of the orders of 2 ppm and is typically coupled to a linear ion trap [i.e. LTQ-Orbitrap] to allow

fragmentation of molecular ions. (Lu et al., 2008, Krauss et al., 2010, Xiao et al., 2012, Zhou et al., 2012)

Metabolites in a profile are tentatively identified based on comparison of the m/z value of the precursor ions and product ions (MS/MS or MSn) with that reported in the metabolite databases or literatures. The accurate mass measurement facilitates the determination of the elemental composition of the molecular ions and provides discrimination of isobaric ions while the MS/MS or MSn spectrum provides structural information based on fragmentation. However, due to the complexity of reported metabolites' mass data and the inability to discriminate isomers, this approach often results in multiple putative identification. In order to guarantee an unequivocal structure identification, mass data from a tentatively identified metabolite such as the *m/z* value of the precursor and product ions and retention time in the chromatogram are compared with those collected from an authentic standard analyzed under identical experimental conditions (Zhou et al., 2009b, Zhou et al., 2012).

To summarize, LC-MS has become a key analytical technology for the provision of metabolite profiles for complex CHM extracts or biological samples owing to its ability to separate metabolites by the LC component and to provide qualitative and quantitative results of the analyzed metabolites with low detection limits. LC-MS-based metabolite profiling has become a research approach for the modernization of Chinese medicine. Continuous improvement has been focused on the separation capacity of the LC [e.g. combination of two separation mechanisms in two-dimensional LC and the application of column with smaller diameter, shorter lengths and smaller particles such as UPLC to improve the separation efficiency] (Patti, 2011, Fanali et al., 2013) and identification ability for the metabolites [e.g. expansion of spectral libraries acquired under different experimental settings and development of software to assist fragmentation prediction and spectral matching]. (Xiao et al., 2012)

1.5 AIMS OF THESIS

Topical immunosuppressant drugs including corticosteroids and calcineurin inhibitors can alleviate inflammation and pruritus associated with AD with limited systemic side effects. However, both classes of drug may result in negative effects on local skin cells. For example, topical corticosteroids may impair the skin barrier (Kao et al., 2003, Sheu and Chang, 1991, Sheu et al., 1991); it accelerates maturation, inhibits epidermal terminal differentiation and inhibits proliferation of keratinocytes (Lange et al., 2000, Fisher and Maibach, 1971, Zendegui et al., 1988) Similarly, corticosteroids inhibits proliferation of fibroblasts and their synthesis of extracellular proteins [e.g. collagen] (Cutroneo et al., 1981, Nuutinen et al., 2001). Calcineurin inhibitors inhibit DNA repair and apoptosis of keratinocytes after ultraviolet B irradiation and this has been linked to the potential risk of skin cancer (Yarosh et al., 2005). Chinese herbal medicines (CHMs) are generally believed to cause less side effects due to their well-documented history of use. Patients that are unresponsive to conventional treatment are likely to resort to Chinese herbal medicines as an adjunctive treatment. However, the mechanisms and effects of the majority of CHMs have not been explained scientifically due to their complex chemical profiles and an incomplete understanding of the disease pathology. Although the pathogenesis of AD is not fully resolved, various in vtiro models have been developed to mimic the changes of cellular activities that are observed in the skin of AD patients (section 1.1.4). These models provide a mean for understanding the activities of tested samples against pathogenic-related factors of AD. In addition, the improvement in analytical technique has driven the efficient qualitative and quantitative analysis of CHMs (section 1.4).

This project aims to investigate the therapeutic potential of a hexa-herbal Chinese formula (HHCF) that is used as a topical preparation for the treatment of AD (section 1.2.3). To achieve this, the research strategy involves:

- analyzing the phytochemical composition of the HHCF using LC-MS.
- understanding the phytochemical contribution of each botanical drugs in the HHCF
- assessing the ability of the HHCF to correct the pathogenic-related factors of AD/skin inflammation *in vitro*.

2 PHYTOCHEMICAL CHARACTERIZATION OF THE HEXA-HERBAL CHINESE FORMULA (HHCF) DECOCTION BY LIQUID-CHROMATOGRAPHY COUPLED WITH TRIPLED QUADRUPOLE MASS SPECTROMETRY

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2.1 INTRODUCTION

Chinese herbal medicines (CHM) are generally prescribed as a formula comprised of multiple botanical drugs that are expected to exert clinical effects based on the combined effects of multiple components against multiple targets. (Che et al., 2013) Characterization of the chemical components in a Chinese herbal preparation is thus vital for understanding its pharmacological mechanism and for achieving reliable clinical effects. Liquid chromatography coupled with mass analyzer(s) has gained increasing popularity among analytical techniques for profiling components in preparations of CHM due to its sensitivity, separation power and mass measurement. (Zhao et al., 2013a, Su et al., 2013, Yan et al., 2015)

To understand the chemical relationship between the hexa-herbal Chinese formula (HHCF) and botanical drugs it is derived from, liquid chromatography coupled with a triple quadrupole mass spectrometry was used in combination with an in-house developed template to characterize key chemical components extracted from each botanical drug making up the HHCF. The six botanical drugs making up the HHCF are the rootstock of *Scutellaria baicalensis* Georgi (SCU), *Rheum tanguticum* Maxim. ex Balf. (RHE), *Sophora flavescens* Aiton (SOP); root bark of *Dictamnus dasycarpus* Turcz. (DIC); bark of *Phellodendron chinense* C.K. Schneid. (PHE) and fruit *of Kochia scoparia* (L.) Schrad. (KOC).

2.2 OBJECTIVES

- Ø To develop a database consisting of the mass of secondary metabolites that have been reported in each botanical drug making up the HHCF.
- Ø To obtain metabolite profiles for the HHCF, DIC, KOC, PHE, RHE, SCU and SOP decoctions using liquid chromatography-mass spectrometry (LC-MS).
- Ø To develop an EXCEL template for sorting the LC-MS data and to find out from which of the six botanical drugs the secondary metabolite in the HHCF decoction are derived from.
- Ø To putatively identified the secondary metabolites in the LC-MS metabolite profile of the HHCF decoction with the use of the mass database of each botanical drug making up the HHCF and MS/MS analys.

2.3 METHODS

2.3.1 Preparation of the HHCF and single botanical drug decoctions for LC-MS analysis

All botanical drugs were purchased from commercial Chinese herbal medicine stores in China. SCU, RHE, SOP, DIC, KOC and PHE were sourced from Hebei (Chengde), Gansu (Maqu county), Hebei (Chengde), Liaoning (Anshan), Hebei (Chengde) and Sichuan (Dujiangyan), respectively. All botanical drugs, except PHE were blended into powder and PHE was cut into small blocks of 1 cm x 1 cm x 0.2 cm before the decoction process. For the HHCF decoction, the same ratio of each botanical drug [i.e. SCU, RHE, SOP, DIC, PHE and KOC] was used. Botanical drugs were first macerated in distilled water (at a volume of 5 folds the dry weight of botanical drugs used) for 1 hour and then heated under reflux for 95 minutes. The extracted solution was filtered through a nylon cloth of pore size ~0.1 mm, followed by centrifugation at 10,000 rpm for 5 minutes. Collected supernatant was lyophilized. Lyophilized extracts were dissolved in LC-MS grade water to achieve a concentration of 20 mg/mL (w/v), centrifuged at 10 000 rpm for 10 minutes and filtered through 0.22 μm filter membrane before analysis.

2.3.2 LC-MS/MS analysis

Chromatography was performed on a 1260 Infinity liquid chromatography system. 15 μL of sample was injected into a Zorbax SB-C18 column (4.6 x 250mm, 5 μm) held at 35 °C. The elution program was as follows: 0 min, 5% B; 110 min, 47% B; 120-125 min, 90% B; 126-135 min, 5% B. The flow rate was 1 mL/min, where A was 0.1% formic acid in water and B was 0.1% formic acid in acetonitrile. The LC system was coupled to an Agilent 6400 series Triple Quadrupole mass spectrometer equipped with an Agilent Jet Stream electrospray ionization source (AJS ESI), operating with 3.5 kV capillary voltage in both positive and negative modes (sheath gas temperature 250 °C, sheath gas flow rate 11 L/min, drying gas temperature 300°C, drying gas flow rate 5 L/min and nebulizer pressure 45 psi in both positive and negative mode). The fragmentor voltage is 135V. Positive and negative ionization mode mass spectra were simultaneously collected across the mass range of 100-1500 m/z. For MS/MS acquisition mode, the parameters were the same except that collision energy settings of 15V was used.

2.3.3 Data mining

Total ion chromatograms (TICs) [both positive and negative ion modes] were obtained for the HHCF and its constituent botanical drugs. Peaks were extracted and integrated in the Agilent MassHunter Qualitative Analysis software to obtain the start time (St), end time (Et), retention time (Rt), abundance and m/z value of ions within each peak of a TIC. Only ions with abundance >1% of the base ion abundance and are within top 100 abundant ions within each peak are outputted by the software. These data were then imported into Excel and each row in the data set is given a code as illustrated in Table 2.1.

Table 2.1 Layout of data imported into Excel.
X=HCCF/DIC/KOC/PHE/RHE/SCU/SOP; P=Peak no.; M=ion no.

Code	**St**	**Et**	**Rt**	***m/z***	**Abundance**	**Abundance %**
X_P1_M1						
X_P1_M2						
⋮						
X_P2_M1						
X_P2_M2						
⋮						

The source(s) [i.e. DIC/KOC/PHE/RHE/SCU/SOP] of ions detected in the HHCF decoction were identified using the match function in Excel. The *m/z* value [Ion_{HCCF} *m/z*] and Rt [Ion_{HCCF} Rt] of ions detected in the HHCF decoction are matched against the *m/z* value [Ion_{SBD} *m/z*] and St [Ion_{SBD} St] and Et [Ion_{SBD} Et] of ions detected in the single botanical drug (SBD) decoction [i.e. DIC/KOC/PHE/RHE/SCU/SOP]. If an ion [e.g. ion x] in the HHCF decoction is having the same mass as an ion [e.g. ion y] present in the SBD decoction and the Rt of ion x is within the St and Et of ion y, then ion x is considered to be sourced from that botanical drug. The developed EXCEL template matches the data using these criteria as illustrated in Table 2.2 and outputs the source of ions in the HHCF decoction (Appendix XV and XVI, Step 1).

After identifying the source of ions in the HHCF decoction, ions in the HHCF decoction were sorted by abundance in descending order. The *m/z* value of ions with abundance > 1.5% of the ion that was present at the highest abundance were matched against the *m/z* value of potential adduct ions [i.e. $[M+H]^+$, $[M]^+$, $[M+Na]^+$. $[M+K]^+$, $[M+NH_4]^+$, $[M+2Na-H]^+$, $[M+2K-H]^+$, $[2M+H]^+$, $[2M+Na]^+$, $[2M+NH_4]^+$, $[M-H]^-$, $[2M-H]^-$, $[M+Cl]^-$, $[M+Br]^-$, $[M+Na-2H]^-$, $[M+K-2H]^-$, $[M+FA-H]^-$, $[2M+FA-H]^-$, $[2M+Na-2H]^-$, $[3M-H]^-$, $[M-H_2O-H]^-$] of reported compounds (Appendix XV and XVI, Step 2) from the identified source. Reported compounds are listed in Appendix XIV. MS/MS analysis was then carried out to aid structural analysis of compounds.

Table 2.2 Criteria set in the match function in Excel.

P= Peak no.; M=*m/z* no. ; $A_{DIC,}$ $A_{KOC,}$ $A_{PHE,}$ $A_{RHE,}$ A_{SCU} and A_{SOP}= Abundance of ions in DIC, KOC, PHE, RHE, SCU and SOP, respectively.

Examples of an ion in the HHCF decoction that is sourced from one of its botanical drugs.

Green row: *m/z* value of the HHCF_P17_M4 ion = *m/z* value of the SOP_P14_M4 ion and the Rt of the HHCF_P17_M4 ion falls within the St and Et of the SOP_P14_M4 ion. Thus, HHCF_P17_M4 ion is considered to be sourced from SOP.

Blue row: *m/z* value of HHCF_P9_M1 ion = *m/z* value of the KOC_P11_M2, PHE_P5_M1, RHE_P13_M3 and SCU_P11_M6 ion and the Rt of the HHCF_P9_M1 ion falls within the St and Et of the KOC_P11_M2, PHE_P5_M1, RHE_P13_M3 and SCU_P11_M6 ion. Since abundance of the PHE_P5_M1 ion is three times the average of the KOC_P11_M2, RHE_P13_M3 and SCU_P11_M6 ion abundance. Thus HHCF_P9_M1 is considered to be sourced from PHE.

Example of an ion in the HHCF decoction that is sourced from more than one of its botanical drugs.

Pink row: *m/z* value of the HHCF_P2_M2 ion = *m/z* value of the DIC_P5_M5, KOC_P5_M2, RHE_P4_M2, SCU_P4_M13 and SOP_P1_M1 ion and the Rt of the HHCF_P2_M2 ion falls within the St and Et of the DIC_P5_M5, KOC_P5_M2, RHE_P4_M2, SCU_P4_M13 and SOP_P1_M1 ion. Thus, the HHCF_P2_M2 ion is considered to be sourced from DIC, KOC, RHE, SCU and SOP.

Code of ions in HHCF	**Code of source ion**												**Source(s)**
	DIC	**A_{DIC}**	**KOC**	**A_{KOC}**	**PHE**	**A_{PHE}**	**RHE**	**A_{RHE}**	**SCU**	**A_{SCU}**	**SOP**	**A_{SOP}**	
HCCF_P2_M2	DIC_P5_M5	28132	KOC_P5_M2	426837	Nil	Nil	RHE_P4_M2	389089	SCU_P4_M13	32246	SOP_P1_M1	559456	Multiple
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
HHCF_P9_M1	Nil	Nil	KOC_P11_M2	10172	PHE_P5_M1	6292219	RHE_P13_M3	2916	SCU_P11_M6	2334	Nil	Nil	PHE
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
HHCF_P17_M4	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	Nil	SOP_P14_M4	1094774	SOP
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮

2.4 RESULTS AND DISCUSSION

A literature search was carried out within the database SciFinder to retrieve articles related to the chemical study of the botanical drug making up the HHCF and reported secondary metabolites are summarized in Appendix XIV.

The total ion chromatogram (TIC) of the HHCF, DIC, KOC, PHE, RHE, SCU and SOP in positive (Fig. 2.1a) and negative (Fig. 2.2a) modes were obtained by LC-MS and analyzed using the EXCEL template. The EXCEL template defined source(s) and putative identities of ions detected in the HHCF decoction as described in section 2.3.3.

Three cases were encountered during identification of compounds detected in the HHCF decoction, 1) mass of a detected ion matched with mass of one reported compound; 2) mass of a detected ion matched with mass of multiple reported compounds and 3) multiple detected ions having same mass (different elution time) matched against mass of multiple reported compounds. For case 1 and 2, the identification of compounds was putatively assigned based on the observed fragmentation patterns illustrated in Fig. 2.3 (compounds putatively identified in positive ionization mode) and Fig.2.4 (compounds putatively identified in negative ionization mode). Detected ions in case 3 having the same mass were putatively ascribed based on the observed fragmentation patterns and reported retention behavior of these compounds in reversed-phase chromatography. Compounds were putatively identified in this study and falls into level 2 or 3 of the four levels identification rigor defined by the Metabolomics Standards Initiative. (Sumner et al., 2007) Overall, evidences considered during the assignment of compounds identity involved mass of precursor ion, elution behavior, relative intensities of fragment ions or characteristic MS/MS fragments that were compared against reported MS/MS spectra

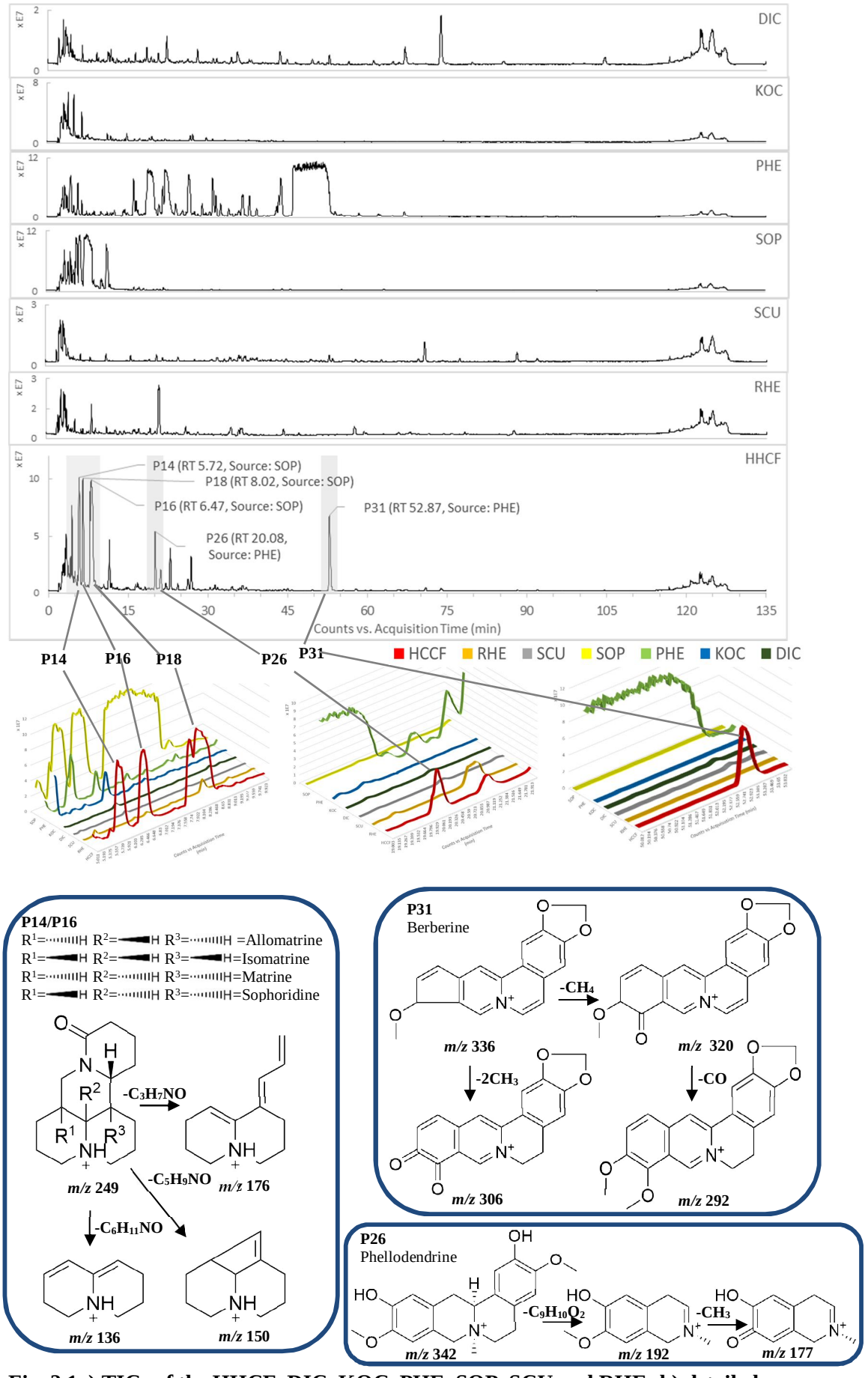


Fig. 2.1a) TICs of the HHCF, DIC, KOC, PHE, SOP, SCU and RHE; b) detailed fragmentation patterns of the top 5 abundance compounds in the HHCF in positive mode.

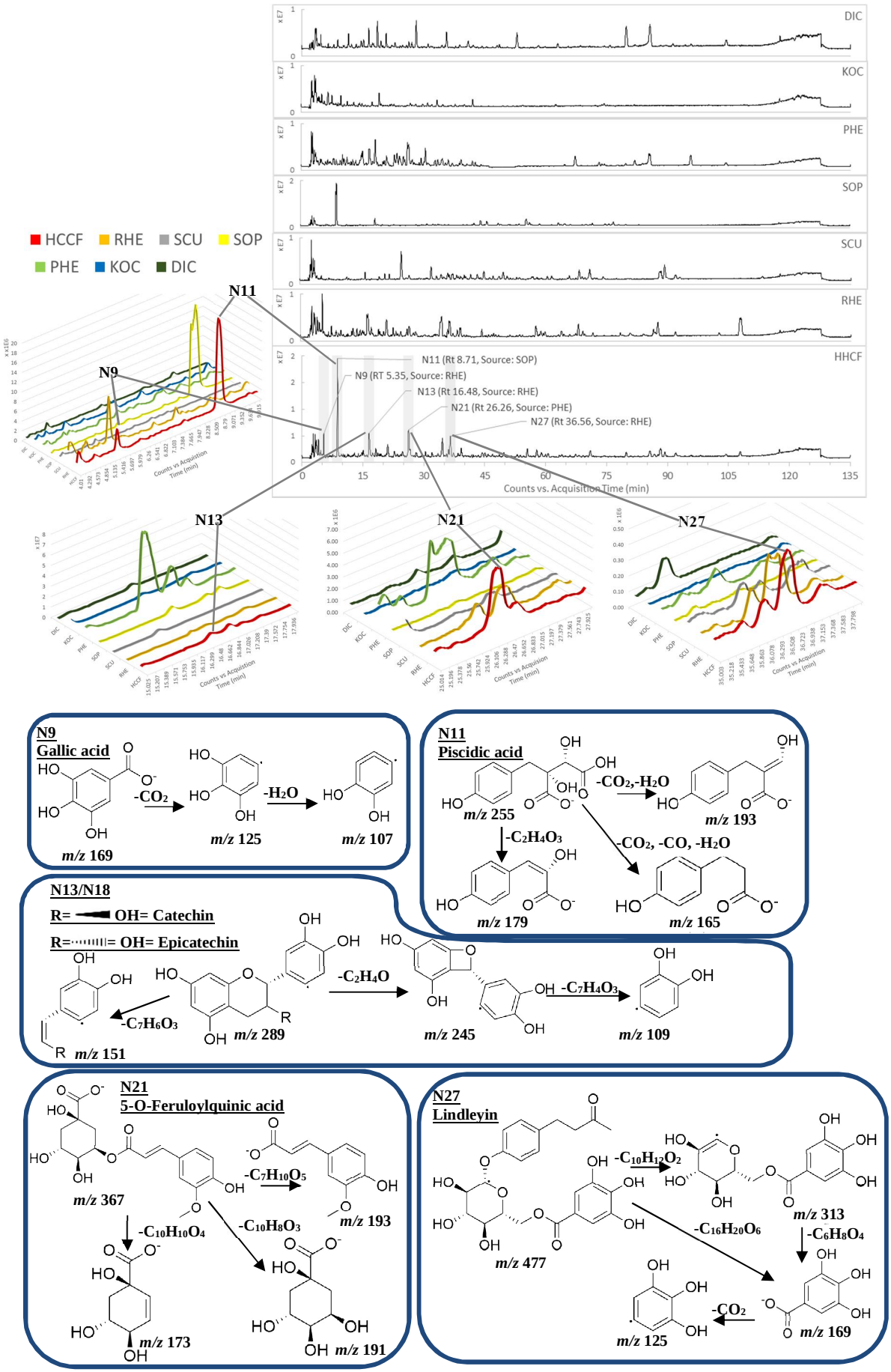


Fig. 2.2a) TICs of the HHCF, DIC, KOC, PHE, SOP, SCU and RHE; b) detailed fragmentation pattern of the top 5 abundance compounds in the HHCF in negative mode.

Based on the mass measurement of precursor and fragment ions, 31 and 37 compounds in the HHCF decoction were putatively identified in positive (Table 2.3 and Fig. 2.3) and negative ionization mode (Table 2.4 and Fig. 2.4), respectively. Ions present in the HHCF and more than one composing botanical drugs are listed in Appendix XVII. Relative intensity of fragment ions produced in the MS/MS analysis for Table 2.3 and 2.4 are available in Appendix XVIII and XIX, respectively. Fragmentation pathways of compounds putatively identified in Table 2.3 and 2.4 are illustrated in Fig. 2.3 and Fig. 2.4, respectively. Reported fragment ions of compounds putatively identified in Table 2.3 and 2.4 are shown in Appendix XVIII and XIX, respectively.

Compound P6, P7, P10, P18 and P23 gave identical $[M+H]^+$ ions at *m/z* 265 in the HHCF and SOP TIC and further yielded similar fragment ions in the MS/MS analysis. They were considered to be isomers extracted from SOP with a molecular weight of 264 e.g. 5α-hydroxymatrine (Fig. 2.3, P6/P10), 9α-hydroxymatrine (Fig. 2.3, P6/10), 14β-hydroxymatrine (Fig. 2.3, P7), oxymatrine (Fig. 2.3, P18/P23) and oxysophoridine (Fig. 2.3, P18/P23) or lamprolobine. (Liu et al., 2011, Ma et al., 2014, Liu et al., 2010a) The observed fragment ions at *m/z* 247 for all these compounds excluded the possibility of them being lamprolobine. Compound P18 and P23 gave and additional $[2M+H]^+$ ions at *m/z* 529 in the TIC and yielded a fragment ion at *m/z* 205 that characterizes them to be oxy-alkaloids i.e. oxymatrine and oxysophoridine. (Lourenço et al., 2002, Yan et al., 2015) Fragment ions at *m/z* 127 were only observed in Compound P7 that characterized the cleavage of bonds of 5-17 and 7-11 and the presence of a hydroxyl group at position 14 of 14β-hydroxymatrine (Fig. 2.3, P7). Compound P6 and P10 were putatively identified as 5α-hydroxymatrine or 9α-hydroxymatrine and the observed fragment ions could not distinguished the position of the hydroxyl group.

Compound P11, P15 and P20 gave identical $[M+H]^+$ ions at *m/z* 247 in the HHCF and SOP TIC and were considered to be isomers extracted from SOP with a molecular weight of 246 e.g. isosophocarpine (Fig.2.3, P11), sophocarpine (Fig.2.3, P15), or 7,11-dehydromatrine (Fig. 2.3, P20). (Liu et al., 2011, Ma et al., 2014) Compound P11, P15 and P20 yielded similar fragment ions at *m/z* 122, 134, 136, 148, 150, 176, 188 that were reported to be fragment ions observed for dehydromatrine. (Murakoshi et al., 1982, Wink and Witte, 1991, Liu et al., 2011, Wu et al., 2013b) A fragment ion at *m/z* 227 was observed in the MS/MS analysis of compounds P15 but not in compound P11 and P20 while a fragment ion at *m/z* 190 was observed in the MS/MS analysis of

compound P20 but not in compound P11 and P15. Fragment ion at *m/z* 227 and *m/z* 190 was reported to be a fragment ion observed for sophocarpine and 7,11-dehydromatrine, respectively. (Murakoshi et al., 1982, Liu et al., 2011) Thus, compound P15 and P20 were putatively assigned to be sophocarpine and 7,11-dehydromatrine, respectively. Compound P11 was putatively identified as isosophocarpine based on the known alkaloids in SOP and it was reported that isosophocarpine was eluted before sophocarpine in reversed-phase chromatography. (Liu et al., 2011)

Compound P12, P17, P21 and P22 gave identical $[M+H]^+$ ions at *m/z* 263 in the HHCF and SOP TIC and were considered to be isomers extracted from SOP with a molecular weight of 262 e.g. (-)-9α-hydroxy-7, 11-dehydromatrine (Fig. 2.3, P12), oxysophocarpine (Fig. 2.3, P17), 9α-hydroxysophocarpine (Fig. 2.3, P21), leontalbinine N-oxide (Fig. 2.3, P22) and mamanine (Liu et al., 2011, Liu et al., 2010a) Compound P17 also gave $[2M+H]^+$ ions at *m/z* 525 in the TIC that characterized it to be oxy-alkaloids i.e. oxysophocarpine. (Liu et al., 2011, Ma et al., 2014) In addition, A fragment ion at *m/z* 195 was seen in the MS/MS analysis of compounds P17 and P21, which characterized cleavage of bonds of 11-12 and 15-16 and the presence of a double bond between position 13 and 14 of oxysophocarpine or 9α-hydroxysophocarpine. Compound P17 and P21 were therefore putatively identified as oxysophocarpine and 9α-hydroxysophocarpine, respectively. Similar to compound P17, P22 gave additional $[2M+H]^+$ ions at *m/z* 525 in the TIC that characterized it to be oxy-alkaloids i.e. leontalbinine N-oxide. Compound P12 gave similar fragment ions as compound P17 e.g. fragment ions at *m/z* 122, 148, and 188 and 245. A fragment ions at *m/z* 180 were seen in the MS/MS analysis of compounds P21 which characterized the presence of a double bond between position 13 and 14 of 9α-hydroxysophocarpine. While the presence of a fragment ion at *m/z* 164 in the MS/MS analysis of compound P12 characterized the presence of a double bond between position 7 and 11 of (-)-9α-hydroxy-7, 11-dehydromatrine.

Compound P14 and P16 gave identical $[M+H]^+$ ions at *m/z* 249, $[2M+H]^+$ ions at *m/z* 497 and $[2M+Na]^+$ ions at *m/z* 519 in the HHCF and SOP TIC. Compound P19 gave $[M+NH_4]^+$ ions at *m/z* 266 in the TIC. Compound P14, P16 and P19 were considered to be isomers extracted from SOP with a molecular weight of 248 e.g. allomatrine (Fig. 2.3, P14/16), isomatrine (Fig. 2.3, P14/16), matrine (Fig. 2.3, P14/P16), sophoridine (Fig. 2.3, P14/P16) or lupanine (Fig. 2.3, P19).(Liu et al., 2011, Ma et al., 2014, Liu et

al., 2010a, Zhang and Chen, 2013)The exhibition of both $[M+H]^+$ ions $[2M+Na]^+$ ions provided further support that compound P14 and P16 may be alkaloids with no substituting groups. (Ma et al., 2014) MS/MS analysis of compound P19 gave fragment ions at *m/z* 206 that was not observed for compound P14 and P16. With reference to the reported fragment ions and retention behavior of these compounds in reversed-phase chromatography, (Liu et al., 2011) compound 14 and 16 were putatively assigned to be stereoiosmers i.e. allomatrine, isomatrine, matrine or sophoridine and compound P19 was putatively ascribed as lupanine.

Compound P24 sourced from DIC produced no fragment ion in the MS/MS analysis under the tested conditions. Compound P24 with precursor ions at *m/z* 243 could be dasycarpuseneste (Fig. 2.3, P24a) or O-ethylnor-γ-fagarine (Fig. 2.3, P24b) that exhibited as adduct ions $[M+H]^+$ and $[M]^+$ in the TIC, respectively. (Lin and Shieh, 1986, Guo et al., 2012b)

Compound N2 and N4 gave identical $[M-H]^-$ ions at *m/z* 191 in the HHCF and PHE TIC. Compound N2 yielded prominent fragment ions at *m/z* 191, 127 and other ions such as *m/z* 173, 111 and 109 due to elimination of neutral molecules of CO, CO_2 and/or H_2O from *m/z* 191. Compound N4 yielded prominent fragment ions at *m/z* 111 and other ions at *m/z* 155, 131 and 129 due to losses of neutral molecules of CO_2, OH and/or H_2O from *m/z* 191. Based on literature data, quinic acid yielded addition and base ion at *m/z* 127, while citric acid yielded base ion at *m/z* 111. (Ng et al., 2004) In addition, it was reported that quinic acid was eluted before citric acid in reversed-phase chromatography. (Deng and Yang, 2013) Therefore, compound N2 and N4 were putatively ascribed to be quinic acid (Fig.2.4, N2) and citric acid (Fig.2.4, N4), respectively.

Compounds N15 and N21 gave identical $[M-H]^-$ ions at *m/z* 367 in the HHCF and PHE TIC and were sourced from PHE. The MS/MS fragmentation behavior of these ions was characterized by the elimination of the [quinic acid-H]$^-$ ion at *m/z* 191, [quinic acid-H_2O-H]$^-$ ion at *m/z* 173 and [ferulic acid-H]$^-$ ion at 193. (Gu et al., 2015) According to previous reports, the linkage position of acyl groups on the quinic acid of these positional isomers were determined based on the base ion produced in the MS/MS analysis. (Parveen et al., 2011, Clifford et al., 2003) Compound N15 and N21 were thus

putatively ascribed as 3-*O*-feruloyl quinic acid (Fig.2.4, N15) and 5-*O*-feruloyl quinic acid (Fig.2.4, N21) on the basis of base ions at *m/z* 193 and 191, respectively.

Compound N25 and N27 gave identical $[M-H]^-$ ions at *m/z* 477 in the HHCF and RHE TIC and further yielded similar fragment ions. They were indicated to be isomers extracted from RHE with a molecular weight of 478 e.g. isolindleyin (Fig.2.4, N25) and lindleyin (Fig.2.4, N27). The fragment ions at *m/z* 313 and 169 suggested that compound N25 and N27 were composed of a rheosmin, a glucose and a galloyl units. After examining the retention behavior of these compounds in reversed-phase chromatography, compound N25 and N27 were putatively determined to be isolindleyin and lindleyin, respectively. (Su et al., 2013, Jin et al., 2007)

Compound N26 and N29 gave identical $[M-H]^-$ ions at *m/z* 547 in the HHCF and SCU TIC and further yielded similar fragment ions in the MS/MS analysis. They were considered to be isomers extracted from SCU with a molecular weight of 548 e.g. chrysin 6-C-arabinosyl 8-C-glucoside (Fig.2.4, N26) or chrysin-6-C-glucosyl-8-C-arabinoside (Fig.2.4, N29). Both compounds yielded fragment ions at *m/z* 427 that indicated the presence of C-glycoside unit attached to the flavone skeleton. Fragment ions at *m/z* and 337 suggested the presence of two sugar units. After examining reported retention behavior of these compounds in reversed-phase chromatography, compound N26 and compound N29 were putatively identified as chrysin 6-C-arabinosyl 8-C-glucoside and chrysin-6-C-glucosyl-8-C-arabinoside, respectively. (Han et al., 2007, Zhang et al., 2007b)

Compound N30 and N31 gave identical $[M-H]^-$ ions at *m/z* 541 in the HHCF and RHE TIC and further yielded similar fragment ions. They were indicated to be isomers extracted from RHE with a molecular weight of 542 e.g. resveratrol-4'-O-β-D-(2"-O-galloyl)-glucoside (Fig. 2.4, N33) or resveratrol-4'-O-β-D-(6"-O-galloyl)-glucoside (Fig. 2.4, N34). Fragment ions at *m/z* 313 and 169 characterized neutral loss of a resveratrol unit *(m/z*=227) and the eliminated galloyl unit, respectively. Based on the reported retention behavior of these compounds in reversed-phase chromatography, compound N30 and N31 were putatively identified as resveratrol-4'-O-β-D-(2"-O-galloyl)-glucoside and resveratrol-4'-O-β-D-(6"-O-galloyl)-glucoside, respectively. (Lin et al., 2006, Jin et al., 2007)

The power to identify compounds in a LC-MS profile using the developed analytical platform is limited by the knowledge of compounds reported in a botanical drug and the inability to discriminate isomers. In order to guarantee an unequivocal structure identification, comparison of mass data from a putatively identified metabolite with authentic compounds is still considered the gold standard for metabolite identification. The identification step could be improved by using high-resolution mass spectrometry that provides accurate mass measurement, hence, facilitates the determination of the elemental composition of the molecular ions and provides discrimination of isobaric ions

2.5 SUMMARY

In this chapter, the chemical composition of the HHCF has been putatively identified using LC-MS/MS and the source(s) of compounds in the HHCF have been identified using the developed EXCEL template. PHE, RHE and SOP contributed the largest number of secondary metabolites identified in the HHCF, while KOC seems to contribute very little. The developed analytical platform allowed us to simultaneously analyze multiple chemical constituents in a TCM decoction in a relative comprehensive and systematic manner. The chemical constituents in the TCM decoction could be monitored by means of mass, retention time and relatively abundance of ions in the TIC. This strategy enables the identification of compounds which are likely to be present in a relatively complex (multi-herbal) preparation.

Table 2.3 Putatively identified compounds in the HHCF by LC-MS/MS in positive ionization mode.

R_t (min)	No.	*m/z*	Adduct ion(s)	MS/MS fragment ions (*m/z*)	Source	Molecular formula	Identity
3.36	**P1**	191	$[M+H]^+$	162, 148	SOP	$C_{11}H_{14}N_2O$ (190.24)	Cytisine
	P2	196	$[M]^+$	153, 137, 119, 109	PHE	$C_{10}H_{12}O_4$ (196.20)	Atraric aid
	P3	205	$[M+H]^+$	162, 146, 108	SOP	$C_{12}H_{16}N_2O$ (204.27)	N-Methylcytisine
	P4	215	$[M]^+$	169, 142, 125	RHE	$C_{10}H_{11}ClO_6$ (214.65)	Mecoprop
	P5	261	$[M+H]^+$	243, 164, 146, 114	SOP	$C_{15}H_{20}N_2O_2$ (260.33)	Baptifoline
3.75	**P6**	265	$[M+H]^+$	247, 164, 148, 136, 112	SOP	$C_{15}H_{24}N_2O_2$ (264.36)	5α-Hydroxymatrine OR 9α-Hydroxymatrine
4.15	**P7**	265	$[M+H]^+$	247, 148, 136, 127, 112	SOP	$C_{15}H_{24}N_2O_2$ (264.36)	14β-Hydroxymatrine
4.40	**P8**	180	$[M]^+$	151, 121, 103	PHE	$C_{11}H_{18}NO$ (180.27)	Candicine
4.75	**P9**	245	$[M+H]^+$	199, 162, 148, 122	SOP	$C_{15}H_{20}N_2O$ (244.33)	Anagyrine
	P10	265	$[M+H]^+$	247, 164, 148, 136, 112	SOP	$C_{15}H_{24}N_2O_2$ (264.36)	5α-Hydroxymatrine OR 9α-Hydroxymatrine
5.00	**P11**	247	$[M+H]^+$	176, 150, 136, 122	SOP	$C_{15}H_{22}N_2O$ (246.35)	Isosophocarpine
5.52	**P12**	263	$[M+H]^+$	245, 188, 164, 148, 122	SOP	$C_{15}H_{22}N_2O_2$ (262.35)	(-)-9α-hydroxy-7, 11-dehydromatrine
5.72	**P13**	192	$[M+H]^+$	177, 163, 149, 119	PHE	$C_{10}H_9NO_3$ (191.18)	Noroxyhydrastinine
	P14	249	$[M+H]^+$	176, 150, 136	SOP	$C_{15}H_{24}N_2O$ (248.36)	Allomatrine OR Isomatrine OR Matrine OR Sophoridine
		519	$[2M+Na]^+$	271			
		497	$[2M+H]^+$	249, 150			
		271	$[M+Na]^+$	No fragment ion			
6.47	**P15**	247	$[M+H]^+$	227, 176, 150, 136, 122	SOP	$C_{15}H_{22}N_2O$ (246.35)	Sophocarpine
	P16	249	$[M+H]^+$	176, 150, 136	SOP	$C_{15}H_{24}N_2O$ (248.36)	Allomatrine OR Isomatrine OR Matrine OR Sophoridine
		250	$[M+2H]^+$	249, 150, 136			
		519	$[2M+Na]^+$	271			
		497	$[2M+H]^+$	248, 249			
8.02	**P17**	263	$[M+H]^+$	245, 195, 150, 177, 138	SOP	$C_{15}H_{22}N_2O_2$ (262.35)	Oxysophocarpine
		525	$[2M+H]^+$	263, 245, 150, 138			

Table 2.3 Putatively identified compounds in the HHCF by LC-MS/MS in positive ionization mode.							
R_t (min)	**No.**	***m/z***	**Adduct ion(s)**	**MS/MS fragment ions (*m/z*)**	**Source**	**Molecular formula**	**Identity**
	P18	265	$[M+H]^+$	247, 205, 148, 136, 112	SOP	$C_{15}H_{24}N_2O_2$ (264.36)	Oxymatrine OR Oxysophoridine
		529	$[2M+H]^+$	265, 247, 205, 136			
	P19	266	$[M+NH_4]^+$	206, 177, 150, 136	SOP	$C_{15}H_{24}N_2O$ (248.36)	Lupanine
10.42	**P20**	247	$[M+H]^+$	190, 176, 150, 136, 122	SOP	$C_{15}H_{22}N_2O$ (246.35)	(+)-7,11-Dehydromatrine
11.30	**P21**	263	$[M+H]^+$	245. 195, 188, 180, 148	SOP	$C_{15}H_{22}N_2O_2$ (262.35)	9α-Hydroxysophocarpine
11.48	**P22**	263	$[M+H]^+$	245, 218, 204, 190, 164	SOP	$C_{15}H_{22}N_2O_2$ (262.35)	Leontalbinine N-oxide
	P23	265	$[M+H]^+$	247, 205, 150, 136, 112	SOP	$C_{15}H_{24}N_2O_2$ (264.36)	Oxymatrine OR Oxysophoridine
		529	$[2M+H]^+$	NA			
11.88	**P24**	243	$[M+H]^+$ OR $[M]^+$	No fragment ions	DIC	$C_{12}H_{18}O_5$ (242.27)	Dasycarpusenester A
						$C_{14}H_{13}NO_3$ (243.26)	O-Ethylnor-γ-fagarine
16.77	**P25**	314	$[M]^+$	No fragment ions	PHE	$C_{19}H_{24}NO_3$ (314.40)	(-)-Oblongine
20.08	**P26**	342	$[M+H]^+$	192, 177	PHE	$C_{20}H_{23}NO_4$ (341.40)	Phellodendrine
22.08	**P27**	344	$[M+H]^+$	299, 267, 175, 137	PHE	$C_{15}H_{25}N_3O_6$ (343.37)	Tembetarine
22.91	**P28**	342	$[M+H]^+$	297, 282, 265, 237	PHE	$C_{15}H_{23}N_3O_6$ (341.36)	Magnoflorine
26.84	**P29**	314	$[M+H]^+$	269, 137, 121, 107	PHE	$C_{19}H_{23}NO_3$ (313.39)	Evoeuropine
31.32	**P30**	356	$[M+H]^+$	311, 247	PHE	$C_{13}H_{21}N_7O_5$ (355.35)	Menisperine
52.87	**P31**	336	$[M]^+$	321, 320, 306, 292, 278	PHE	$C_{20}H_{18}NO_4$ (336.36)	Berberine

Table 2.4 Putatively identified compounds in the HHCF by LC-MS/MS in negative ionization mode.							
Rt (min)	**No.**	***m/z***	**Adduct ion(s)**	**MS/MS fragment ions (*m/z*)**	**Source**	**Molecular formula**	**Identity**
2.34	**N1**	193	$[M-H]^-$	113, 103	SCU	$C_{10}H_{10}O_4$ (194.18)	Glucuronic acid
2.46	**N2**	191	$[M-H]^-$	173, 127, 111	PHE	$C_7H_{12}O_6$ (192.17)	Quinic acid
	N3	223	$[M-H]^-$	205, 129, 111	SOP	$C_{10}H_{14}N_2O_5$ (242.23)	Sinapic acid
3.50	**N4**	191	$[M-H]^-$	155, 131, 129, 111	PHE	$C_6H_8O_7$ (192.12)	Citric acid
	N5	331	$[M-H]^-$	271, 241, 211, 169, 125	RHE	$C_{13}H_{16}O_{10}$ (332.26)	Galloylglucose (i.e. 1-*O*-Galloyl-β-D-glucose or 6-*O*-Galloyl-β-D-glucose) OR Glucopyranosyloxyl gallic acid (i.e. Gallic acid-3-O-β-D-glucoside or Gallic acid-4-O-β-D-glucoside)
4.08	**N6**	331	$[M-H]^-$	271, 241, 211, 169, 125	RHE	$C_{13}H_{16}O_{10}$ (332.26)	
4.61	**N7**	331	$[M-H]^-$	271, 241, 211, 169, 125	RHE	$C_{13}H_{16}O_{10}$ (332.26)	
5.35	**N8**	125	$[M-H]^-$	125	RHE	$C_6H_6O_3$ (126.11)	Pyrogallol
	N9	169	$[M-H]^-$	125, 107	RHE	$C_7H_6O_5$ (170.12)	Gallic acid
	N10	331	$[M-H]^-$	271, 241, 211, 169, 125	RHE	$C_{13}H_{16}O_{10}$ (332.26)	Galloylglucose (i.e. 1-*O*-Galloyl-β-D-glucose or 6-*O*-Galloyl-β-D-glucose) OR Glucopyranosyloxyl gallic acid (i.e. Gallic acid-3-O-β-D-glucoside or Gallic acid-4-O-β-D-glucoside)
8.71	**N11**	255	$[M-H]^-$	193, 179, 165, 107	SOP	$C_{11}H_{12}O_7$ (256.21)	Piscidic acid
		511	$[2M-H]^-$	255, 165, 193, 179			
		533	$[2M+Na-2H]^-$	255, 165, 179, 193			
13.88	**N12**	577	$[M-H]^-$	425, 407, 289, 245, 125	RHE	$C_{30}H_{26}O_{12}$ (578.52)	Procyanidin B (Catechin dimers)
16.48	**N13**	289	$[M-H]^-$	245, 205, 151, 125, 109	RHE	$C_{15}H_{14}O_6$ (290.27)	Catechin
		579	$[2M-H]^-$	289, 245, 205, 151, 125			
	N14	353	$[M-H]^-$	205, 191, 179, 127, 109	PHE	$C_{16}H_{18}O_9$ (354.31)	Chlorogenic acid
		707	$[2M-H]^-$	NA			
18.15	**N15**	367	$[M-H]^-$	193, 191, 173, 149	PHE	$C_{17}H_{20}O_9$ (368.34)	3-*O*-Feruloylquinic acid
21.10	**N16**	325	$[M-H]^-$	NA	RHE	$C_{16}H_{22}O_7$ (326.34)	4-(4'-Hydroxylphenyl)-2-butanone 4'-O-β-D-glucoside
		371	$[M+FA-H]^-$	163, 121, 101			
		651	$[2M-H]^-$	NA			
	N17	415	$[M+Na-2H]^-$	NA	RHE	$C_{19}H_{22}O_9$ (394.37)	6-Hydroxymusizin-8-O- β-D-glucoside
		439	$[M+FA-H]^-$	393, 231, 113			
22.77	**N18**	289	$[M-H]^-$	245, 205, 151, 125, 109	RHE	$C_{15}H_{14}O_6$ (290.27)	Epicatechin
	N19	337	$[M-H]^-$	191, 173, 163	PHE	$C_{16}H_{18}O_8$ (338.38)	*p*-coumaroylquinic acid

Table 2.4 Putatively identified compounds in the HHCF by LC-MS/MS in negative ionization mode.

Rt (min)	No.	*m/z*	Adduct ion(s)	MS/MS fragment ions (*m/z*)	Source	Molecular formula	Identity
24.72	**N20**	303	$[M-H]^-$	177, 151, 125	SCU	$C_{15}H_{12}O_7$ (304.25)	2',3,5,6',7-Pentahydroxyflavanone (Ganhuangemin)
26.26	**N21**	367	$[M-H]^-$	193, 191, 173	PHE	$C_{17}H_{20}O_9$ (368.34)	5-*O*-Feruloylquinic acid
		735	$[2M-H]^-$	191, 367, 173, 193			
26.65	**N22**	389	$[M-H]^-$	NA	RHE	$C_{20}H_{22}O_8$ (390.38)	Resveratrol-4'-O-β-D-glucoside OR Resveratrol 3-O-β-glucoside (Pieceid)
		435	$[M+FA-H]^-$	389, 227, 191, 185			
		779	$[2M-H]^-$	NA			
		825	$[2M+FA-H]^-$	NA			
32.06	**N23**	301	$[M-H]^-$	283, 151, 125	SCU	$C_{15}H_{10}O_7$ (302.24)	3,5,7,2',6'-Pentahydroxyflavone (Viscidulin I)
34.57	**N24**	441	$[M-H]^-$	289, 271, 169, 125	RHE	$C_{22}H_{18}O_{10}$ (442.37)	Epicatechin 3-O-gallate
	N25	477	$[M-H]^-$	313, 169, 125	RHE	$C_{23}H_{26}O_{11}$ (478.45)	Isolindleyin
	N26	547	$[M-H]^-$	457, 427, 367, 337	SCU	$C_{26}H_{28}O_{13}$ (548.49)	Chrysin-6-C-arabinosyl-8-C-glucoside
36.56	**N27**	477	$[M-H]^-$	313, 169, 125	RHE	$C_{23}H_{26}O_{11}$ (478.45)	Lindleyin
		955	$[2M-H]^-$	477, 313			
	N28	545	$[M-H]^-$	NA	RHE	$C_{25}H_{22}O_{14}$ (546.43)	Rhein-8-O-D-[6'-O-(3''-methoxylmalonyl)] glucoside
37.25	**N29**	547	$[2M-H]^-$	457, 427, 367, 337	SCU	$C_{26}H_{28}O_{13}$ (548.49	Chrysin-6-C-glucosyl-8-C-arabonoside
38.43	**N30**	541	$[M-H]^-$	313, 227, 169	RHE	$C_{27}H_{26}O_{12}$ (542.49)	Resveratrol-4'-O-β-D-(2''-O-galloyl) glucoside
39.20	**N31**	541	$[M-H]^-$	313, 227, 169	RHE	$C_{27}H_{26}O_{12}$ (542.49)	Resveratrol-4'-O-β-D-(6''-O-galloyl) glucoside
45.08	**N32**	301	$[M-H]^-$	161, 139, 124	SCU	$C_{16}H_{14}O_6$ (302.28)	Trihydroxy-methoxyflavanone
46.91	**N33**	431	$[M-H]^-$	311, 269, 225	RHE	$C_{21}H_{20}O_{10}$ (432.38)	Emodin-1-O-β-D-glucoside OR Emodin-8-O-β-D-glucoside OR Aloe-emodin 8-O-β-D-glucoside OR Aloe-emodin-3-CH_2-O-β-D-glucoside.
55.48	**N34**	481	$[M+Cl]^-$	NA	SOP	$C_{22}H_{22}O_{10}$ (446.40)	(-)-Maackiain-3-O-glucoside (Trifolirhizin)
		483	$[M+K-2H]^-$	NA			
		491	$[M+FA-H]^-$	283, 255			
58.94	**N35**	431	$[M-H]^-$	311, 269, 225	RHE	$C_{21}H_{20}O_{10}$ (432.38)	Emodin-1-O-β-D-glucoside OR Emodin-8-O-β-D-glucoside OR Aloe-emodin 8-O-β-D-glucoside OR Aloe-emodin-3-CH_2-O-β-D-glycoside.
63.95	**N36**	233	$[M-H]^-$	191, 175, 147	RHE	$C_{12}H_{10}O_5$ (234.20)	(5Z)-6-Hydroxy-3,4-dioxo-6-phenyl-5-hexenoic acid
71.02	**N37**	269	$[M-H]^-$	251, 223, 169,	SCU	$C_{15}H_{10}O_5$ (270.24)	5,6,7-Trihydroxyflavone (Baicalein) OR 5,7,8-Trihydroxyflavone (Norwogonin)

Fig. 2.3 Fragmentation pathways of putatively identified compounds in positive ionization mode.

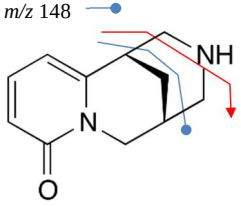
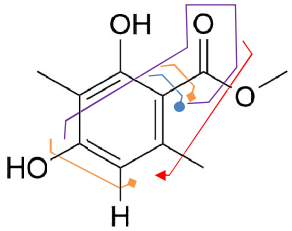
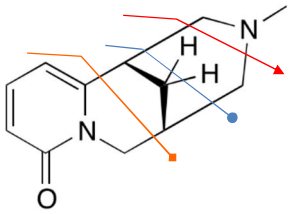
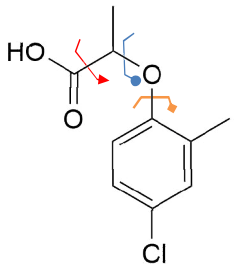
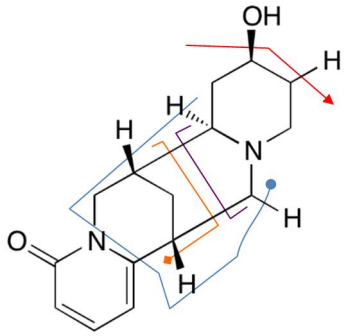
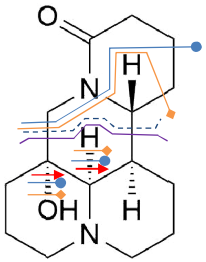
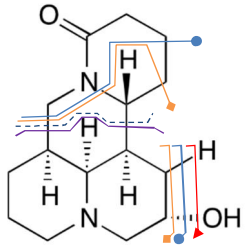
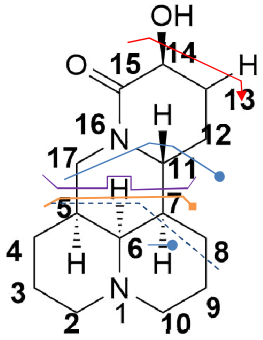
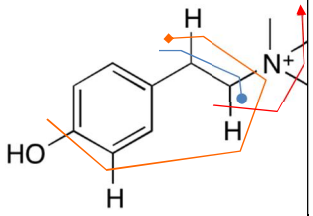
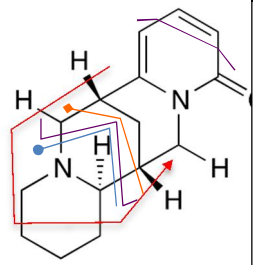
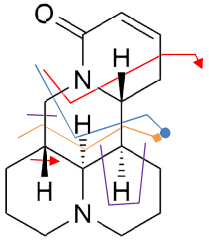
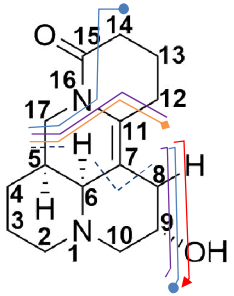
m/z 162 *m/z* 148 	*m/z* 151 *m/z* 137 *m/z* 119 *m/z* 109 	*m/z* 162 *m/z* 146 *m/z* 108 	*m/z* 169 *m/z* 142 *m/z* 125 	*m/z* 243 *m/z* 164 *m/z* 146 *m/z* 114 	*m/z* 247 *m/z* 164 *m/z* 148 *m/z* 136 *m/z* 112 
P1 Cytisine	**P2** Atraric aid	**P3** N-Methylcytisine	**P4** Mecoprop	**P5** Baptifoline	**P6/P10** 5α-Hydroxymatrine
m/z 247 *m/z* 164 *m/z* 148 *m/z* 136 *m/z* 112 	*m/z* 247 *m/z* 148 *m/z* 136 *m/z* 127 *m/z* 112 	*m/z* 151 *m/z* 121 *m/z* 103 	*m/z* 199 *m/z* 162 *m/z* 148 *m/z* 122 	*m/z* 176 *m/z* 150 *m/z* 136 *m/z* 122 	*m/z* 245 *m/z* 188 *m/z* 164 *m/z* 148 *m/z* 122 
P6/P10 9α-Hydroxymatrine	**P7** 14β-Hydroxymatrine	**P8** Candicine	**P9** Anagyrine	**P11** Isosophocarpine	**P12** (-)-9α-hydroxy-7, 11-dehydromatrine

Fig. 2.3 Fragmentation pathways of putatively identified compounds in positive ionization mode.

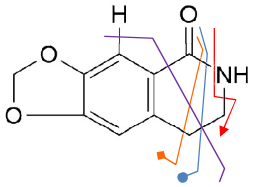
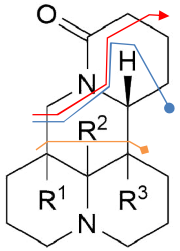
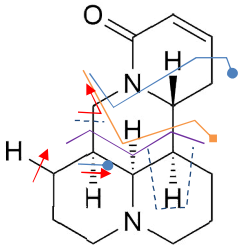
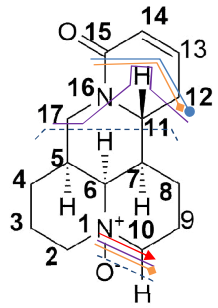
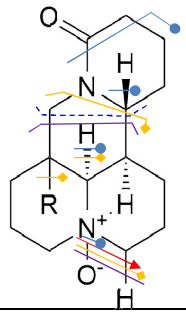
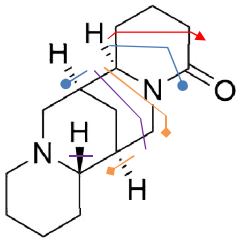
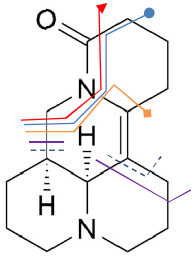
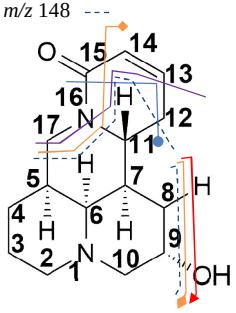
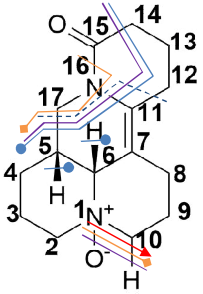
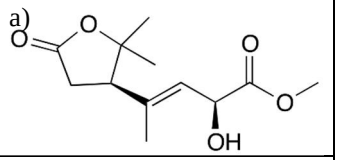
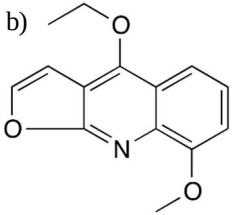
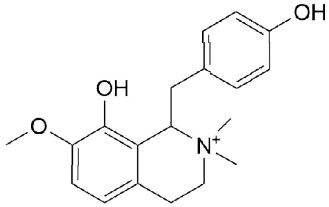
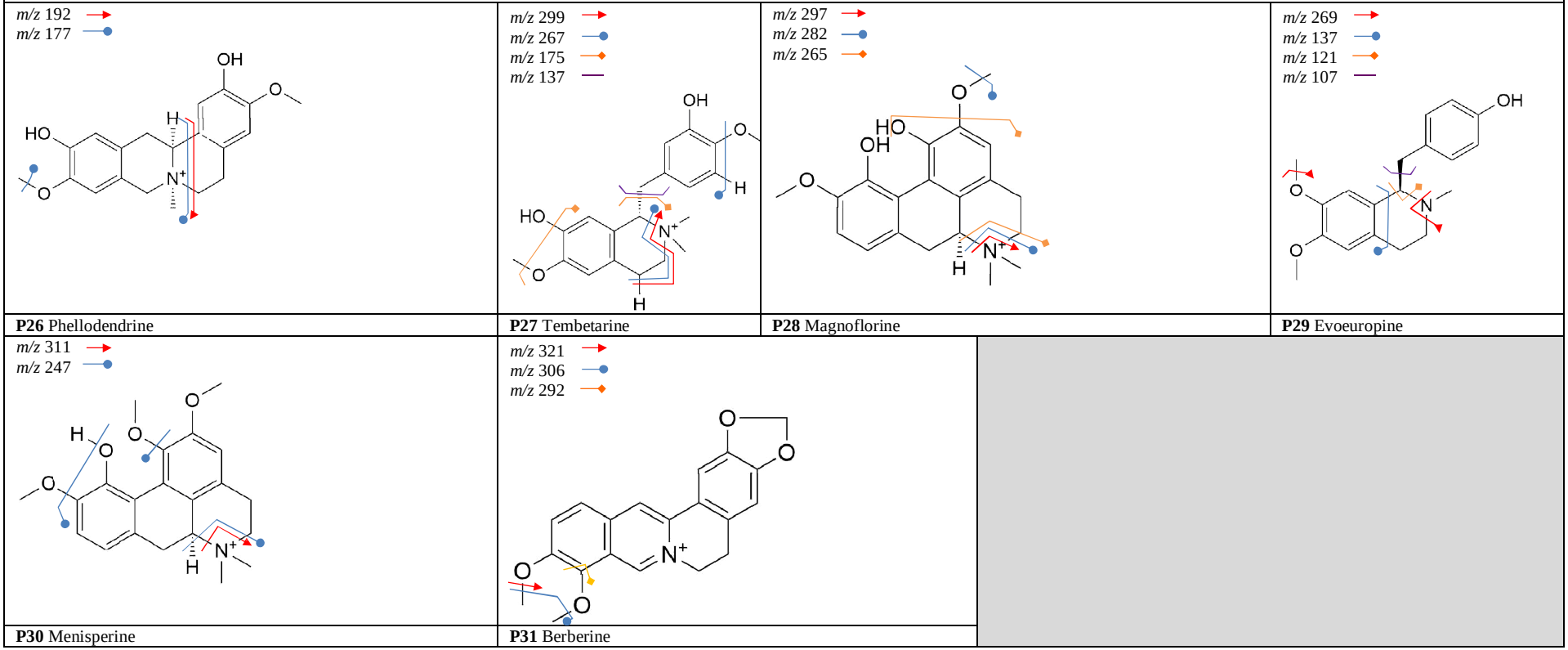
m/z 177 *m/z* 163 *m/z* 149 *m/z* 133 	*m/z* 176 *m/z* 150 *m/z* 136 		*m/z* 227 *m/z* 176 *m/z* 150 *m/z* 136 *m/z* 122 	*m/z* 245 *m/z* 195 *m/z* 177 *m/z* 150 *m/z* 138 	*m/z* 247 *m/z* 205 *m/z* 148 *m/z* 136 *m/z* 112 
P13 Noroxyhydrastinine	**P14/P16** R¹=⋯H R²=◀H R³=⋯H =Allomatrine R¹=◀H R²=◀H R³=◀H=Isomatrine R¹=⋯H R²=⋯H R³=⋯H=Matrine R¹=◀H R²=⋯H R³=⋯H=Sophoridine		**P15** Sophocarpine	**P17** Oxysophocarpine	**P18/P23** R= ◀H= Oxysophoridine R=⋯H= Oxymatrine
m/z 206 *m/z* 177 *m/z* 150 *m/z* 136 	*m/z* 190 *m/z* 176 *m/z* 150 *m/z* 136 *m/z* 122 	*m/z* 245 *m/z* 195 *m/z* 188 *m/z* 180 *m/z* 148 	*m/z* 245 *m/z* 204 *m/z* 218 *m/z* 190 *m/z* 164 	a)  b) 	
P19 Lupanine	**P20** (+)-7,11-Dehydromatrine	**P21** 9α-Hydroxysophocarpine	**P22** Leontalbinine N-oxide	**P24a)** Dasycarpusenester A or **b)**O-Ethylnor-γ-fagarine	**P25** (-)-Oblongine

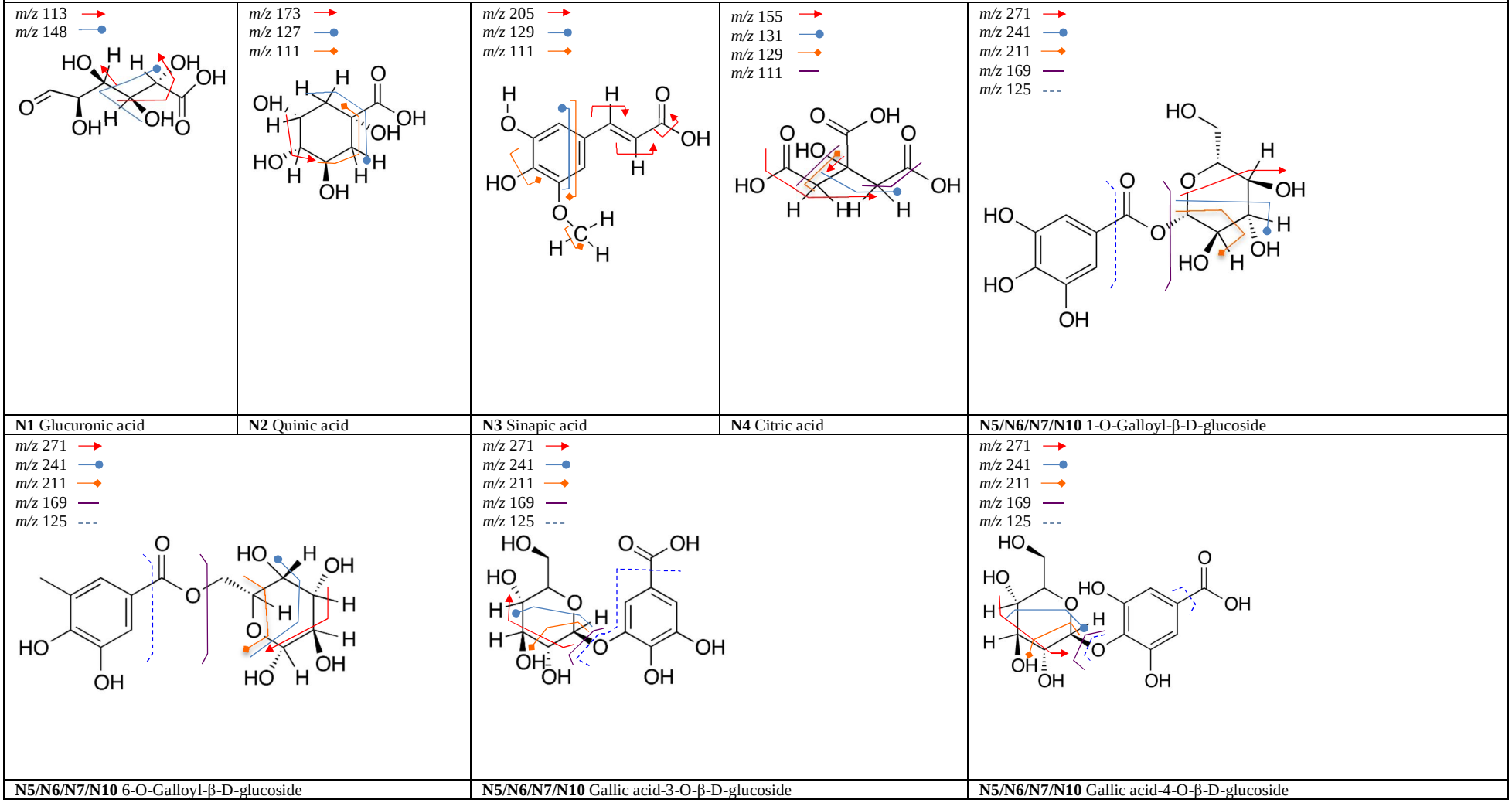
Fig. 2.3 Fragmentation pathways of putatively identified compounds in positive ionization mode.



P26 Phellodendrine | **P27** Tembetarine | **P28** Magnoflorine | **P29** Evoeuropine

P30 Menisperine | **P31** Berberine

Fig. 2.4 Fragmentation pathways of putatively identified compounds in negative ionization mode.

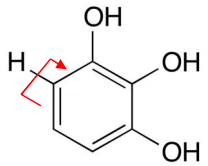


N1 Glucuronic acid | **N2** Quinic acid | **N3** Sinapic acid | **N4** Citric acid | **N5/N6/N7/N10** 1-O-Galloyl-β-D-glucoside

N5/N6/N7/N10 6-O-Galloyl-β-D-glucoside | **N5/N6/N7/N10** Gallic acid-3-O-β-D-glucoside | **N5/N6/N7/N10** Gallic acid-4-O-β-D-glucoside

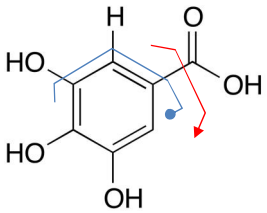
Fig. 2.4 Fragmentation pathways of putatively identified compounds in negative ionization mode.

m/z 113



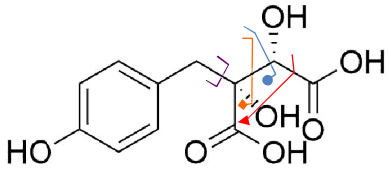
N8 Pyrogallol

m/z 125
m/z 107



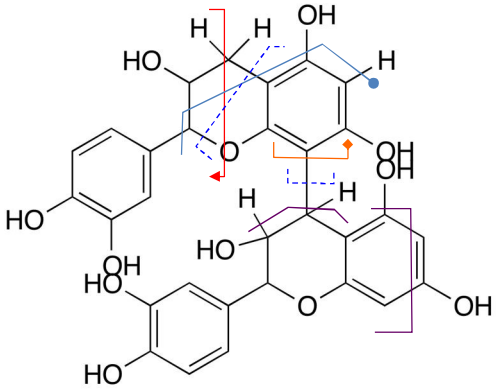
N9 Gallic acid

m/z 193
m/z 179
m/z 165
m/z 107



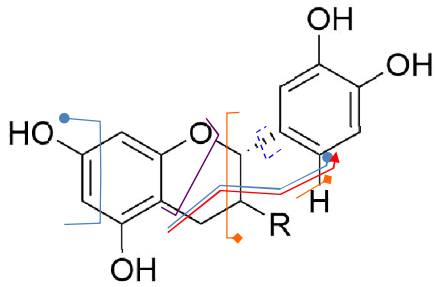
N11 Piscidic acid

m/z 425
m/z 407
m/z 289
m/z 245
m/z 125



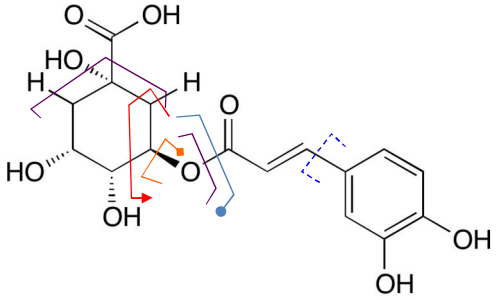
N12 Procyanidin B (Catechin dimers)

m/z 245
m/z 205
m/z 151
m/z 125
m/z 109



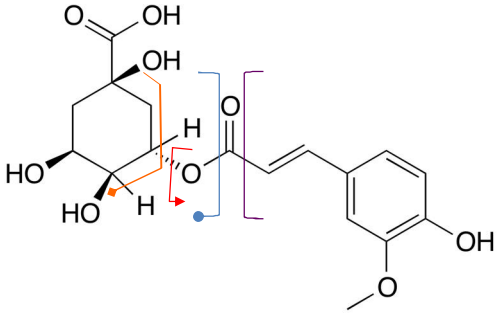
N13/N18
R= OH= Catechin
R= OH= Epicatechin

m/z 205
m/z 191
m/z 179
m/z 127
m/z 109



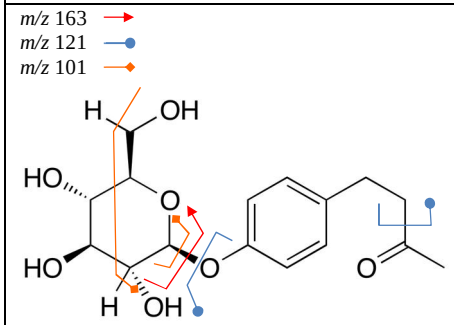
N14 Chlorogenic acid

m/z 193
m/z 191
m/z 173
m/z 149

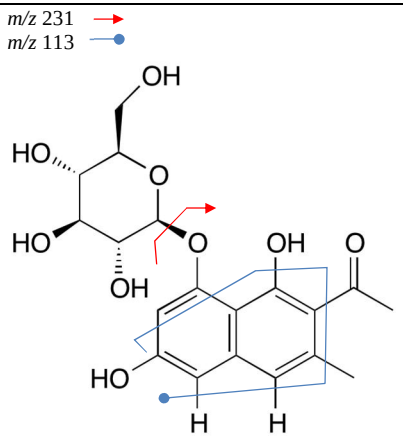


N15 3-*O*-Feruloylquinic acid

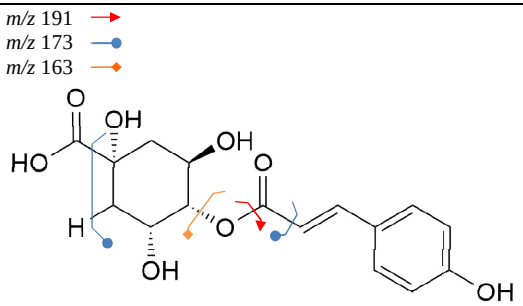
Fig. 2.4 Fragmentation pathways of putatively identified compounds in negative ionization mode.



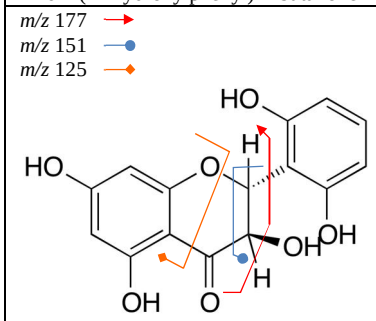
N16 4-(4'-Hydroxylphenyl)-2-butanone 4'-O-β-D-glucoside



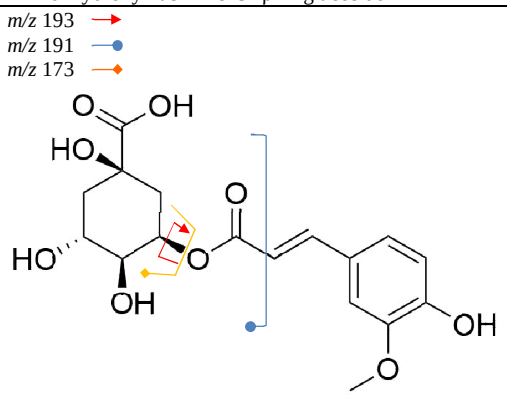
N17 6-Hydroxymusizin-8-O- β-D-glucoside



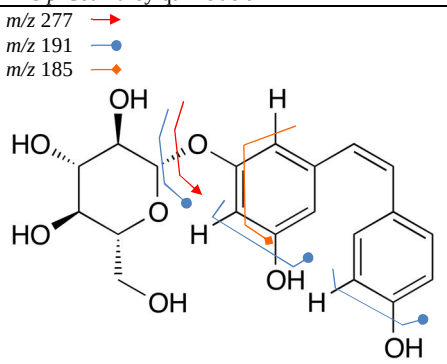
N19 *p*-Coumaroylquinic acid



N20 2',3,5,6',7-Pentahydroxyflavanone (Ganhuangemin)

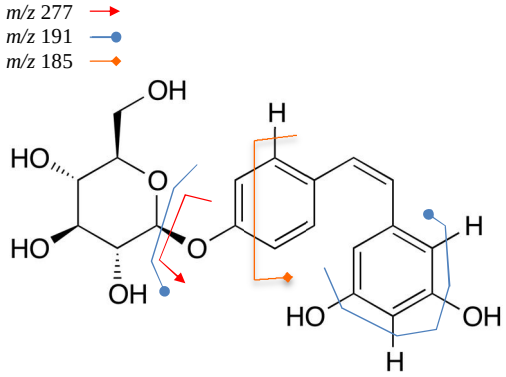


N21 5-*O*-Feruloylquinic acid

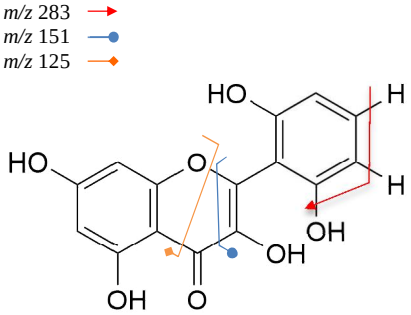


N22 Resveratrol 3-O-ß-glucoside

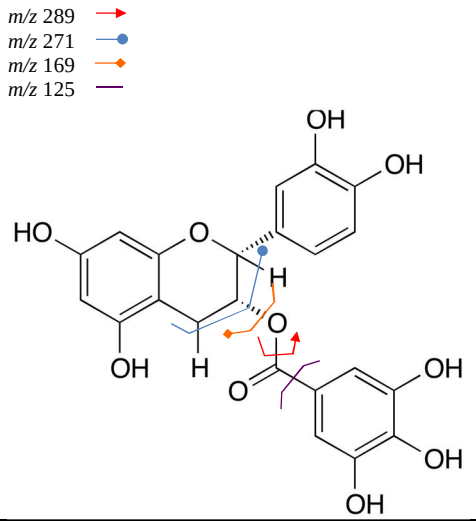
Fig. 2.4 Fragmentation pathways of putatively identified compounds in negative ionization mode.



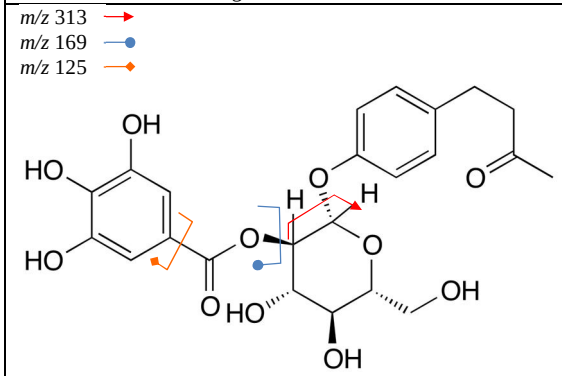
N22_Resveratrol 4'-O-ß-glucoside



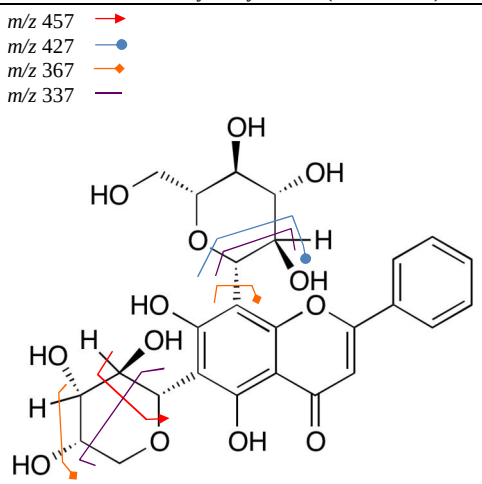
N23 3,5,7,2',6'-Pentahydroxyflavone (Viscidulin I)



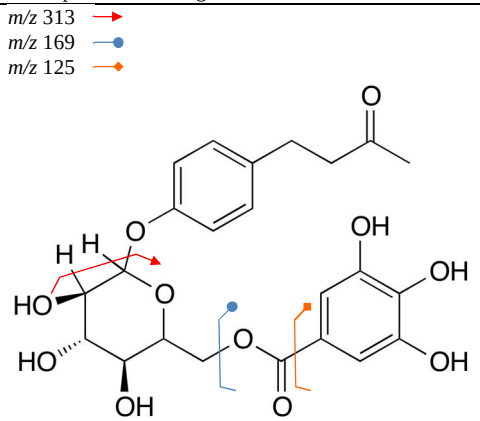
N24 Epicatechin 3-O-gallate



N25 Isolindleyin

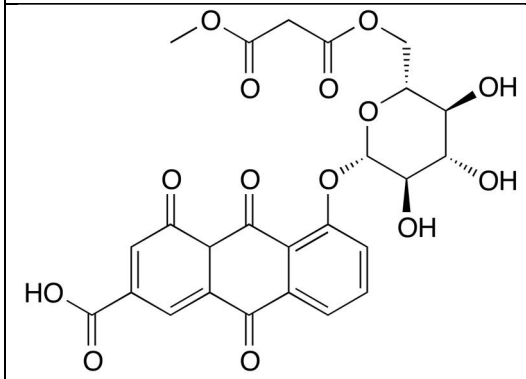


N26 Chrysin-6-C-arabinosyl-8-C-glucoside

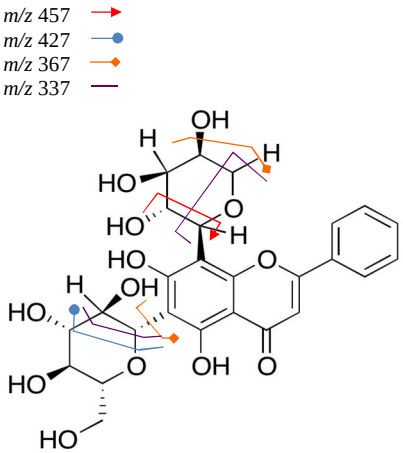


N27 Lindleyin

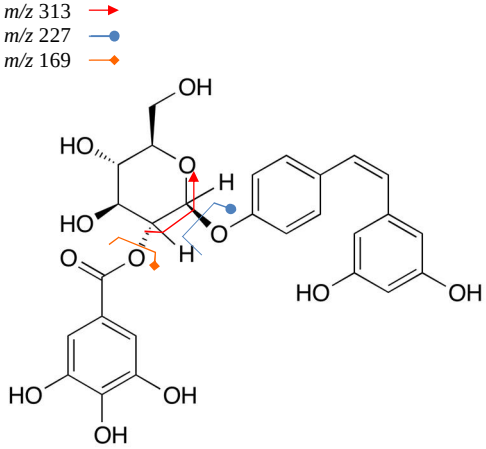
Fig. 2.4 Fragmentation pathways of putatively identified compounds in negative ionization mode.



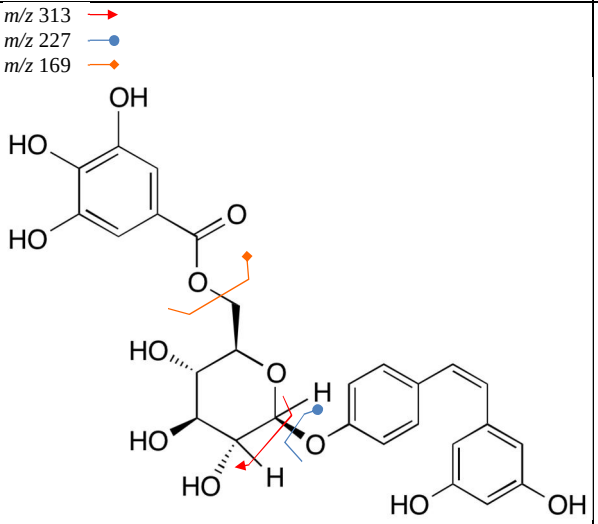
N28 Rhein-8-O-D-[6'-O-(3"-methoxylmalonyl)] glucoside



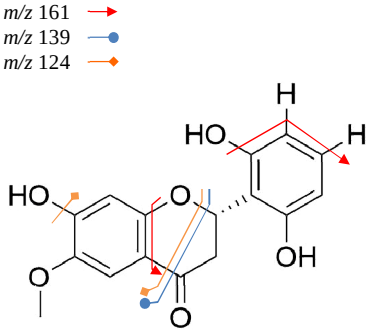
N29 Chrysin-6-C-glucosyl-8-C-arabonoside



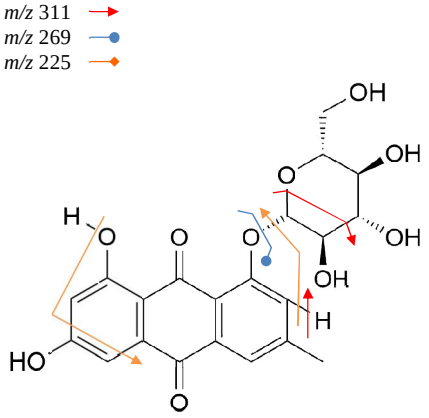
N30 Resveratrol-4'-O-β-D-(2"-O-galloyl) glucoside



N31 Resveratrol-4'-O-β-D-(6"-O-galloyl) glucoside

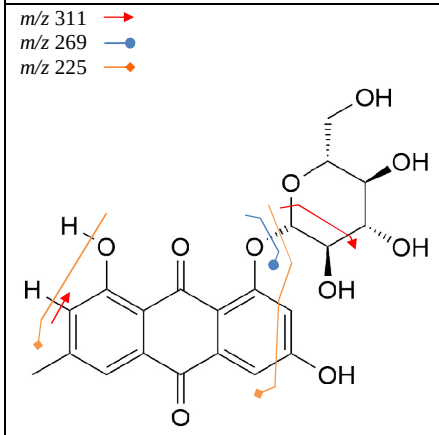


N32 Trihydroxy-methoxyflavanone

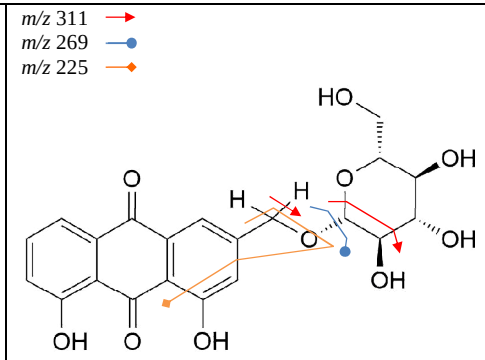


N33/N35 Emodin-1-O-ß-D-glucoside

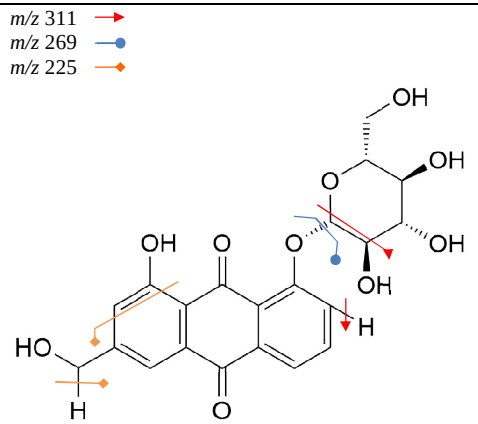
Fig. 2.4 Fragmentation pathways of putatively identified compounds in negative ionization mode.



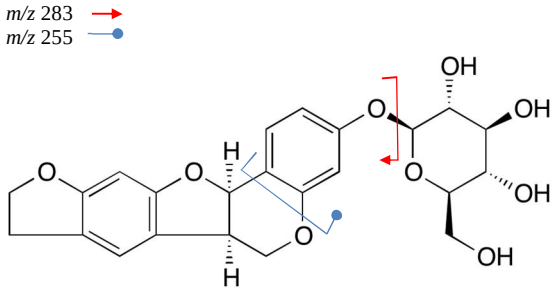
N33/N35 Emodin-8-O-ß-D-glucoside



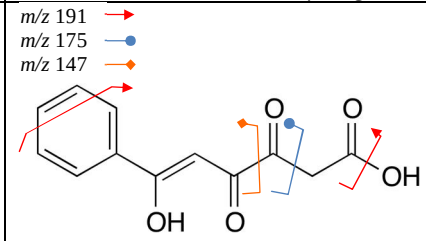
N33/N35 Aloe-emodin-3-CH_2-O-β-D- glucoside



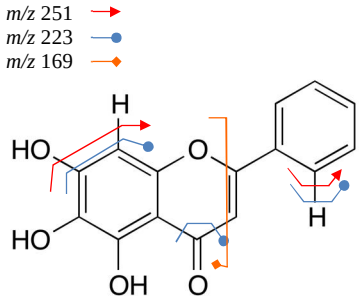
N33/N35 Aloe-emodin 8-O-ß-D-glucoside



N34 (-)-Maackiain-3-O-glucoside (Trifolirhizin)



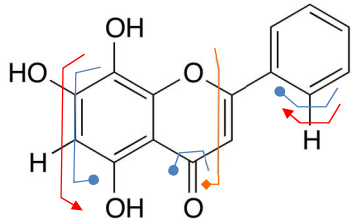
N36 (5Z)-6-Hydroxy-3,4-dioxo-6-phenyl-5-hexenoic acid



N37 Baicalein

Fig. 2.4 Fragmentation pathways of putatively identified compounds in negative ionization mode.

m/z 251
m/z 223
m/z 169



N37 Norwogonin

3 BIOLOGICAL ACTIVITES OF THE HEXA-HERBAL CHINESE FORMULA (HHCF) DECOCTION

3.1 INTRODUCTION

To investigate the possible underlying molecular mechanisms by which the HHCF could support the treatment of atopic dermatitis (AD)/skin inflammation in clinical practice, this chapter investigated the effects of the HHCF against some of the pathogenesis-related targets of AD/skin inflammation *in vitro*.

3.2 OBJECTIVES

- To study the effect of the HHCF decoction against TNF-α plus IFN-□- induced CCL17 using spontaneously immortalized human epidermal keratinocytes (HaCaT) and to predict the active compound(s) by correlating the LC-MS profiles of the HHCF and its twelve variation formulae to their effects on CCL17 levels in HaCaT using multivariate regression analysis.
- To study the effect of decoctions prepared from the HHCF, the botanical drug making up the HHCF and the knock-one botanical drug-out HHCF against IL-1β-induced IL-6, IL-8 and PGE_2 production using human fibroblasts. This study was carried out by Dr. Bernd L. Fiebich at the University of Freiburg.
- To study the effect of decoctions prepared from the HHCF and the botanical drug making up the HHCF against hyaluronidase. This study was carried out at the University of Copenhagen under the supervision of Prof. Anna Jäger.
- To study the effect of decoctions prepared from the HHCF and the botanical drug making up the HHCF against two gram-positive (*Staphylococcus aureus* ATCC 6538 and *Bacillus subtilis* ATCC6633) and two-gram-negative bacteria (*Escherichia coli* ATCC 1229 and *Pseudomonas aeruginosa* ATCC9027). This study was carried out at the University of Copenhagen under the supervision of Prof. Anna Jäger.

3.3 METHODS

3.3.1 Sample preparation

Decoctions of the HHCF, single botanical drug (RHE, SCU, DIC, SOP, KOC and PHE), knock-RHE-out HHCF (NRHE), knock-SCU-out HHCF (NSCU), knock-DIC-out HHCF (NDIC), knock-SOP-out HHCF (NSOP), knock-KOC-out HHCF (NKOC), knock-PHE-out HHCF (NPHE) and twelve variation of the HHCF [i.e. V1-V12; Table 3.1] were prepared using the method described 2.3.1. The lyophilized decoctions, SB202190 monohydrochloride hydrate and streptomycin were dissolved in water and filtered using a 0.22 μm filter membrane. The lyophilized decoctions prepared for the hyaluronidase assay were dissolved in water and not filtered.

A six-factor, twelve-level uniform design was applied to establish differences among the twelve variations formulae of the HHCF [i.e. V1-V12; Table 3.1]. Table 3.1 was developed based on the $U_{12}(12^5)$ uniform deign table and method described in (Fang, 1994).

Table 3.1 Percentage of 6 botanical drugs in the twelve variation formulae of the HHCF under uniform design.

	SOP	SCU	PHE	RHE	DIC	KOC
V1	47%	17%	12%	4%	1%	19%
V2	34%	12%	8%	18%	4%	25%
V3	27%	6%	1%	53%	3%	11%
V4	22%	1%	31%	5%	12%	29%
V5	18%	33%	9%	13%	10%	17%
V6	14%	19%	3%	41%	10%	12%
V7	12%	10%	39%	3%	20%	17%
V8	9%	3%	20%	18%	31%	19%
V9	7%	51%	3%	21%	13%	5%
V10	5%	25%	46%	1%	19%	5%
V11	3%	14%	23%	13%	42%	6%
V12	1%	6%	10%	38%	43%	2%

3.3.2 Cell culture, ELISA and MTT assay

HaCaT: The HaCaT ((Boukamp et al., 1988); supplied by Cell Lines Service, Eppelheim, Germany) were cultured in high glucose Dulbecco's modified Eagle medium (DMEM; Gibco) containing 10% heat inactivated foetal bovine serum (Sigma) and 100 U/ml penicillin and 100 μg/ml streptomycin (Gibco). Cells were grown in tissue culture flasks and maintained at 37 °C in a humidified incubator containing 5 % CO_2 and 95% air. Cells were passaged when ~80% confluent. To subculture, cells were washed once with Ca^{2+} and Mg^{2+} -free phosphate buffer saline (PBS; Gibco), and

trypsinzed by 10 minutes incubation at 37 °C in 0.25 % trypsin/ethylenediaminetetraacetic acid (EDTA) (Gibco). Trypsinization was stopped by adding complete DMEM. HaCaT were harvested and pelleted by centrifugation at 310 g for 5 minutes and re-suspended in fresh media. (Turksen, 2005) **ELISA:** HaCaT were seeded into a 96-well plate (200 µl per well of 2 x 10^4 cells/ml). After 24 hours, the medium was replaced with the serum-free medium and cells were cultured for another 24 hours. Then, the medium was removed and cells were treated with fresh serum-free medium containing the tested sample. After 5 minutes, 30 ng/ml TNF-α and 30 ng/ml IFN-□ were added and the cells were cultured for 24 hours. (Fujita et al., 2011) After incubation, the medium was collected and analyzed for CCL17 by ELISA (R&D Systems) according to the manufacturer's instruction and the cells were assessed for viability using the (3-(4,5-dimethylthizaol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. **MTT assay**: HaCaT were washed once with PBS and exposed to 0.5mg/ml of MTT (Sigma) for 3 hours at 37 °C in a humidified incubator containing 5 % CO_2 and 95% air. Then, cells were washed once with PBS and the formazan precipitate was dissolved in 200 µl of dimethyl sulphoxide (DMSO) and the absorbance at 570 nm was measured using a microplate reader. The percentage of cell viability was assessed by (mean absorbance in tested wells)/(mean absorbance in control wells) x 100 (Qi et al., 2009). Assays were performed with two replicates in three independent experiments (n=3).

Human fibroblasts: Human fibroblasts were supplied and cultured by Dr. Bernd L. Fiebich at the University of Freiburg. Briefly, cells were pre-incubated with tested samples for 30 minutes followed by stimulation with IL-1β (10 U/ml) for 24 hours. ***ELISA:*** Supernatants were harvested and centrifuged, and levels of PGE_2 were measured by enzyme immunoassay (PGE_2: AssaDesign, distributed by Biotren, Köln, Germany) and levels of IL-6 and IL-8 were measured by ELISA (ELISA ready-SET-GO kit, distributed by eBioscience) according to manufacturer's instructions.

Release of inflammatory mediators [i.e. PGE_2, IL-6 or IL-8] from human fibroblasts after pre-incubation with tested samples and IL-1β treatment were expressed relative to the corresponding IL-1-treated negative control i.e. Assays were performed with one replicate in one experiment (n=1).

$$\frac{\text{Amount of inflammatory mediators released into the medium from fibroblasts treated with tested extracts and IL}-1}{\text{Amount of inflammatory mediators released into the medium from fibroblasts treated with solvent for dissolving tested extracts and IL}-1\text{ (Negative Control)}} x\ 100\%$$

3.3.3 LC-MS profiling of 12 variation formulae of the HHCF

Decoctions prepared from the twelve variations formulae (Table 3.1) were profiled by LC-MS using the same method that was used to profile the HHCF decoction (section 2.3.2).

3.3.4 Chemometrics

The chemical compounds characterized in the HHCF in both positive (Table 2.3) and negative ionization mode (Table 2.4) were monitored by extracting their abundance in the twelve variation formulae and these value of abundance were regarded as independent variables. (Table 3.3a) The value of abundance in Table 3.3a were mean-centered and scaled as shown in Table 3.3b. The levels of CCL17 produced by HaCaT after treatment with the HCCF and its twelve variation formulae at a concentration of 30 μg/ml were regarded as dependent variables. A lower absolute value of CCL17 levels represents a higher inhibition effect, thus, a reciprocal was applied to the obtained data. These data were then centered and scaled as shown in Table 3.4.

The preprocessed data were imported to the Unscrambler ® v 10.4.1(trial version-CAMO Software AS, Oslo, Norway) for carrying out partial least-squares regression (PLS-R) and principal component regression (PC-R) analysis. Cross-validation was carried out to find out the optimal number of latent variables for PLS-R and PC-R based on the root-mean-square error of cross-validation (RMSECV) value.

3.3.5 Determination of hyaluronidase inhibition

Hyaluronidase activity was determined according to turbidimetric methods described by Yingprasetchai S (Yingprasertchai et al., 2003) with slight modification for carrying out the assay in microplate format. The assay was based on measuring the amount of turbidity [i.e. insoluble complexes] developed after the addition of cetyltrimethylammonium bromide (CTAB) to the remaining substrates [i.e. hyaluronic acid (acid mucopolysaccharides)] after incubation with hyaluronidase; since the amount

of turbidity developed was found to be proportional to the amount of acid mucopolysacchrides in the systems by Di Ferrante (Di Ferrante, 1956).

In this experiment, *Gloydius blomhoffi brevicaudus* venom was used as the source of hyaluronidase. Before the inhibition assay, reaction progress curve (Fig. 3.10) was developed by mixing different concentration of venom [i.e. enzyme source] with one hyaluronic acid [i.e. substrate] concentration and measured the amount of remaining hyaluronic acid at various times after enzymatic reaction. This is to determine the initial velocity region of the enzymatic reaction and the follow on inhibition assay was conducted within this linear range, with a reaction time that less than 50% of the hyaluronic acid has been degraded by enzyme.

Once the initial velocity condition has been established, the hyaluronic acid concentration was varied to generate a saturation curve for the determination of Michaelis constant (Km) and maximum velocity (Vmax) value at initial velocity conditions. (Fig. 3.11) According to Michaelis-Menten kinetic model, Km=[substrate concentration] at Vmax/2. Substrate concentration for the inhibition test has to be around or below the Km so as to identified competitive inhibitors (Brooks et al., 2004).

In the inhibition assay, acetate buffer [i.e. 0.2 M sodium acetate-acetic acid, pH 5.0, containing 0.15 M NaCl] was the solvent used to dissolve all the components in the reaction mixtures [i.e. venom, tested extracts and hyaluronic acid]. 25 µl acetate buffer containing 15 µg venom, 25 µl acetate buffer containing different amounts [i.e. 0, 1, 3, 5, 7 µg] of tested samples [i.e. HHCF, RHE, SCU, DIC, SOP, KOC and PHE] were added to each well of the 96 well plate and pre-incubated at 37°C for 15 minutes. Then 50µl acetate buffer containing 15 µg hyaluronic acid was added into each well to make up a reaction mixture with total volume of 100µl. 200µl of CTAB [i.e. 2.5% CTAB in 2% NaOH] was then added to each well after incubation at 37°C [i.e. enzymatic reaction; reaction time determined from the reaction progress curve] to stop the reaction. 10 minutes after the addition of CTAB, turbidity developed [i.e. indicates the amount of remaining hyaluronic acid in the reaction systems] was measured at absorbance of 400 nm. To remove background noise, procedures described above were repeated with the exclusion of incubation at 37°C [i.e. enzymatic reaction]. Assays were performed with three replicates in one experiment (n=1). To compare the amount of hyaluronic acid left in the reaction system in the presence and absence of tested extracts,

in another word, the hyaluronidase inhibitory percentage of the tested samples, equation shown in Table 3.2 was used.

Table 3.2 Determination of the percentage of hyaluronidase inhibition.		
Reaction mixture 1b: (Absorbance at 400nm measured before enzymatic reaction; without incubation at 37°C) ✕ extract (replace with buffer) ✓ hyaluronidase ✓ hyaluronic acid	**Reaction mixture 1a: (Absorbance at 400 nm Measured after enzymatic reaction; with incubation at 37°C)** ✕ extract (replace with buffer) ✓ hyaluronidase ✓ hyaluronic acid	**Absorbance$_{1b-1a}$:** The amount of hyaluronic acid presence in the system after enzymatic reaction in the absence of the tested extract.
Reaction mixture 2b: (Absorbance at 400 nm measured before enzymatic reaction; without incubation at 37°C) ✓ extract ✓ hyaluronidase ✓ hyaluronic acid	**Reaction mixture 2a: (Absorbance at 400 nm measured after enzymatic reaction; with incubation at 37°C)** ✓ extract ✓ hyaluronidase ✓ hyaluronic acid	**Absorbance$_{2b-2a}$:** The amount of hyaluronic acid presence in the system after enzymatic reaction in the presence of the tested extract.
Inhibition (%) = [(Absorbance$_{1b-1a}$)- Absorbance$_{2b-2a}$]/ (Absorbance$_{1b-1a}$)] x 100		

3.3.6 Determination of bacterial growth inhibition

Two Gram-negative bacterial strains (*Escherichia coli* ATCC 1229 and *Pseudomonas aeruginosa* ATCC9027) and two Gram-positive bacterial strains (*Bacillus subtilis* ATCC6633, *Staphylococcus aureus* ATCC 6538) were used in the anti-bacterial assy. All bacteria were growth in sterile Mueller-Hinton nutrient broth for 24 hrs. The bacterial concentration was first adjusted to of 2 x 10^8 CFU/ml (Mcfarland Standard no. 0.67). At optical density (OD) of 600 nm, the absorbance measured for 67 µl 1% barium chloride and 9.933 ml 1% sulfuric acid was 0.236. Thus, absorbance of 0.236 at OD=600nm indicates the presence of 2 x 10^8 CFU/ml bacteria.

The anti-bacterial assays were carried out in 96-well microtiter plates using the microdilution method. Each well consists of 100 µl tested extract and 100 µl bacterial solution. Wells consist of 200 µl nutrient broth were used as sterile control. Wells consist of 100 µl nutrient broth and 100 µl bacterial solution were used as growth control (negative control). Streptomycin (S) was used as the positive control. Each

experiment was run in triplicate. Bacterial growth was determined by measuring the turbidity of solution in each well at optical density of 600 nm using a microplate reader before and after incubation at 37 °C.

The prepared 2 x 10^8 CFU/ml inoculum was diluted 100 times to 2 x 10^6 CFU/ml, followed by two-fold dilution to 1 x 10^6 CFU/ml once dispensed into the 96-well sterile microtitre plates during the assay. The concentrations of the HHCF decoction tested were 4, 2, 1, 0.5, 0.25, 0.125 and 0.0625 mg/ml. The concentrations of Streptomycin tested were 25, 12.5, 6.25, 3.12, 1.56, 0.78 and 0.39 μg/ml.

Minimum inhibitory concentration (MIC) was determined as the lowest concentration of the tested extracts capable of inhibiting the growth of bacteria. Percentage of bacterial growth inhibition was calculated by the following equation:

$$\frac{Bacterial\ growth\ in\ the\ absence\ of\ extract - Bacterial\ growth\ in\ the\ presence\ of\ extract}{Bacterial\ growth\ in\ the\ abasence\ of\ extract}\ x\ 100\%$$

3.4 RESULTS AND DISCUSSION

3.4.1 Effects of the HHCF decoction and its twelve variation formulae against TNF-α plus IFN-□- induced CCL17 production in HaCaT

CCL17 were demonstrated to be linked to the pathogenesis of atopic dermatitis (Table 1.3) and the HHCF has demonstrated the ability to inhibit the production of CCL17 in HaCaT stimulated with TNF-α plus IFN-□ (Fig. 3.1). To investigate which compounds in the LC-MS profile of the HHCF were most likely to be the contributors to the observed CCL17 inhibition, decoctions of twelve variation formulae [i.e. V1-V12; Table 3.1] of the HHCF were profiled by LC-MS [using the same method that was used to profile the HHCF decoction] and their effects against CCL17 production in HaCaT were also investigated. Contributors to the observed CCL17 inhibition were then predicted by correlating the abundance of chemical compounds in the LC-MS profiles of the HHCF and its twelve variation formulae (Table 3.3b) to their effects on CCL17 levels in HaCaT (Table 3.4) using multivariate regression analysis [i.e. PLS-R and PC-R]. The HHCF decoction and its twelve variation formulae showed different degree of CCL17 inhibition in the HaCaT (Fig. 3.1). Results from the MTT assay demonstrated that the decreased in CCL17 levels was not due to a toxic effect (Fig. 3.2) of the

samples to the cells. HHCF and all its variation formulae [i.e. V1-V12] were able to inhibit the production of CCL17 in HaCaT stimulated with TNF-α plus IFN-□ in a dose-dependent manner. Among them, formulae consisting of higher concentration of RHE e.g. V3, V6, V9 and V12 tend to provide better inhibition.

Table 3.3a Abundance of 68 putatively identified compounds in the LC-MS profile of the HHCF and its twelve variation formulae.
V1-V12 represented the twelve variation formulae. P1-P31 and N1-N37 represent compounds putatively identified in the HHCF LC-MS profile obtained under positive and negative ionization mode, respectively. The putatively assigned identity of P1-P31 and N1-N37 compounds can be found in Table 2.3 and 2.4, respectively.

	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16
HHCF	89035	216562	442439	53048	101265	126641	641651	3107457	81570	462085	127402	394883	83105	4457229	1379597	1991381
V1	0	0	23199	0	0	702504	702504	118044	26131	702504	66351	0	0	41775	16436	41775
V2	0	99125	551437	41681	173278	233999	762820	1860732	132113	722600	143700	799841	0	0	1981552	3583919
V3	64590	63805	398781	11580	65846	83922	59147	346962	35224	56576	192564	168799	0	0	1115048	2256584
V4	80216	6063	873061	43130	91286	572655	895249	0	210624	2053826	39368	505680	0	0	2252029	3475230
V5	91490	157505	400609	44609	157830	183144	571302	2539223	76131	427386	108718	386882	62550	0	2426695	3266521
V6	0	0	267160	0	117999	89139	358802	855832	31759	220610	24133	139511	0	0	1344707	1960926
V7	116464	251495	573288	0	237504	133985	548453	3725700	104624	334902	178606	0	0	0	2580601	2972611
V8	0	0	199609	0	90893	58577	439297	2730339	56616	283072	126653	0	163539	5089906	1886782	2435333
V9	48790	46534	189459	73119	93908	59457	196029	427329	19656	97984	12181	0	0	0	1206832	1367978
V10	0	503470	258338	42402	119668	83362	398161	3753405	67424	216748	89297	0	0	4085939	2153013	2696451
V11	0	298310	136199	54157	68699	36190	177370	2888926	23274	99047	76538	0	0	0	1043613	1132962
V12	0	102963	42599	81177	0	11739	68806	1286749	0	7419	10857	0	48925	675806	141068	158252
	P17	**P18**	**P19**	**P20**	**P21**	**P22**	**P23**	**P24**	**P25**	**P26**	**P27**	**P28**	**P29**	**P30**	**P31**	**N1**
HHCF	196110	3171403	512407	147453	23326	97353	1093183	85942	207336	1617996	116437	660146	750636	67973	12607	14626
V1	0	16742	2982	16436	0	0	16742	0	0	0	0	0	0	0	0	0
V2	529478	0	903957	152298	37707	175807	2065866	0	146116	1442663	58172	0	0	37032	16700	11438
V3	1100105	2912264	414837	73096	28065	27380	157744	0	24778	74807	26183	35953	26138	27943	3647	0
V4	1632570	4707932	751748	247514	22505	34573	146637	3558	0	5094077	7716	31187	178367	0	15614	0
V5	1417220	3652967	564069	108847	17801	101215	1127558	0	90819	1484447	83791	0	591471	88034	13959	0
V6	2027950	40681	4545	23873	13869	13869	139049	0	4367	291243	13717	65968	123929	5760	21907	0
V7	353606	0	758069	172037	17408	121986	1336477	98283	446806	2545795	474120	4534144	3601626	1159293	0	0
V8	180737	4449471	646673	123313	9963	55127	756259	0	176718	2286957	142841	1244420	1700751	205506	20302	0
V9	1086294	24802	0	36110	0	19267	341392	62139	13550	352302	12949	87565	98250	4510	16570	0
V10	172644	4623822	678060	82792	9484	70254	928720	111221	934997	2868199	820301	0	3402574	918678	0	0
V11	653153	15316	2012	13952	4212	4212	38977	0	152524	2005715	150791	979958	1198467	114376	16370	0
V12	133011	4832	0	4429	0	0	20410	7431	0	360066	25646	131451	227903	25808	23148	0

Table 3.3a Abundance of 68 putatively identified compounds in the LC-MS profile of the HHCF and its twelve variation formulae.
V1-V12 represented the twelve variation formulae. P1-P31 and N1-N37 represent compounds putatively identified in the HHCF LC-MS profile obtained under positive and negative ionization mode, respectively. The putatively assigned identity of P1-P31 and N1-N37 compounds can be found in Table 2.3 and 2.4, respectively.

	N2	N3	N4	N5	N6	N7	N8	N9	N10	N11	N12	N13	N14	N15	N16	N17
HHCF	35138	7964	37172	28289	64187	39018	14147	52216	23918	843196	14754	189793	20057	32138	12317	11088
V1	0	0	1530	1501	0	0	0	0	0	0	0	0	0	0	0	0
V2	25628	0	34711	0	69694	34036	0	29283	23633	0	0	192383	8507	12010	10062	1508
V3	85915	30875	36865	16676	145099	0	0	11445	5255	6724	0	8006	3676	7557	691	227
V4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
V5	0	7663	34488	0	45915	45915	0	37285	0	840771	0	181990	13851	0	9346	11925
V6	0	8567	14436	66449	125351	72827	0	100799	42486	0	0	280578	5299	7838	24560	5744
V7	66788	8109	52254	0	10234	10234	1849	4789	10234	0	1176	109041	11183	41724	1992	2051
V8	40091	7714	15547	0	0	0	0	61434	0	317272	17720	0	0	0	16202	695
V9	0	4135	15453	0	100325	49794	10503	44525	23040	257840	0	269798	4846	7430	15070	0
V10	60402	0	30930	0	0	0	469	595	0	408482	0	13163	51594	39171	0	0
V11	0	0	37137	0	83888	31833	0	61514	25360	40617	0	161053	15580	24174	11201	0
V12	30720	6318	15820	83032	0	97560	16265	86752	0	18864	32838	215901	6398	10745	28581	2766
	N18	**N19**	**N20**	**N21**	**N22**	**N23**	**N24**	**N25**	**N26**	**N27**	**N28**	**N29**	**N30**	**N31**	**N32**	**N33**
HHCF	28905	8295	17350	14677	54346	23139	42603	6703	20179	171391	5704	27438	28492	89055	27155	28609
V1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
V2	28081	0	0	13321	35576	5668	14609	0	11269	82146	2533	14574	18251	55431	15736	14969
V3	8439	0	4199	12886	2853	0	2528	0	1085	12664	1312	1093	58053	58053	0	88303
V4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
V5	0	0	36583	0	36430	12964	5900	0	41427	135192	4473	35527	18984	45403	39802	0
V6	31678	0	3586	7130	49461	14739	0	0	11770	169450	0	18770	38453	77926	19929	29118
V7	0	0	0	114614	9895	5689	898	2637	0	62795	2449	18195	0	0	14812	5925
V8	0	0	0	0	30610	7375	26760	0	3737	179358	5979	0	14354	101333	0	22213
V9	28198	0	0	5435	34609	0	0	0	39761	156179	4754	39241	26853	98361	41517	0
V10	0	0	0	171348	9810	0	0	0	0	22572	0	40467	0	0	31635	0
V11	30692	0	12395	69628	16398	0	7384	0	18833	86343	2694	16738	28172	73003	22219	19640
V12	0	0	2012	12692	65508	21346	12219	0	0	154538	0	8228	54424	90299	0	0

Table 3.3a Abundance of 68 putatively identified compounds in the LC-MS profile of the HHCF and its twelve variation formulae.
V1-V12 represented the twelve variation formulae. P1-P31 and N1-N37 represent compounds putatively identified in the HHCF LC-MS profile obtained under positive and negative ionization mode, respectively. The putatively assigned identity of P1-P31 and N1-N37 compounds can be found in Table 2.3 and 2.4, respectively.

	N34	N35	N36	N37
HHCF	26925	41691	7390	69203
V1	0	0	0	0
V2	64009	0	24270	0
V3	0	0	0	0
V4	0	0	0	0
V5	14505	25189	16292	78503
V6	0	0	37845	40539
V7	7063	6786	3424	25123
V8	16633	45962	0	0
V9	0	30169	0	0
V10	12305	3275	0	102370
V11	0	0	10743	48133
V12	0	0	12606	19078

Table 3.3b Mean-centered and scaled abundance of 68 putatively identified compounds in the LC-MS profile of the HHCF and its twelve variation formulae.
V1-V12 represented the twelve variation formulae. P1-P31 and N1-N37 represent compounds putatively identified in the HHCF LC-MS profile obtained under positive and negative ionization mode, respectively. The putatively assigned identity of P1-P31 and N1-N37 compounds can be found in Table 2.3 and 2.4, respectively.

	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16
HHCF	1.1391	0.5488	0.4492	0.6529	-0.0020	-0.2643	0.7209	0.9300	0.2626	0.0462	0.5825	0.8118	1.1094	1.6929	-0.1508	-0.0961
V1	-0.8380	-0.8958	-1.3051	-1.1869	-1.5607	2.4501	0.9470	-1.2269	-0.7067	0.4943	-0.4228	-0.7103	-0.5501	-0.5362	-1.8278	-1.7732
V2	-0.8380	-0.2346	0.9053	0.2586	1.1064	0.2417	1.1712	0.0305	1.1464	0.5317	0.8509	2.3729	-0.5501	-0.5573	0.5898	1.2738
V3	0.5963	-0.4702	0.2665	-0.7853	-0.5472	-0.4657	-1.4438	-1.0618	-0.5477	-0.7095	1.6555	-0.0597	-0.5501	-0.5573	-0.4762	0.1321
V4	0.9433	-0.8554	2.2512	0.3089	-0.1556	1.8381	1.6633	-1.3121	2.5192	3.0128	-0.8671	1.2389	-0.5501	-0.5573	0.9225	1.1803
V5	1.1936	0.1548	0.2742	0.3602	0.8686	0.0020	0.4595	0.5200	0.1675	-0.0185	0.2748	0.7810	0.6990	-0.5573	1.1374	1.0008
V6	-0.8380	-0.8958	-0.2843	-1.1869	0.2555	-0.4411	-0.3302	-0.6946	-0.6083	-0.4038	-1.1180	-0.1726	-0.5501	-0.5573	-0.1937	-0.1223
V7	1.7482	0.7818	0.9968	-1.1869	2.0950	-0.2297	0.3746	1.3761	0.6658	-0.1908	1.4256	-0.7103	-0.5501	-0.5573	1.3268	0.7480
V8	-0.8380	-0.8958	-0.5669	-1.1869	-0.1617	-0.5852	-0.0311	0.6579	-0.1737	-0.2874	0.5702	-0.7103	2.7157	2.0123	0.4732	0.2858
V9	0.2454	-0.5854	-0.6094	1.3490	-0.1153	-0.5810	-0.9351	-1.0038	-0.8200	-0.6324	-1.3148	-0.7103	-0.5501	-0.5573	-0.3633	-0.6323
V10	-0.8380	2.4627	-0.3212	0.2837	0.2812	-0.4683	-0.1839	1.3961	0.0153	-0.4110	-0.0450	-0.7103	-0.5501	1.5054	0.8007	0.5104
V11	-0.8380	1.0941	-0.8323	0.6913	-0.5033	-0.6907	-1.0044	0.7723	-0.7567	-0.6304	-0.2551	-0.7103	-0.5501	-0.5573	-0.5641	-0.8345
V12	-0.8380	-0.2090	-1.2240	1.6284	-1.5607	-0.8059	-1.4079	-0.3837	-1.1637	-0.8012	-1.3366	-0.7103	0.4269	-0.2161	-1.6745	-1.6730
	P17	**P18**	**P19**	**P20**	**P21**	**P22**	**P23**	**P24**	**P25**	**P26**	**P27**	**P28**	**P29**	**P30**	**P31**	**N1**
HHCF	-0.8094	0.6487	0.3119	0.7400	0.7764	0.7646	0.7196	1.3185	0.1455	0.0324	-0.1355	0.0497	-0.1309	-0.3603	0.0277	2.5564
V1	-1.1071	-0.8622	-1.1406	-1.0234	-1.2037	-1.0124	-0.9470	-0.6491	-0.6428	-1.0870	-0.6249	-0.4764	-0.7273	-0.5400	-1.4523	-0.4061
V2	-0.3035	-0.8702	1.4282	0.8052	1.9971	2.1966	2.2256	-0.6491	-0.0873	-0.0889	-0.3804	-0.4764	-0.7273	-0.4421	0.5082	1.9107
V3	0.5625	0.5246	0.0337	-0.2608	1.1787	-0.5126	-0.7287	-0.6491	-0.5486	-1.0352	-0.5148	-0.4478	-0.7066	-0.4661	-1.0242	-0.4061
V4	1.3706	1.3846	0.9943	2.0868	0.7067	-0.3813	-0.7459	-0.5676	-0.6428	2.4374	-0.5924	-0.4516	-0.5856	-0.5400	0.3807	-0.4061
V5	1.0438	0.8794	0.4592	0.2204	0.3074	0.8351	0.7728	-0.6491	-0.2975	-0.0600	-0.2727	-0.4764	-0.2574	-0.3072	0.1864	-0.4061
V6	1.9707	-0.8507	-1.1362	-0.9233	-0.0264	-0.7592	-0.7576	-0.6491	-0.6262	-0.8855	-0.5672	-0.4239	-0.6289	-0.5248	1.1195	-0.4061
V7	-0.5704	-0.8702	1.0123	1.0709	0.2740	1.2142	1.0963	1.6010	1.0559	0.6744	1.3680	3.1374	2.1344	2.5254	-1.4523	-0.4061
V8	-0.8328	1.2609	0.6947	0.4151	-0.3580	-0.0062	0.1980	-0.6491	0.0290	0.4953	-0.0245	0.5154	0.6240	0.0034	0.9311	-0.4061
V9	0.5416	-0.8583	-1.1491	-0.7586	-1.2037	-0.6607	-0.4443	0.7735	-0.5913	-0.8432	-0.5705	-0.4066	-0.6493	-0.5281	0.4929	-0.4061
V10	-0.8450	1.3444	0.7842	-0.1303	-0.3986	0.2699	0.4650	1.8972	2.9121	0.8974	2.8230	-0.4764	1.9762	1.8892	-1.4523	-0.4061
V11	-0.1158	-0.8629	-1.1434	-1.0569	-0.8462	-0.9355	-0.9126	-0.6491	-0.0629	0.3007	0.0089	0.3046	0.2249	-0.2376	0.4695	-0.4061
V12	-0.9052	-0.8679	-1.1491	-1.1850	-1.2037	-1.0124	-0.9413	-0.4790	-0.6428	-0.8379	-0.5171	-0.3717	-0.5463	-0.4718	1.2652	-0.4061

Table 3.3b Mean-centered and scaled abundance of 68 putatively identified compounds in the LC-MS profile of the HHCF and its twelve variation formulae.
V1-V12 represented the twelve variation formulae. P1-P31 and N1-N37 represent compounds putatively identified in the HHCF LC-MS profile obtained under positive and negative ionization mode, respectively. The putatively assigned identity of P1-P31 and N1-N37 compounds can be found in Table 2.3 and 2.4, respectively.

	N2	N3	N4	N5	N6	N7	N8	N9	N10	N11	N12	N13	N14	N15	N16	N17
HHCF	0.2875	0.2062	0.7697	0.4713	0.2780	0.3062	1.7976	0.4262	0.8506	2.0191	0.9365	0.6021	0.6693	1.1929	0.2441	1.9740
V1	-0.8840	-0.7560	-1.5033	-0.4840	-0.9444	-0.9262	-0.5524	-1.1114	-0.8339	-0.6709	-0.4969	-1.1547	-0.7880	-0.9278	-1.0545	-0.6572
V2	-0.0295	-0.7560	0.6127	-0.5375	0.3828	0.1488	-0.5524	-0.2491	0.8305	-0.6709	-0.4969	0.6261	-0.1699	-0.1353	0.0064	-0.2994
V3	1.9806	2.9743	0.7501	0.0572	1.8188	-0.9262	-0.5524	-0.7744	-0.4638	-0.6494	-0.4969	-1.0806	-0.5209	-0.4292	-0.9817	-0.6034
V4	-0.8840	-0.7560	-1.6009	-0.5375	-0.9444	-0.9262	-0.5524	-1.1114	-0.8339	-0.6709	-0.4969	-1.1547	-0.7880	-0.9278	-1.0545	-0.6572
V5	-0.8840	0.1698	0.5985	-0.5375	-0.0700	0.5240	-0.5524	-0.0134	-0.8339	2.0114	-0.4969	0.5299	0.2184	-0.9278	-0.0691	2.1726
V6	-0.8840	0.2791	-0.6803	1.8320	1.4428	1.3740	-0.5524	1.8569	2.1583	-0.6709	-0.4969	1.4425	-0.4030	-0.4106	1.5350	0.7059
V7	1.3428	0.2237	1.7315	-0.5375	-0.7495	-0.6030	-0.2453	-0.9704	-0.1131	-0.6709	-0.3826	-0.1454	0.0245	1.8254	-0.8445	-0.1705
V8	0.4527	0.1760	-0.6094	-0.5375	-0.9444	-0.9262	-0.5524	0.6977	-0.8339	0.3413	1.2247	-1.1547	-0.7880	-0.9278	0.6537	-0.4923
V9	-0.8840	-0.2564	-0.6154	-0.5375	0.9662	0.6465	1.1923	0.1998	0.7887	0.1517	-0.4969	1.3427	-0.4359	-0.4375	0.5344	-0.6572
V10	1.1299	-0.7560	0.3716	-0.5375	-0.9444	-0.9262	-0.4745	-1.0939	-0.8339	0.6323	-0.4969	-1.0329	2.9607	1.6570	-1.0545	-0.6572
V11	-0.8840	-0.7560	0.7674	-0.5375	0.6531	0.0792	-0.5524	0.7001	0.9521	-0.5413	-0.4969	0.3361	0.3440	0.6674	0.1265	-0.6572
V12	0.1402	0.0073	-0.5920	2.4234	-0.9444	2.1552	2.1495	1.4433	-0.8339	-0.6107	2.6934	0.8438	-0.3231	-0.2188	1.9589	-0.0008
	N18	**N19**	**N20**	**N21**	**N22**	**N23**	**N24**	**N25**	**N26**	**N27**	**N28**	**N29**	**N30**	**N31**	**N32**	**N33**
HHCF	1.1565	3.3282	1.0712	-0.3315	1.2733	1.9078	2.6208	3.0845	0.5911	1.0944	1.4796	0.6990	0.3264	0.8963	0.6914	0.5106
V1	-0.8209	-0.2774	-0.5457	-0.6053	-1.2186	-0.8265	-0.6711	-0.3703	-0.7659	-1.3551	-0.9996	-1.1285	-1.1067	-1.3168	-1.0493	-0.6534
V2	1.1002	-0.2774	-0.5457	-0.3568	0.4126	-0.1567	0.4578	-0.3703	-0.0081	-0.1811	0.1013	-0.1578	-0.1887	0.0607	-0.0406	-0.0444
V3	-0.2436	-0.2774	-0.1544	-0.3649	-1.0878	-0.8265	-0.4757	-0.3703	-0.6930	-1.1741	-0.4293	-1.0557	1.8133	0.1258	-1.0493	2.9393
V4	-0.8209	-0.2774	-0.5457	-0.6053	-1.2186	-0.8265	-0.6711	-0.3703	-0.7659	-1.3551	-0.9996	-1.1285	-1.1067	-1.3168	-1.0493	-0.6534
V5	-0.8209	-0.2774	2.8635	-0.6053	0.4518	0.7055	-0.2152	-0.3703	2.0200	0.5770	0.9445	1.2377	-0.1518	-0.1885	1.5021	-0.6534
V6	1.3462	-0.2774	-0.2115	-0.4723	1.0493	0.9152	-0.6711	-0.3703	0.0256	1.0666	-0.9996	0.1216	0.8274	0.6197	0.2282	0.5313
V7	-0.8209	-0.2774	-0.5457	1.5333	-0.7649	-0.1542	-0.6017	0.9888	-0.7659	-0.4577	0.0648	0.0833	-1.1067	-1.3168	-0.0998	-0.4123
V8	-0.8209	-0.2774	-0.5457	-0.6053	0.1849	0.0450	1.3967	-0.3703	-0.5146	1.2082	1.5991	-1.1285	-0.3847	1.2014	-1.0493	0.2504
V9	1.1082	-0.2774	-0.5457	-0.5039	0.3683	-0.8265	-0.6711	-0.3703	1.9080	0.8770	1.0667	1.4851	0.2440	1.1275	1.6120	-0.6534
V10	-0.8209	-0.2774	-0.5457	2.5920	-0.7688	-0.8265	-0.6711	-0.3703	-0.7659	-1.0325	-0.9996	1.5667	-1.1067	-1.3168	0.9785	-0.6534
V11	1.2788	-0.2774	0.6094	0.6939	-0.4667	-0.8265	-0.1005	-0.3703	0.5006	-0.1211	0.1713	-0.0137	0.3103	0.4973	0.3750	0.1457
V12	-0.8209	-0.2774	-0.3582	-0.3685	1.7851	1.6960	0.2731	-0.3703	-0.7659	0.8535	-0.9996	-0.5805	1.6307	0.9272	-1.0493	-0.6534

Table 3.3b Mean-centered and scaled abundance of 68 putatively identified compounds in the LC-MS profile of the HHCF and its twelve variation formulae.
V1-V12 represented the twelve variation formulae. P1-P31 and N1-N37 represent compounds putatively identified in the HHCF LC-MS profile obtained under positive and negative ionization mode, respectively. The putatively assigned identity of P1-P31 and N1-N37 compounds can be found in Table 2.3 and 2.4, respectively.

	N34	N35	N36	N37
HHCF	0.8820	1.7154	-0.1082	1.1202
V1	-0.5980	-0.6752	-0.7379	-0.8303
V2	2.9204	-0.6752	1.3302	-0.8303
V3	-0.5980	-0.6752	-0.7379	-0.8303
V4	-0.5980	-0.6752	-0.7379	-0.8303
V5	0.1993	0.7692	0.6504	1.3823
V6	-0.5980	-0.6752	2.4870	0.3123
V7	-0.2098	-0.2861	-0.4461	-0.1222
V8	0.3162	1.9603	-0.7379	-0.8303
V9	-0.5980	1.0547	-0.7379	-0.8303
V10	0.0783	-0.4874	-0.7379	2.0550
V11	-0.5980	-0.6752	0.1776	0.5264
V12	-0.5980	-0.6752	0.3363	-0.2925

Table 3.4 The levels of CCL17 produced by TNF-α plus IFN-□-stimulated HaCaT after treatment with the HHCF and its twelve variation formulae decoctions at a concentration of 60 μg/ml.			
	Raw data [CCL17 levels (% of control)]	**Reciprocal of raw data**	**Mean-centered and scaled data**
HHCF	58.602	1.706	-0.796
V1	71.857	1.392	-0.982
V2	50.617	1.976	-0.637
V3	30.587	3.269	0.128
V4	61.641	1.622	-0.846
V5	46.571	2.147	-0.536
V6	20.562	4.863	1.070
V7	63.006	1.587	-0.867
V8	24.785	4.035	0.580
V9	19.365	5.164	1.248
V10	56.446	1.772	-0.758
V11	32.249	3.101	0.028
V12	14.165	7.060	2.369

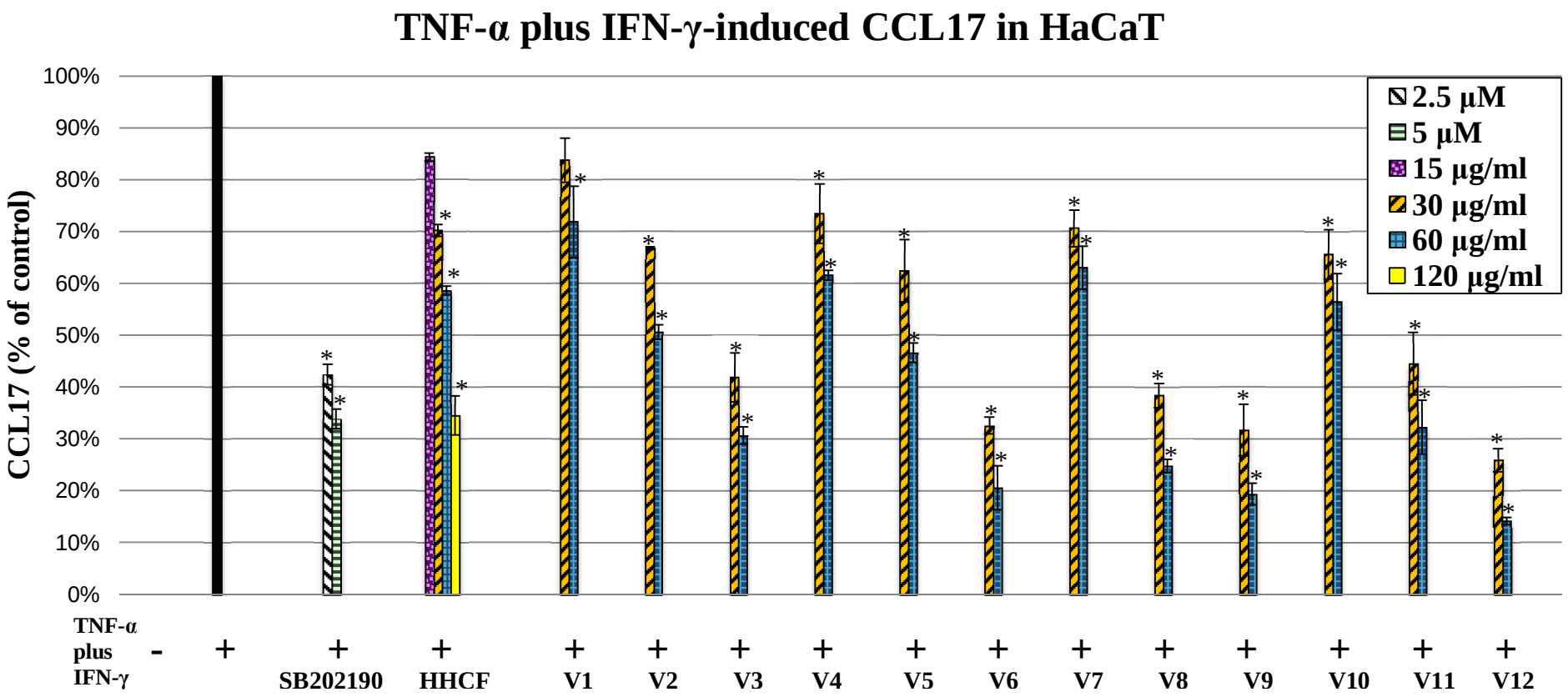


Fig. 3.1 Effect of the HHCF (15, 30, 60 and 120 µg/ml) and its twelve variation formulae (V1-V12; 30 and 60 µg/ml), SB202190 monohydrochloride hydrate (positive control; 2.5 and 5 µM) on TNF-α plus IFN-γ-induced CCL17 production in HaCaT. Data are represented as mean ± standard error of three independent experiments (n=3). Statistical significance was determined using one-way analysis of variance with Dunnett's multiple comparisons test. * $p<0.05$ versus TNF-α plus IFN-γ treatment alone.

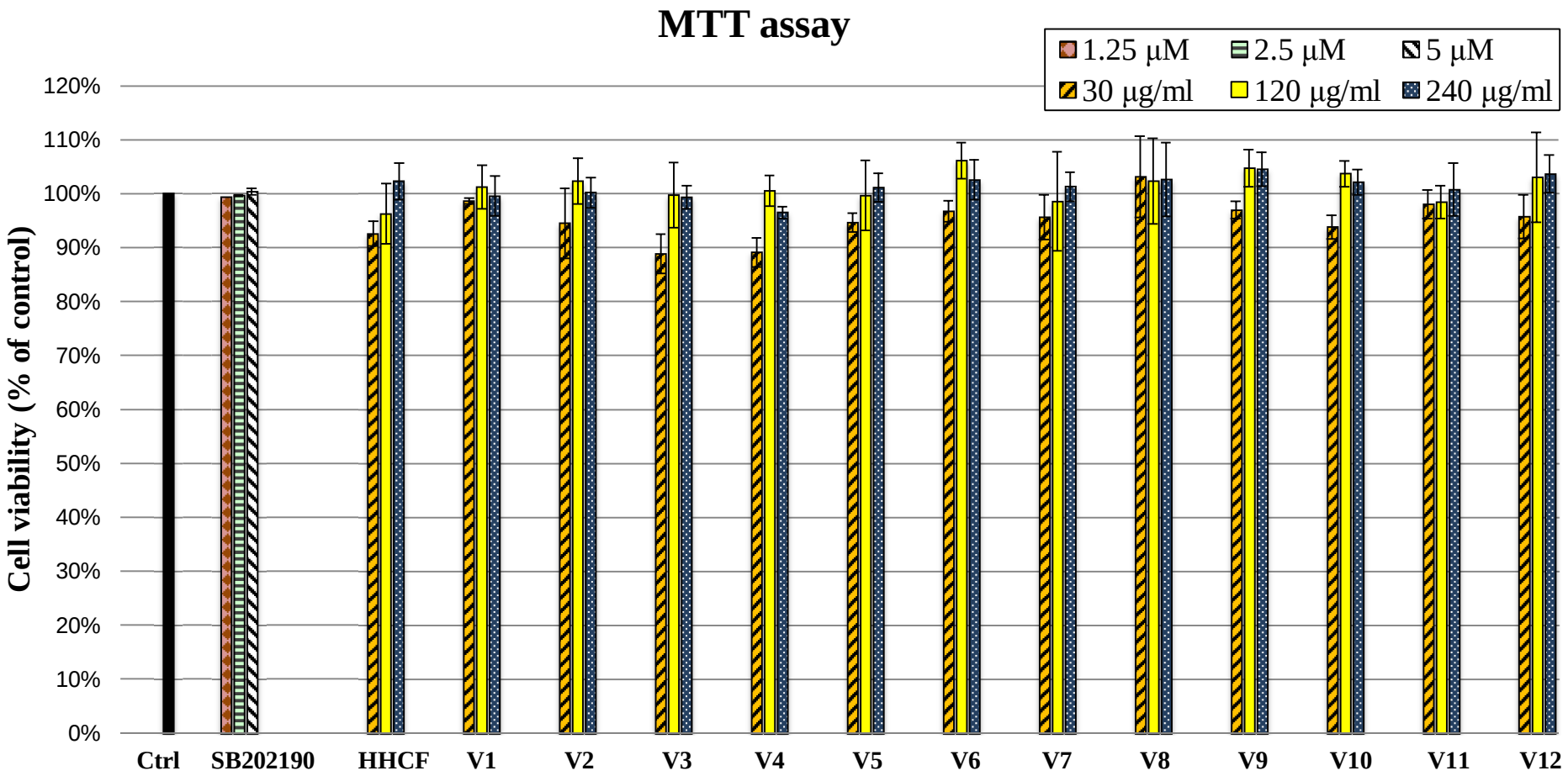
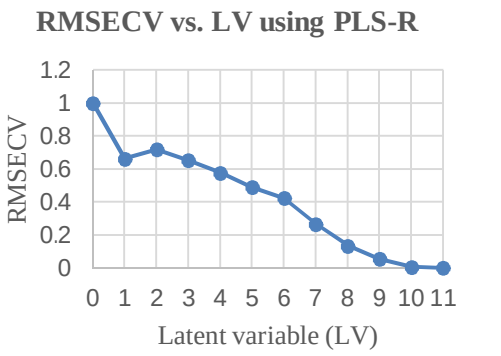


Fig. 3.2 Effect of the HHCF and its twelve variation formulae (V1-V12) (30, 120 and 240 µg/ml) and SB202190 monohydrochloride hydrate (1.25, 2.5 and 5 µM) on the viability of HaCaT. Data are represented as mean ± standard error of three independent experiments (n=3). Statistical significance was determined using one-way analysis of variance with Dunnett's multiple comparisons test. * $p<0.05$ versus control (Ctrl).

Twelve variation formulae of the HHCF (Table 3.1) were developed by uniform mixture design that seeks to spread the experimental points (amounts of the chemical compounds) uniformly over the design space and hence, facilitates the exploration of the relationship between the biological response and the chemical compounds with a reasonable number of runs (Fang and Lin, 2003). PLS-R and PCA-R analysis were used since 1) the number of dependent variables (response; Table 3.4) was less than the number of independent variables (also known as predictor variable; Table 3.3b) and 2) both methods use linear combinations of the independent variables and settle the multicollinearity problem among the variables (Miller and Miller, 2005). The number of latent variable for the PLS-R and PC-R analysis was selected based on the root-mean-square error of cross-validation (RMSECV) value (Fig. 3.3) and the percentage of variance explained by the PLS-R (Table 3.5) and PC-R (Table 3.6) model. The optimal number of latent variable selected for PLS-R and PC-R was 9.



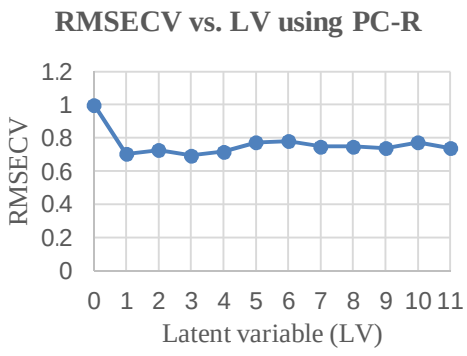


Fig. 3.3 Latent variables (LV) versus RMSECV for PCR and PLS.

For the optimal number of latent variable (LV) in the PLS-R and PC-R model, 88.19% and 92.68% of the variance was explained by the regressors, respecitvely. The 9 latent variables in the PLS-R model and PC-R model explained 100% and 89.05% of the variation, respectively.

Table 3.5 Percentage of variance explained by the PLS-R-model.				
	X Variables		Y Variables	
LV	This LV	Total	This LV	Total
1	23.97	23.97	79.69	79.69
2	9.69	33.66	14.54	94.23
3	9.76	43.42	0.58	98.89
4	13.34	56.76	0.41	99.48
5	8.46	65.22	0.08	99.89
6	6.81	72.04	0.03	99.96
7	4.22	76.26	0.00	99.99
8	5.76	82.01	0.00	100.00
9	**6.18**	**88.19**	**0.00**	**100.00**
10	3.98	92.17	0.00	100.00
11	3.89	96.06	0.00	100.00
12	3.94	100.00	0.00	100.00

Table 3.6 Percentage of variance explained by the PC-R-model.				
	X Variables		Y Variables	
LV	This LV	Total	This LV	Total
1	24.62	24.62	64.14	64.14
2	18.61	43.23	0.92	65.06
3	13.76	56.99	7.34	72.40
4	9.05	66.04	0.31	72.71
5	7.94	73.98	0.44	73.15
6	5.82	79.80	1.65	74.80
7	4.77	84.57	12.51	87.32
8	4.19	88.76	1.62	88.94
9	**3.92**	**92.68**	**0.11**	**89.05**
10	3.06	95.75	4.82	93.88
11	2.68	98.42	4.63	98.50
12	1.58	100	1.50	100

Table 3.7 shows the regression coefficient of independent variables calculated using PLS-R and PC-R analysis. The positive and negative value of the regression coefficient (RC) indicates a positive and negative contribution to the response [i.e. CCL17 inhibition], respectively. And a higher absolute value represents a larger contributing effect. The root mean square error of calibration (RMSEC) and root mean square error of cross validation (RMSECV) value in Table 3.8 were used to evaluate the performance of the model. The RMSEC indicates how well the model fits the data while the RMSECV describes the ability of the model to predict new samples (Yeniay and Goktas, 2002). The model developed by PLS-R analysis demonstrated a lower value of RMSEC and RMSECV that indicated a better fit of data and prediction power,

respectively. Both models generated similar regression coefficient for the independent variables (Fig. 3.4). The top five contributors in the HHCF toward the CCL17 inhibition in the PC-R and PLS-R model were P31 (berberine), N5 (galloylglucose), N9 (gallic acid), N12 (catechin dimers), N16 (4-(4'-hydroxylphenyl)-2-butanone 4'-O-β-D-glucoside) and P31 (berberine), N8 (pyrogallol), N12(catechin dimers), N16 (4-(4'-hydroxylphenyl)-2-butanone 4'-O-β-D-glucoside) and N31 (resveratrol 4'-O-β-D-(6''-O-galloyl) glucoside), respectively.

The multivariate regression models developed here only covered 68 chemical compounds that were putatively identified and present in high amounts in the HHCF decoction. Chemical compounds that were present in low amounts or cannot be detected by the LC-MS were not considered by the regression model. To improve the predictive efficiency of the model, metabolite profiles generated by other analytical methods can be processed and input into the model. Also, compounds present at relatively low amounts can also be considered. In addition, by correlating chemical profiles to more pathogenesis-related targets would give a better prediction on compounds that possess anti-inflammatory activities.

Inhibition of the production of CCL17 may suppress the infiltration of Th2 cells into the cutaneous site of inflammation (Table 1.3). This could explain as a possible underlying molecular mechanism by which the HHCF could support the treatment of AD or skin inflammation. The HHCF decoction did not demonstrate toxicity to HaCaT, however, its safety on primary skin cells requires further study. Multivariate regression models were developed to explain the relationship between the chemical compounds in the HHCF and the observed CCL17 inhibition in HaCaT. 68 chemical compounds were considered in the PC-R and PLS-R model. Among them, 24 and 31 chemical compounds were predicted to confer positive contribution to the CCL17 inhibition in the PC-R and PLS-R model, respectively. The accuracy of the predicted contributor should be validated using authentic compounds.

Table 3.7 Relevance [regression coefficient (RC)] between the chemical compounds putatively identified in the LC-MS profile of the HHCF decoction and CCL17 response. The top five contributors in the HHCF toward the CCL17 inhibition in the PC-R and PLS-R model were bolded and highlighted in yellow.

Ingredients	PC-RC	PLS-RC	Ingredients	PCR-RC	PLS-RC
P1	-0.029	-0.012	N1	-0.071	-0.068
P2	-0.024	-0.043	N2	0.009	0.058
P3	-0.027	0.000	N3	0.024	0.049
P4	-0.008	0.075	N4	-0.010	-0.039
P5	0.002	0.007	N5	**0.080**	0.075
P6	-0.073	-0.111	N6	-0.010	0.004
P7	-0.066	-0.104	N7	0.067	0.079
P8	0.009	-0.047	N8	0.010	**0.088**
P9	-0.036	-0.021	N9	**0.087**	0.053
P10	-0.044	-0.046	N10	-0.002	-0.027
P11	-0.035	-0.065	N11	-0.034	-0.043
P12	-0.050	-0.037	N12	**0.068**	**0.086**
P13	0.042	0.019	N13	0.033	0.051
P14	-0.003	0.005	N14	-0.027	-0.021
P15	0.005	0.021	N15	-0.021	-0.032
P16	-0.008	0.019	N16	**0.092**	**0.099**
P17	0.031	0.036	N17	-0.002	-0.065
P18	-0.011	0.007	N18	-0.029	-0.034
P19	-0.023	0.005	N19	-0.061	-0.084
P20	-0.029	-0.005	N20	-0.014	-0.100
P21	-0.036	-0.027	N21	-0.004	-0.007
P22	-0.034	-0.019	N22	0.058	0.076
P23	-0.032	-0.010	N23	0.048	0.014
P24	-0.034	0.029	N24	-0.016	-0.042
P25	-0.014	0.000	N25	-0.051	-0.079
P26	-0.006	-0.012	N26	-0.022	-0.004
P27	-0.002	0.007	N27	0.065	0.071
P28	0.028	-0.013	N28	-0.017	-0.006
P29	0.019	0.002	N29	-0.021	0.028
P30	0.013	0.015	N30	0.052	0.077
P31	**0.075**	**0.086**	N31	0.049	**0.080**
			N32	-0.030	-0.002
			N33	-0.003	-0.012
			N34	-0.043	-0.025
			N35	-0.006	0.022
			N36	0.048	-0.015
			N37	-0.009	-0.068

Table 3.8 RMSEC and RMSECV values for all prediction methods.		
	PLS-R	**PC-R**
RMSEC	0.0008	0.3309
RMSECV	0.0557	0.7401

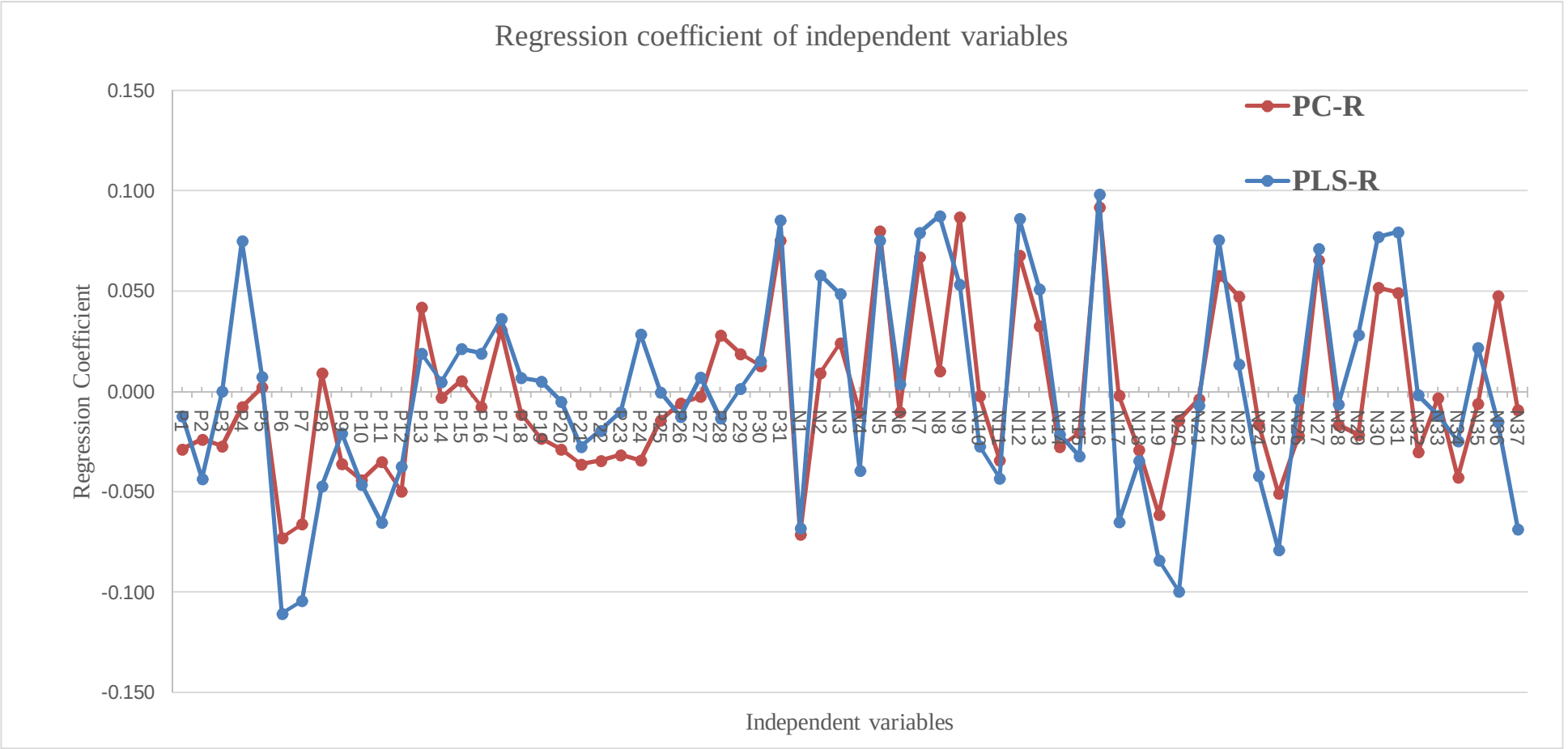
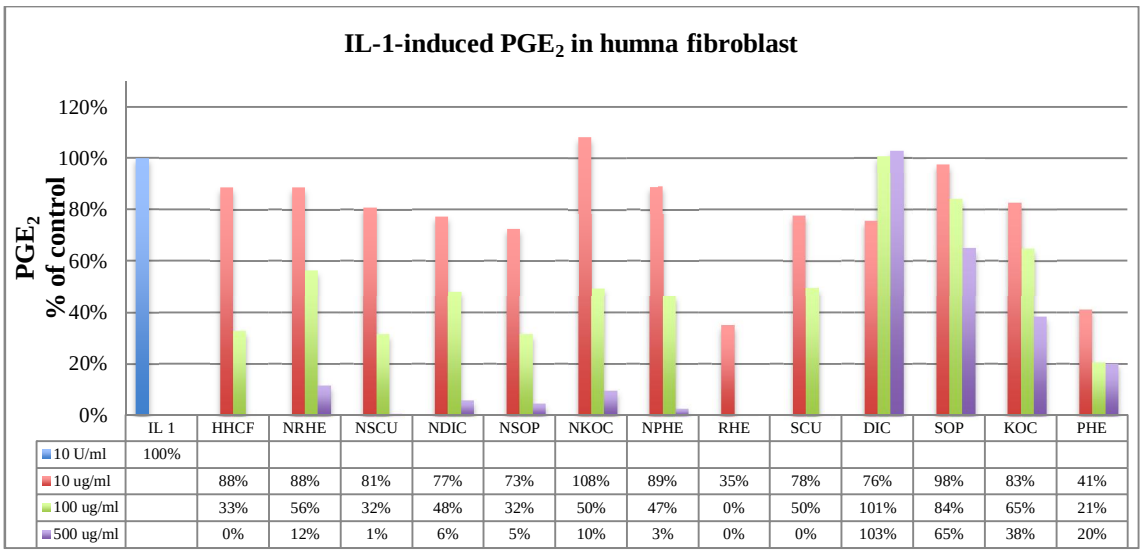


Fig. 3.4 Regression coefficient of independent variables in PC-R and PLS-R models.

3.4.2 Effects of the HHCF, single botanical drug and knock-one botanical drug-out HHCF against IL-1β- induced IL-6, IL-8 and PGE_2 production in human fibroblasts

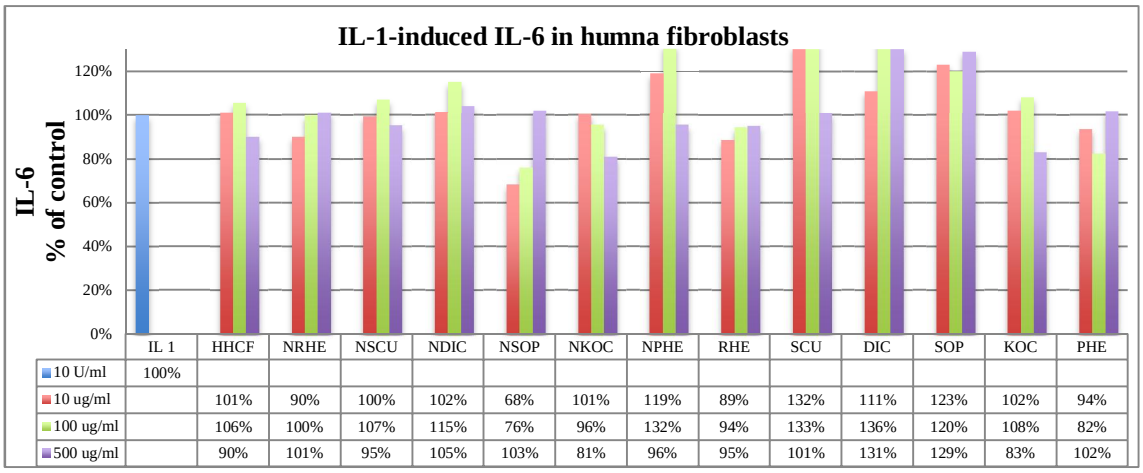
Decoctions of the HHCF, single botanical drug [i.e.RHE, SCU, DIC, SOP, KOC and PHE], knock-one botanical drug-out-HHCF [i.e. NRHE, NSCU, NDIC, NSOP, NKOC, NPHE] were examined for their effect on IL-1β-induced IL-6, IL-8 and PGE_2 production in cultured human fibroblasts. IL-6 maybe linked to the hyperproliferation and disregulated differentiation of keratinocytes in AD (Shiraishi et al., 2012, Masuoka et al., 2012, Taniguchi et al., 2014) and IL-8 are chemokine that recruit and activate neutrophils and lymphocytes to the site of cutaneous inflammation. (Boxman et al., 1996). PGE_2 regulate T helper (Th) cells differentiation and promote Th2 response *in vitro* (Betz and Fox, 1991, Hilkens et al., 1996, Harris et al., 2002, Fedyk and Phipps, 1996). Moreover, lesional skin of AD patients consists of elevated levels of PGE_2 when compared with uninvolved skin (Fogh et al., 1989).

All tested samples, except DIC decoction, caused a dose-dependent decrease of IL-1β-induced PGE_2 secretion in human fibroblasts at concentration of 10, 100 and 500 μg/ml (Fig. 3.5). The inhibitory effect on PGE_2 was most pronounced in the RHE decoction. Decoctions of the HHCF and knock-one botanical drug-out HHCF [i.e. NRHE, NSCU, NDIC, NSOP, NKOC and NPHE] showed similar PGE_2 inhibitory effect in human fibroblast treated with IL-1β, demonstrating that the effect of the HHCF is not solely depending on ingredient(s) extracted from a single botanical drug. Although the PGE_2 inhibitory effect of the HHCF decoction was shown to be similar to the SCU and weaker than RHE and PHE decoctions, the presence of other botanical drugs in the formula could be acting against other targets involved in the pathogenesis of AD that required further investigation. DIC decoction has no effect on the inhibition of PGE_2, and excluding DIC from the HHCF [i.e. NDIC-D] didn't lead to significant variation on the PGE_2 inhibitory activity of the HHCF; it seems that the presence of DIC in the formula does not play an important role in the PGE_2 inhibitory activity of the HHCF decoction. All tested samples showed no effect on IL-6 (Fig. 3.6) and IL-8 (Fig. 3.7) production in human fibroblast treated with IL-1β.



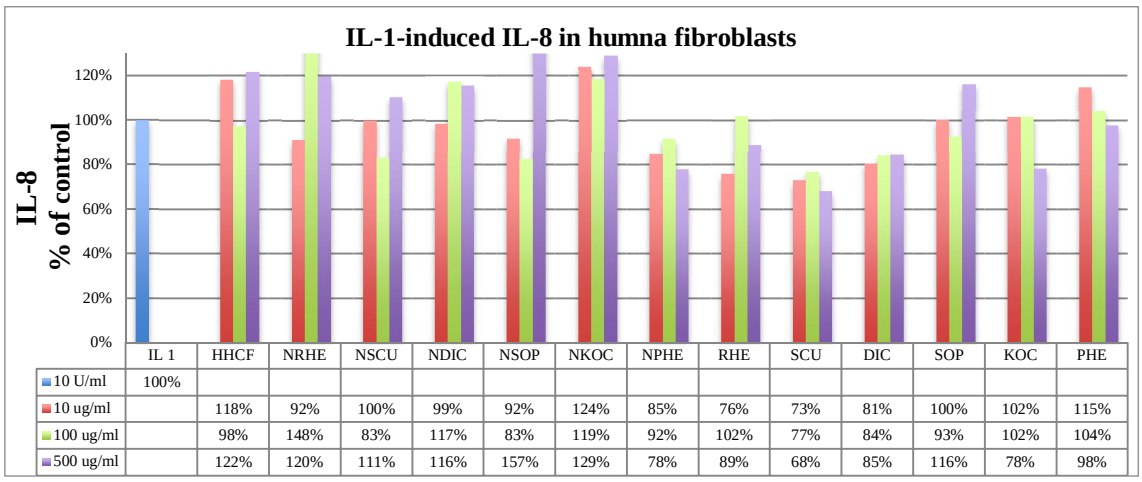
	IL 1	HHCF	NRHE	NSCU	NDIC	NSOP	NKOC	NPHE	RHE	SCU	DIC	SOP	KOC	PHE
10 U/ml	100%													
10 ug/ml		88%	88%	81%	77%	73%	108%	89%	35%	78%	76%	98%	83%	41%
100 ug/ml		33%	56%	32%	48%	32%	50%	47%	0%	50%	101%	84%	65%	21%
500 ug/ml		0%	12%	1%	6%	5%	10%	3%	0%	0%	103%	65%	38%	20%

Fig. 3.5 Effects of the HHCF, knock-one botanical drug-out-HHCF and single botanical drug decoctions on IL-1 induced PGE_2 production in human fibroblasts. Data represent results from one experiment (n=1).



	IL 1	HHCF	NRHE	NSCU	NDIC	NSOP	NKOC	NPHE	RHE	SCU	DIC	SOP	KOC	PHE
10 U/ml	100%													
10 ug/ml		101%	90%	100%	102%	68%	101%	119%	89%	132%	111%	123%	102%	94%
100 ug/ml		106%	100%	107%	115%	76%	96%	132%	94%	133%	136%	120%	108%	82%
500 ug/ml		90%	101%	95%	105%	103%	81%	96%	95%	101%	131%	129%	83%	102%

Fig. 3.6 Effects of the HHCF, knock-one botanical drug-out-HHCF and single botanical drug decoctions on IL-1 induced IL-6 production in human fibroblasts. Data represent results from one experiment (n=1).



	IL 1	HHCF	NRHE	NSCU	NDIC	NSOP	NKOC	NPHE	RHE	SCU	DIC	SOP	KOC	PHE
10 U/ml	100%													
10 ug/ml		118%	92%	100%	99%	92%	124%	85%	76%	73%	81%	100%	102%	115%
100 ug/ml		98%	148%	83%	117%	83%	119%	92%	102%	77%	84%	93%	102%	104%
500 ug/ml		122%	120%	111%	116%	157%	129%	78%	89%	68%	85%	116%	78%	98%

Fig 3.7 Effects of the HHCF, knock-one botanical drug-out-HHCF and single botanical drug decoctions on IL-1-induced IL-8 production in human fibroblasts. Data represent results from one experiment (n=1).

Cultured skin fibroblasts produce different inflammatory mediators e.g. prostanoids and cytokines after stimulated with IL-1β (Inoue et al., 2001). In this section, decoctions of the HHCF and the botanical drugs making up the HHCF [i.e. RHE, SCU, SOP, KOC and PHE] inhibited PGE_2 without diminishing the cytokine [i.e. IL-6 and IL-8] response. This immunomodulatory profile was different to that observed for steroids and was similar to a selective cyclogenase-2 (COX-2) inhibitor known as NS-398. For example, in a study carried out by Furuhashi, I. et. al. (Furuhashi et al., 2005), dexamethasone was able to inhibit PGE_2, IL-6 and IL-8 production in IL-1β treated human dermal fibroblasts while NS-398 was only able to inhibit PGE_2 production but not IL-6 and IL-8 production (Furuhashi et al., 2005). Similarly, indomethacin [i.e. a non-selective COX inhibitor] decreased LPS-induced PGE_2 production and only slightly decreased LPS-induced IL-6 and IL-8 production in human gingival fibroblasts (Kitamura et al., 2014).

Extracts of the botanical drugs making up the HHCF have demonstrated PGE_2 inhibitory effect in previous studies using other cell types. For example, 70% ethanol extract of *Rheum* species (Cheon et al., 2009), decoction and 70-100% ethanol of SCU (Kim et al., 2009a, Yoon et al., 2009b, Choi et al., 2014a), flavonoid enriched fractions of SOP (Jin et al., 2010) and methanol extract of KOC(Shin et al., 2004) reported to possess PGE_2 inhibition in RAW 264.7 murine macrophages treated with lipopolysaccharide (LPS). Ethanol extracts of PHE inhibited PGE_2 in animal models (Xian et al., 2011). Secondary metabolites that might at least in part contribute to the

PGE_2 inhibitory effects observed for RHE, SOP, SCU and PHE could be epicatechin (Singh and Katiyar, 2011) and aloe-emodin (Kim et al., 2010c), oxysophocarpine (Yang et al., 2015b) and sinapic acid (Yun et al., 2008), baicalein (Choi et al., 2014a), and berberine (Kuo et al., 2004, Singh et al., 2011), respectively. Unlike the 70% ethanol extract of *Rheum* species (Cheon et al., 2009) and the 70% methanol extract of SCU (Yoon et al., 2009a, Hong et al., 2013)] that were reported to demonstrate IL-6 or IL-8 inhibitory effect in LPS-treated RAW 264.7 murine macrophages, the RHE and SCU decoctions prepared in this study did not demonstrate IL-6 or IL-8 inhibitory effect in IL1β-treated human dermal fibroblasts. This may due to the difference in the cell type used, biological variation in botanical drugs, or variation in contents of extracts. For example, among the flavonoids present in extracts of SCU, wogonin, baicalein but not the glucuronide form of baicalein (i.e. baicalin) inhibited IL-6 and IL-8 in a human retinal pigment epithelial cell line treated with IL-1β (Nakamura et al., 2003); variation in the contents of these flavonoids in the SCU decoction and the cell type used might explain the absence of IL-6 or IL-8 inhibitory effect in this study.

Decoctions prepared from the HHCF and the botanical drug it is derived from attenuated IL-1β-induced PGE_2 production in human fibroblasts. Demonstrating botanical drugs that possess clearing heat properties in Chinese medicine are able to inhibit PGE_2 production *in vitro*. This might contribute to their clinical anti-inflammatory action.

3.4.3 Effects of the HHCF and single botanical drug on hyaluronidase activity

Hyaluronidase are liberated during skin inflammation that degrades hyaluronic acid (HA) distributed in the extracellular matrix into pro-inflammatory low molecular weight HA fragments. (Mayer, 1950, Girish and Kemparaju, 2007, Esser et al., 2012, Stern et al., 2006) Moreover, hyaluronidase have been associated with the increased capillary permeability in immediate hypersensitivity reaction. (Sakamoto et al., 1980) Hyaluronidase inhibitors may therefore be crucial for maintaining HA hemostasis and serving as anti-inflammatory agents.

The hyaluronidase inhibitory effects of the HHCF, RHE, SCU, DIC, SOP, KOC and PHE decoctions were shown in Fig. 3.8. The inhibitory effect of the RHE decoction was the strongest among the tested samples, reaching a 90% inhibition at the concentration

of 70 µg/ml. While KOC, SCU and HHCF decoctions showed weaker hyaluronidase inhibitory activity at the concentration of 70 µg/ml with inhibition percentage of 57%, 54% and 46%, respectively. RHE, KOC, SCU and HHCF decoctions showed a dose-dependent hyaluronidase inhibition. SOP and DIC decoctions showed negligible hyaluronidase inhibition with maximum inhibition of ~30%.

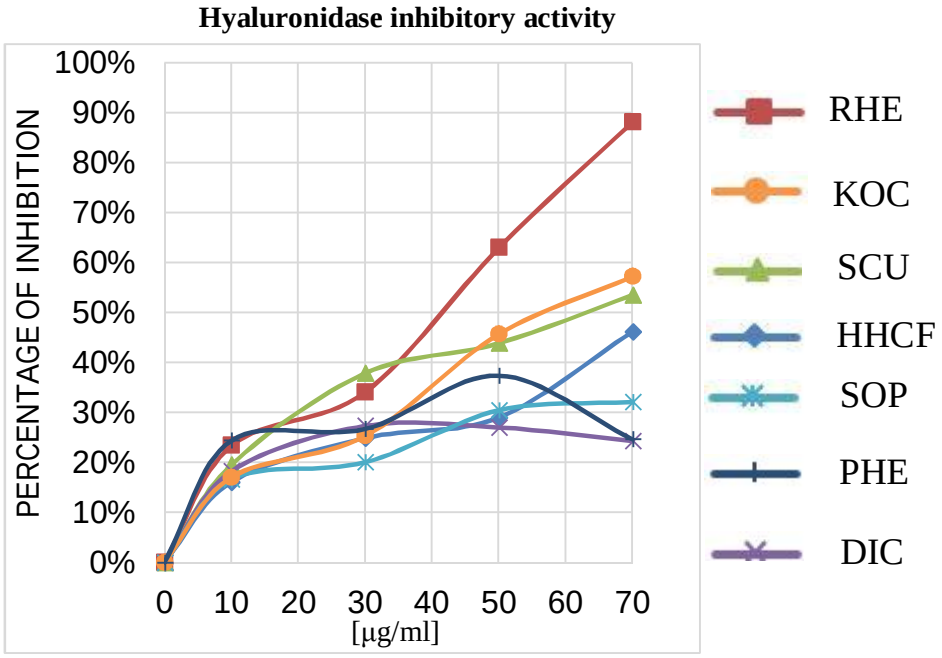


Fig 3.8 The hyaluronidase-inhibitory activity of the HHCF and single botanical drug decoctions. All values are presented as mean of triplicate measurements conducted in one experiment (n=1).

In the plot of reaction progress curve (Fig. 3.9), at venom concentration of 150 µg/ml [i.e. 15 µg in 100 µl reaction mixture], the rate of hyaluronic acid hydrolysis was linear [at initial velocity region] during the first 30 minutes of reaction time. At 20 minutes, ~ 50% of the hyaluronic acid has been degraded by enzyme and this was chosen as the incubation time for the inhibition assay.

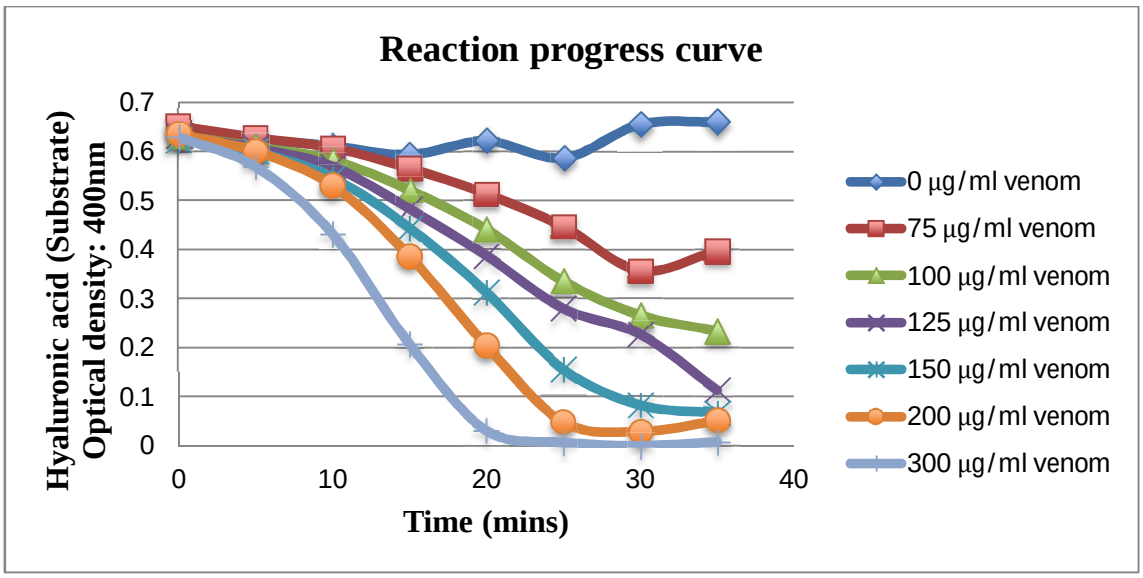


Fig. 3.9 Reaction progress curve; amount of hyaluronic acid at time 0 = 15µg. All values are presented as mean of triplicate measurements conducted in one experiment (n=1).

The plot of the initial rates as a function of hyaluronic acid [i.e. substrate] concentration did not show simple Michaelis-Menten kinetics (Fig.3.10), reported similarly by Yingprasertchai S. (Yingprasertchai et al., 2003) who also used snake venoms [i.e. *Naja kaouthia* and *Calloselasma rhodostoma*] as the source of hyaluronidase. This could be due to the presence of other compounds in the snake venom that act on hyaluronidase to affect its kinetic characteristics (Yingprasertchai et al., 2003).

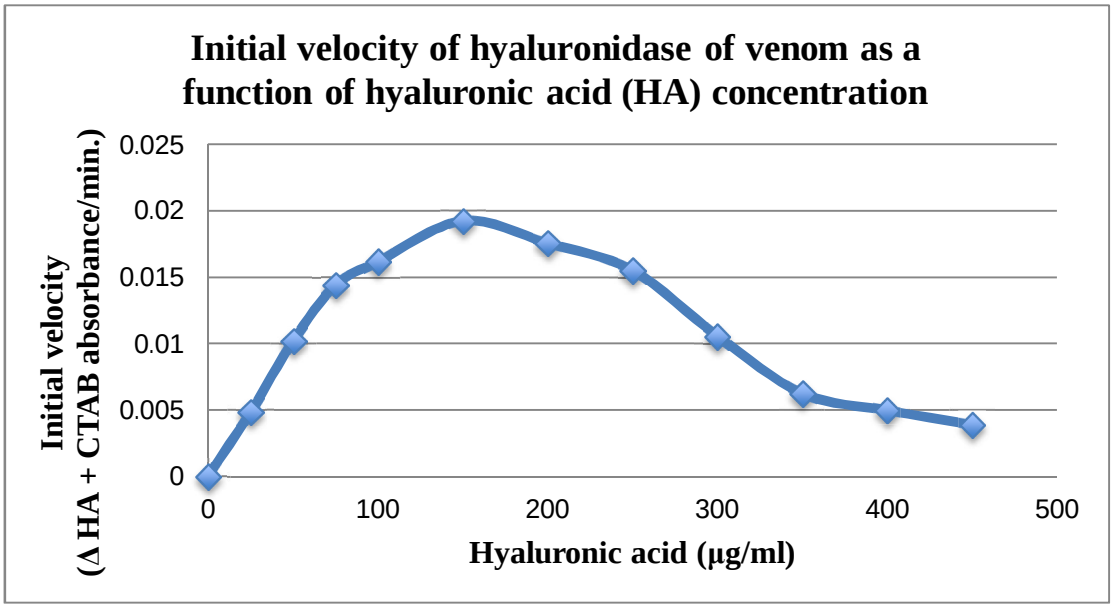


Fig. 3.10 The initial velocity of hyaluroniase of *Gloydius blomhoffi brevicaudus* venom (150 µg/ml) as a function of hyaluronic acid (substrate) concentration. All values are presented as mean of triplicate conducted in one experiment (n=1).

Secondary metabolites that might at least in part contribute to the hyaluronidase inhibitory effects observed for RHE and SCU could be (+)-catechin and baicalein, respectively. (+)-catechcin has been demonstrated to inhibit hyaluronidase type IV from bovine testes with 50% inhibitory concentration (IC_{50}) of 20 μg/ml (Samee et al., 2009). In another study, (+)-catechcin was able to inhibit mast cell degranulation and $CaCl_2$-activated hyaluronidase. Similarly, baicalein inhibited antigen-/calcium ionophore A23187-/compound 48/80-induced histamine release in rat peritoneal exudate cells and inhibited hyaluronidase in a dose-dependent manner (Kakegawa et al., 1992). In addition to baicalein, apigenin from SCU also possess anti-hyaluronidase activity (Kuppusamy et al., 1990).

The close relationship between hyaluronidase inhibitory activity and that of histamine degranulation from mast cells has been demonstrated in various studies. Compounds that possess anti-allergic properties could usually inhibit hyaluronidase activity (Fujitani et al., 2001, Kakegawa et al., 1985, Maeda et al., 1990). This could indirectly indicate that the HHCF and some of the botanical drug [i.e. RHE, SCU and KOC] that possess anti-hyaluronidase activity might also possess anti-allergic property.

3.4.4 Anti-bacterial activity of the HHCF

Staphylococcus aureus can be found in skin lesions of AD patients even in the absence of any clinical signs of infection (Friedman and Goldman, 2011, Hauser et al., 1985). Several studies showed correlation of disease severity to the *Staphylococcus aureus* colonization density (Pascolini et al., 2011, Alenizi, 2013, Farajzadeh et al., 2008, Mallinckrodt, 2000). This may be linked to the superantigenic property of *Staphylococcus aureus* toxins that trigger the activation, infiltration, cytokines production and proliferation of lymphocytes as summarized in Table 1.2. Therefore, decoction of the HHCF, RHE, SCU, DIC, SOP, KOC and PHE were tested against *Staphylococcus aureus* ATCC 6538 (SA) and also other bacterial strains including *Bacillus subtilis* ATCC6633 (BS), *Escherichia coli* ATCC 1229 (EC) and *Pseudomonas aeruginosa* ATCC9027 (PA).

Fig. 3.11a shows the amount of bacterial growth [i.e. the difference between turbidity of solution in each well measured at optical density of 600 nm at 24 hrs and at 0 hr] after 24 hrs incubation with 1 x 10^6 CFU/ml inoculum in the presence of the HHCF

decoction. No anti-bacterial activity was observed. Activity of streptomycin (S) against the four bacterial strains was performed as a positive control. The minimum inhibitory concentration (MIC) for streptomycin against *Escherichia coli* (EC), *Pseudomonus aeruginosa* (PA), *Staphylococcus aureus* (SA) and *Bacillus subtilis* (BS) were 12, 25, 3.12 and 12 μg/ml, respectively (Fig. 3.11b).

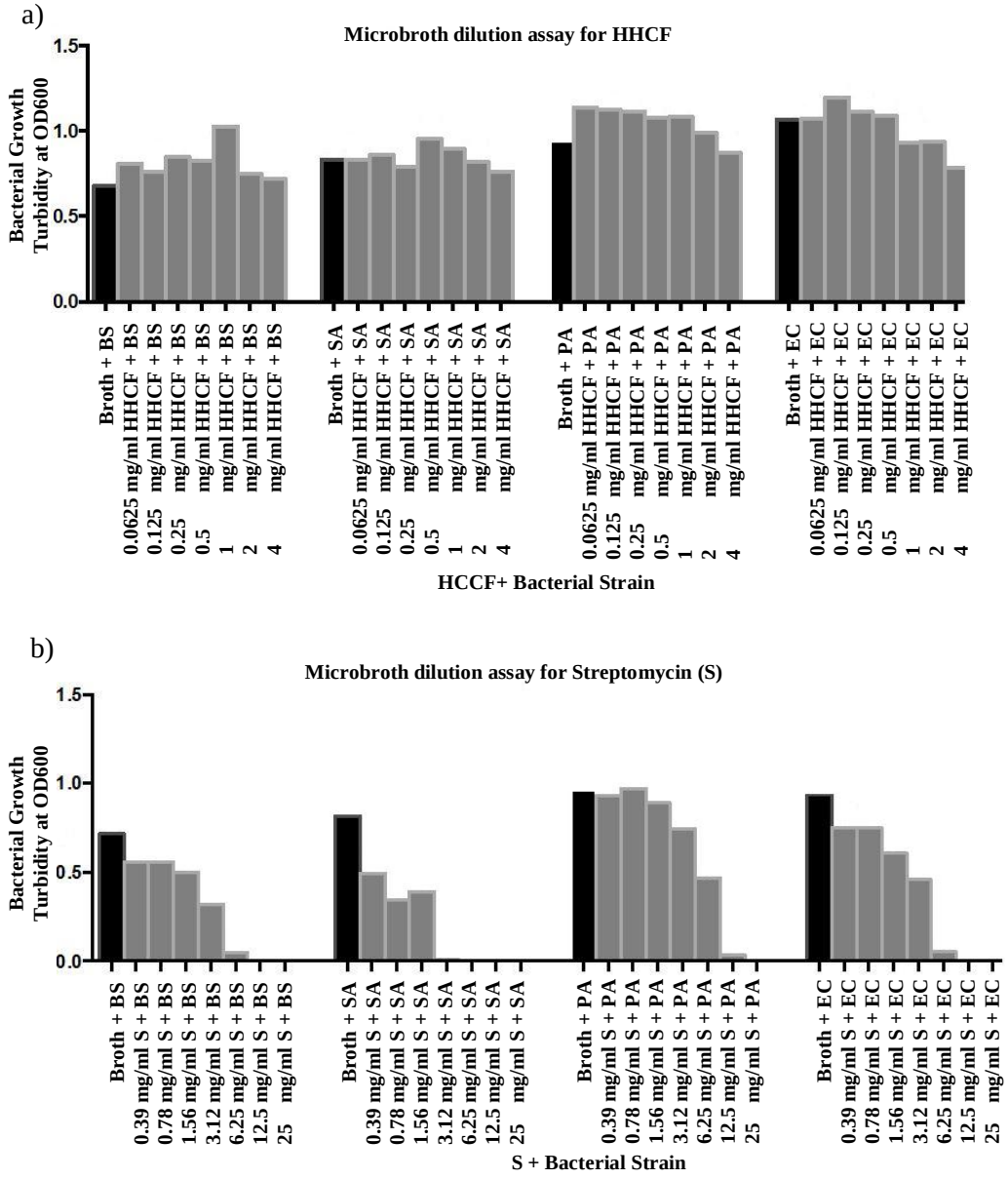


Fig. 3.11 Microbroth dilution assay for a) HHCF decoction and b) streptomycin (S) against BS (*Bacillus subtilis* ATCC6633), SA (*Staphylococcus aureus* ATCC 6538), PA (*Pseudomonas aeruginosa* ATCC9027) and EC (*Escherichia coli* ATCC 1229) with an inoculum size of 1 x 10^6 CFU/ml. All values are presented as mean of triplicate measurements conducted in one experiment (n=1).

The HHCF decoction at a concentration of 4 mg/ml showed a weak inhibition [i.e. 16%] against *Escherichia coli*, while no inhibitory activity was observed against other three tested bacterial strains. Although previous studies have reported anti-bacterial activity of extracts prepared from the botanical drugs making up the HHCF (see Table 3.9), anti-bacterial activity was not observed in the HHCF decoction, this could be due to biological (i.e. botanical drugs and bacterial strains) and technical variation (e.g. extraction techniques of botanical drugs and methods of anti-bacterial assay).

Table 3.9 Anti-bacterial activity of botanical drugs making up the HHCF.

Botanical Drug	Crude extract /compound	Method	Bacteria	MIC	Ref.
RHE	Decoction	Macrobroth dilution method; Inoculum: 10^5~10^6 organisms/ml	*Staphylococcus aureus*	MIC: 1.56 mg/ml	Lin 2011b
			Escherichia. Coli	MIC: 100 mg/ml	
	60% Ethanol	Macrobroth dilution method; Inoculum: 10^5~10^6 organisms/ml	*Staphylococcus aureus*	MIC: 3.13 mg/ml	Lin 2011b
			Escherichia. Coli	MIC: 3.13 mg/ml	
SCU	Water infusion	Disc diffusion method Inoculum : N/A	*Escherichia coli B*, coagulase-negative staphylococcus	1g/6ml; 0.15 ml in each wells (13 mm in diameters)	(Leach, 2011)
	80% Ethanol	Broth dilution assay Inoculum 10^4 CFU/ML (50µl in each well) +100µl tested sample in each well	*Staphylococcus aureus*	MIC:12.5 mg/mL MBC: 25 mg/ml	(Lu et al., 2011)
DIC	Essential oil	Broth microdilution method; Inoculum $2x10^4$ cfu/ml.	*Staphylococcus aureus* ATCC 25923 and methicillin-resistant *Staphylococcus aureus* (MRSA)	MIC: 3.13 mg/ml, MBC:3.13 mg/ml	(Lei et al., 2008)
			Staphylococcus aureus ATCC 25923 and MRSA	MIC: 3.13 mg/ml, MBC:3.13 mg/ml	
			Pseudomonas aeruginosa ATCC 27853	MIC: 25.0 mg/ml, MBC: 50.0 mg/ml	
			Escherichia coli ATCC 27853	MIC:6.25 mg/ml, MBC: 12.5 mg/ml	
SOP	(2S)-2-methoxykurarinone	Microdilution method (Oh et al., 2008) Inoculum: 1 x 10^4 cells/mL	*Staphylococcus aureus* ATCC 6538p	MIC: 27.7 µM	(Oh et al., 2011)
			Bacillus subtilis ATCC 6633	MIC: 55.3 µM	
	Kuraridin		*Staphylococcus aureus*	MIC: 8.81 µM	

Table 3.9 Anti-bacterial activity of botanical drugs making up the HHCF.					
Botanical Drug	**Crude extract /compound**	**Method**	**Bacteria**	**MIC**	**Ref.**
			Bacillus subtilis ATCC 6633	MIC: 17.7 μM	
	Kurarinone		*Staphylococcus aureus* ATCC 6538p	MIC: 7.12 μM	
			Bacillus subtilis ATCC 6633	MIC: 6.25 μM	
	Kushenol I		*Staphylococcus aureus* ATCC 6538p	MIC: 27.5 μM	
			Bacillus subtilis ATCC 6633	MIC: 13.8 μM	
	Kushenol M		*Staphylococcus aureus* ATCC 6538p	MIC: 24.6 μM	
			Bacillus subtilis ATCC 6633	MIC: 12.3 μM	
	Kushenol N		*Staphylococcus aureus* ATCC 6538p	MIC: 27.5 μM	
			Bacillus subtilis ATCC 6633	MIC: 27.5 μM	
	Kuraridin	Microdilution method, Inoculum: 1 x 10^6 CFU/mL	MRSA	MBC: 8-16 μg/ml	(Chan et al., 2012)
	Sophoraflavanone G		MRSA	MBC: 2-4 μg/ml	
KOC	Ethanol extract	Broth microdilution method Inoculum: 0.5 McFarland standard	MRSA ATCC25923	MIC: 1mg/ml	(Joung et al., 2012)
			MRSA ATCC33591	MIC: 0.25mg/ml	
	Essential oil	Broth dilution method Inoculum: 2 x 10^6 CFU/ml	*Staphylococcus aureus* ATCC 29213	MIC: 25mg/ml	(El Shamy et al., 2012)
			Bacillus subtilis NRRL-B4219	MIC: 12.5ug/ml	
			Escherichia coli ATCC 25922	MIC: 12.5ug/ml	

3.5 SUMMARY

This chapter investigated the effects of the HHCF against a few pathogenesis-related targets of AD. Effects against other pathogenesis-related targets need to be investigated to further understand the molecular mechanism underlying anti-inflammatory activities of the HHCF decoction.

4 LIMITATIONS

This study investigated the therapeutic potential for the hexa-herbal Chinese formula (HHCF) that is used as a topical preparation for the treatment of AD. To achieve this, the phytochemical composition of the HHCF has been profiled using LC-MS and its effects against selected pathogenesis-related targets of AD or skin inflammation have been studied. In this section, limitations for this research project are considered.

First, some *in vitro* assays were conducted as a pilot screening for biological activities with one single experiment (n=1). To be convincing, these experiments should be performed independently several times.

Second, there is no perfect model that can cover all the pathogenesis-related targets of AD and *in vitro* models used in this project only cover minor hallmarks of AD. Further studies on the action of the HHCF against other pathogenesis-related targets of AD is required for obtaining data with higher degree of valid extrapolation to the humans.

Third, metabolites in the HHCF decoction are profiled using LC-MS approach and were tentatively identified based on the observed fragmentation patterns. Authentic standards analysed under identical experimental conditions are required to confirm their identification. This approach particularly favours the metabolite profiling of botanical drugs with well known photochemistry.

Lastly, the predictability of active components of a multivariate regression model constructed using the abundance of metabolites in the LC-MS profiles (as the X matrix) and their respective biological activities (as y matrix) is dependent on the robustness of the analytical technique. Components that are poorly ionizable are underdetermined in this regard.

5 CONCLUSION AND FUTURE WORK

The multifactorial aetiology of atopic dermatitis reflect the disease may not be tackled easily by an ‘one drug-one target’ approach. Increasing evidence suugests that a combination of two or more drugs at lower doses could offer higher therapeutic efficacy and safety in treatment of complex diseases via simultaneous modulation of multiple targets (Zimmermann et al., 2007, Koeberle and Werz, 2014, Fitzgerald et al., 2006). This concept is similar to the theory of Chinese medicine that views a disease condition as a result of different syndromes and handles the diagnosed syndromes using a combination of botanical drugs – a formulation and the proportion of each botanical drug in a Chinese herbal medicine (CHM) formula are optimized based on centuries of clinical experiences. Thus, formulae of CHM are acting as mixtures-based libraries for the development of multicomponent therapeutic agents that could favourably interacts with multiple targets to achieve a therapeutic effects with fewer side effects. To achieve this, characterization of a Chinese herbal formula forms an important basis. In addition, CHMs are used worldwide as an adjunctive medicines and, therefore, characterization of the chemical components in a Chinese herbal formula is vital for understanding its pharmacological mechanism and for achieving reliable clinical effects and safety.

Due to the long history of Chinese medicine, the chemical composition of many of the commonly used CHMs has been well studied. And this support the characterization of CHM formula using a metabolite profiling approach. Moreover, metabolite profiles of botanical drug preparations can be used as a fingerprint for quality control.

To understand the therapeutic potential of this hexa-herbal Chinese formula for the treatment of atopic dermatitis, metabolite profiling was performed using liquid chromatography (LC) coupled with a triple quadrupole mass spectrometry (MS) Although the low-resolution triple quadrupole mass spectrometry cannot provide an accurate mass measurement and information on the elemental composition of the molecular ions, characteristic fragment ions detected using MS/MS analysis have assisted the putative identification of chemical components in the HHCF decoction. Moreover, the source(s) of chemical components in the HHCF can be identified based on the developed EXCEL template that match the mass and retention time of ions in the

HHCF to those present in the decoction prepared from the six individual botanical drugs making up the HHCF. Knowing the source(s) of chemical components in the HHCF reflects the importance of each composing botanical drug in terms of the overall chemical composition. The developed EXCEL template indicated that PHE, RHE and SOP contributed the largest number of chemical compounds identified in the HHCF, while KOC seems to contribute very little. However, the contribution of KOC to the HHCF cannot be determined based on this study, since components extracted from KOC may be non-ionizable that hinder its detection by the LC-MS. This also reflects the challenge of creating a fingerprint for quality control of botanical drugs. 68 chemical compounds including alkaloids, anthraquinones, coumarins, flavonoids, naphthalene derivatives, phenylbutanone glucosides, phenolic acids, pterocarpans, stilbenes and tannins were putatively identified in the LC-MS profile of the HHCF based on mass measurement and characteristic fragment ions. In order to guarantee an unequivocal structure identification, *m/z* value of the precursor and fragment ions and retention time in the chromatogram need to be compared with those collected from an authentic standard analyzed under identical experimental conditions. The EXCEL template developed to match data across ions from different MS profiles can further be developed into a software that can operate the data in a more user-friendly manner make it compatible with different formats of raw data files.

For the study of potential anti-inflammatory effects, factors that have been linked to the pathogenesis of atopic dermatitis and skin inflammation were chosen. The HHCF decoction inhibited TNF-α- plus IFN-□-induced thymus and activation-regulated chemokine (CCL17) production in spontaneously immortalized human epidermal keratinocytes (HaCaT) and IL-1β-induced Prostaglandin E_2 (PGE_2) in human fibroblasts with no effects on IL-8 and IL-6. The HHCF decoction also inhibited hyaluronidase activity. The therapeutic potential of the HHCF for the treatment of atopic dermatitis cannot be ascertained based on the limited number of pathogenesis-related targets studied. Further studies on the action of the HHCF against other pathogenesis-related targets of AD were needed to confirm its therapeutic potential for the treatment of AD.

An approach on how to process data from a LC-MS profile of a CHM preparation and the subsequent correlation of these data to the results from *in vitro* study was demonstrated. The abundance of 68 chemical compounds in LC-MS profiles of the

HHCF and twelve of its variation formulae (independent variables) were correlated to the levels of CCL17 in the medium of HaCaT after treatment with the HHCF and twelve of its variation formulae (dependent variables) using multivariate regression models. Based on the regression coefficient calculated by the principal component regression (PC-R) and partial least-squares regression (PLS-R) models, it was indicated the major contributors to the CCL17 inhibition were berberine, catechin dimers, gallic acid, galloylglucose, 4-(4'-hydroxylphenyl)-2-butanone 4'-O-β-D-glucoside, pyrogallol and resveratrol 4'-O-β-D-(6''-O-galloyl) glucoside. The anti-CCL17 activity of these chemical compounds need to be validated by carrying further experiments. In addition, the number of chemical compounds considered by the regression model can be improved by involving data of chemical profiles acquired using different analytical methods. Moreover, to get a better prediction on compounds that possess anti-inflammatory activities, effects against other pathogenesis-related targets should be involved in the model.

Overall, this thesis demonstrated the ability to characterize a CHM formula using LC-MS coupled with data processing and the potential of predicting active compounds by establishing relationship between chemical profiles and biological activities. The effects of the HHCF against other pathogenesis-related targets need to be further study to conclude its therapeutic efficacy against atopic dermatitis.

6 APPENDIX

Appendix I *In vitro* studies on principal cellular constituents orchestrating cutaneous inflammation in Atopic dermatitis (AD).	
Appendix Ia T lymphocytes	
T lymphocytes from AD skin lesions:	
A predominant mononuclear cell infiltrated at AD skin lesions [i.e. around the superficial capillary venous, superficial venous plexus of the papillary and upper reticular dermis] in both acute and chronic phase; the majority express: · $CD4^+$ [i.e. T helper lymphocytes] or CD8+ [i.e. cytotoxic T lymphocytes] and/or · $CD45RO^+$ [i.e. memory T lymphocytes] and/or · CLA^+ [i.e cutaneous lymphocyte-associated antigen; the skin-selective homing receptor and a major T lymphocytes ligand for the endothelial leukocyte adhesion molecule 1 (ELAM-1)/E-selectin] and/or · $CD30^+$ [i.e. activation marker for Th2 lymphocytes] and/or · HLA-DR [i.e. human histocompatibility leukocyte antigen-DR; activation marker] and/or Fas and Fas-ligand.	(Wakita et al., 1994, Leung et al., 1983a, Soter, 1989, Babi et al., 1995, Akdis et al., 1999b, Rho et al., 2004, Dummer et al., 1998, Del Prete et al., 1995, Lugovic et al., 2001, Akdis et al., 2000c, Akdis et al., 2000a)
In vitro expansion of T lymphocytes isolated from extrinsic and intrinsic AD skin lesions did not express detectable amounts of IL-4 protein in the cytoplasm [i.e. agree with the absence of IL-4 proteins in biopsies of AD skin lesions]. Significant amount of cytoplasmic IL-5 only in extrinsic AD, while IFN-γ only expressed in intrinsic AD.	(Akdis et al., 1999a)
Isolated T lymphocytes from extrinsic AD skin lesions induced significant IgE production in co-cultured normal B cells via IL-13 production; but not those from intrinsic AD skin, possibly due to lower IL-13 production in intrinsic AD.	(Akdis et al., 1999a)

Appendix I *In vitro* studies on principal cellular constituents orchestrating cutaneous inflammation in Atopic dermatitis (AD).	
Infiltrating T lymphocytes induced keratinocytes apoptosis by 1) signaling Fas receptor (FasR) expressed on keratinocytes with their surface Fas ligand (FasL) or with the secreted soluble FasL or 2) up-regulating FasR expression on keratinocytes by the secreted IFN- γ and hence, increased their susceptibility to apoptosis.	(Trautmann et al., 2000)
T lymphocytes from peripheral blood of AD patients:	
$CD4^+$ and $CD8^+$ CLA^+ $CD45RO^+$ T lymphocytes were activated *in vivo*; as shown by · increased expression of activation marker: CD25 and human histocompatibility leukocyte antigen-DR (HLA-DR), · presence of IL-5 and IL-13 in cytoplasm of T lymphocytes right after isolation without further stimulation [i.e. at significantly higher levels than T lymphocytes from healthy individuals]; while little or no IL-4 and IFN-γ were found in the cytoplasm of T lymphocytes from AD patients and healthy controls, · spontaneous proliferation and secretion of Th2 cytokines [i.e. dominantly IL-5 and IL-13 and little or no IL-4; at significantly higher amount than T lymphocytes from healthy control]] and IFN-γ [i.e. no significant differences when compared with healthy control] and undetectable amount of IL-2, IL-3 and GM-CSF, · spontaneously induced IgE production in B cells [i.e. IL-13 being the major IgE-inducing cytokines] *in vitro* without further stimulation, · up-regulated expression of Fas receptor and Fas ligand and spontaneous activation-induced apoptosis that can be inhibited by blocking Fas/Fas-ligand interaction.	(Akdis et al., 1999b, Akdis et al., 1999a, Akdis et al., 2000c, Aleksza et al., 2002)
Decreased amounts and functions of $CD8^+$ suppressor/cytotoxic T lymphocytes in peripheral blood mononuclear cells (PBMC) from individuals with AD.	(Leung et al., 1981, Leung et al., 1983b, Reinhold et al., 1990)

Appendix I *In vitro* studies on principal cellular constituents orchestrating cutaneous inflammation in Atopic dermatitis (AD).		
PBMCs/T cell clones isolated from AD patients show a propensity for differentiation of the Th2 phenotype [i.e. producing IL-4 and IL-5 but little or no IFN-γ and IL-2] in response to stimulants. The TH2 cytokine profile may contribute to the increased levels of IgE in individuals with AD.		(van Reijsen et al., 1992, Wierenga et al., 1990, Reinhold et al., 1990, Jujo et al., 1992, van der Heijden et al., 1991)
T lymphocytes-mediated effector mechanisms in AD:		
IL-4	Primarily produced from activated T lymphocytes, may also be secreted by activated mast cells.	(Plaut et al., 1989, Burd et al., 1995, Hamid et al., 1994)
	Elevated IL-4 mRNA expression in acute and chronic AD skin lesions when compared with normal control and uninvolved skin of individuals with AD; elevation was more prominent in acute AD skin lesions, indicating its role in the initiation of acute AD.	(Hamid et al., 1994)
	Increased IL-4 receptor mRNA expression and IL-4 production by PBMC isolated from individuals with AD that could be inhibited by interferon (IFN)-γ.	(Renz et al., 1992, Jujo et al., 1992)
	Contributed to the recruitment of leukocytes [e.g. eosinophils and basophils] from the blood stream to tissue sites of inflammation via induction of vascular endothelial cell adhesion molecule 1 (VCAM-1) [i.e. binds to very late antigen-4 (VLA-4) expressed on eosinophil and basophils], P-selectin and L-selectin ligands.	(Masinovsky et al., 1990, Spertini et al., 1991, Schleimer et al., 1992, Luscinskas et al., 1994, Yao et al., 1996)
	Promoted differentiation of Th0 cells to Th2-like phenotype [i.e. producing IL-4 and IL-5 but little IFN-γ or IL-2]	(Swain et al., 1990, Coffman et al., 1991)
	Attenuated expression of filaggrin, loricrin and involucrin and anti-microbial peptides in cultures of keratinocytes.	(Howell et al., 2008, Oh et al., 2008, Nomura et al., 2003)
	Upregulated chemokines mRNA or protein expression in cultures of human keratinocytes [i.e. CXCL9, CXCL10, CXCL11, CCL2, IL-8 and eotaxin-3] or dermal fibroblasts [eotaxin-1].	(Nishi et al., 2008, Albanesi et al., 2000, Albanesi et al., 2001)

Appendix I *In vitro* studies on principal cellular constituents orchestrating cutaneous inflammation in Atopic dermatitis (AD).		
	In vitro studies indicated increase in IL-4 or decrease in interferon (IFN)-γ production may account for the increased levels of serum IgE. i.e. · IL-4 induced IgE synthesis in PBMC isolated from healthy individuals and may enhanced spontaneous IgE synthesis in PBMC isolated from atopic individuals. The later was suppressed by interferon (IFN)-γ/α, prostaglandin E_2 (PGE_2), IL-12 and anti-IL-4 antiserum. · Serum levels of soluble CD23 (specifically induced by IL-4) were increased. · IL-4 mediated IgE isotype switch in B cells. · IL-4 may affect other cytokines that are involved in IgE synthesis [i.e. IL-4 inhibited IFN-γ production in mitogen/allogeneic cells-stimulated PBMCs].	(Pene et al., 1988, Peleman et al., 1989, Gauchat et al., 1990, Rousset et al., 1991, Gascan et al., 1991, Vollenweider et al., 1991, Vercelli and Geha, 1993, Kiniwa et al., 1992)
IL-5	Primarily produced from activated T cells, may also be secreted by activated mast cells.	(Hamid et al., 1994, Burd et al., 1995, Plaut et al., 1989)
	Elevated IL-5 mRNA expression in acute and chronic AD skin lesions [i.e. predominantly expressed by T cells] when compared with normal control and uninvolved skin of individuals with AD; elevation was more prominent in chronic AD skin lesions.	(Hamid et al., 1994)
	Key molecule for eosinophils differentiation and proliferation; may support eosinophil survival and differentiation in chronic phase of AD as shown by the increased infiltration of eosinophils in chronic AD skin lesions and inhibited apoptotic eosinophil death *in vitro*.	(Akdis et al., 1999b, Lopez et al., 1988, Saito et al., 1988, Hamid et al., 1994, Simon et al., 1997, Yamaguchi et al., 1991)
IL-10	Primarily produced from T cells and monocytes/macrophages.	(Sabat et al., 2010)

Appendix I *In vitro* studies on principal cellular constituents orchestrating cutaneous inflammation in Atopic dermatitis (AD).		
	Elevated IL-10 mRNA expression in AD skin lesions that may be linked to the down-regulated Th1 responses in AD.	(Ohmen et al., 1995)
	Down-regulated the expression of anti-microbial peptide e.g. human beta-defensin (HBD)-2 and human cathelicidin (LL-37) in AD.	(Howell et al., 2005)
IL-13	Primarily produced from activated T cells of Th2 sub-type; may also be secreted by activated mast cells.	(Hamid et al., 1996, Burd et al., 1995)
	Elevated IL-13 mRNA expression in acute and chronic skin lesions and to a lesser extent in uninvolved skin of individuals with AD when compared with normal control; elevation was more prominent in acute AD skin lesions.	(Hamid et al., 1996)
	Promoted IgE synthesis in B cells via mediating the IgE isotype switch and enhanced CD23 [i.e. low-affinity receptor for the Fc portion of IgE] expression on B cells.	(McKenzie et al., 1993, Punnonen et al., 1993, Defrance et al., 1994)
	Attenuated expression of filaggrin, loricrin and involucrin and anti-microbial peptides in cultures of keratinocytes.	(Howell et al., 2008, Oh et al., 2008, Nomura et al., 2003)
	May be involved in the recruitment of inflammatory cells [e.g. eosinophils] to the cutaneous sites of inflammation via the induction of VACM-1 expression on human endothelial cells or enhanced production of eotaxin-3 in keratinocytes.	(Kagami et al., 2005, Bochner et al., 1995)
IFN-γ	mRNA expression of IFN-γ in acute and chronic AD skin lesions remained normal when compared with normal control and uninvolved skin of individuals with AD. In another study, mRNA expression of IFN-γ in AD skin lesions was increased and maybe correlated to disease severity; down-regulated after successful treatment [i.e. accompanied with down-regulated expression of ICAM-1 that could be induced by IFN-γ on keratinocytes] and remained unchanged in non-responders.	(Hamid et al., 1994, Grewe et al., 1994)

Appendix I *In vitro* studies on principal cellular constituents orchestrating cutaneous inflammation in Atopic dermatitis (AD).		
	Decreased IFN- γ production in PMBCs isolated from individuals with AD that has been inversely correlated to serum IgE levels and may be due to the increased expression of IL-4, IL-10 and prostaglandin E_2 (PGE_2) observed in AD.	(Reinhold et al., 1988, Reinhold et al., 1990, Rousset et al., 1991, Jujo et al., 1992, Lester et al., 1995, Chan et al., 1993)
	Inhibited spontaneous IgE production, IL-4 receptor mRNA expression and IL-4 production in PBMCs isolated from atopic individuals and inhibited IL-4 induced IgE production in PBMCs/CD23 expression on highly purified B cells isolated from normal individuals.	(Pene et al., 1988, Vercelli et al., 1990, Rousset et al., 1991, Renz et al., 1992)
	May inhibit IgE synthesis via inhibiting proliferation of Th2 cells or promoting the differentiation of Th0 cells to Th1 phenotype [i.e. producing IFN-γ but not IL-4].	(Fernandez Botran et al., 1988, Gajewski and Fitch, 1988, Coffman et al., 1991, Jujo et al., 1992, Scott, 1991)
	A key molecule for macrophage activation and their anti-microbial activity.	(Murray et al., 1987, Nathan et al., 1983, Nacy et al., 1985, Lehn et al., 1989, Liew et al., 1989)
	Associated with dermal thickening in chronic AD lesions.	(Yamanaka and Mizutani, 2011)
	Participates in development of eczema i.e eczema formation was observed in transgenic mice expressing IFN-γ in the epidermis and alleviated in IFN-γ knockout mice.	(Carroll et al., 1997, Spergel et al., 1999b)
	Induced Fas receptor expression on keratinocytes that enhance their susceptibility to apoptosis.	(Trautmann et al., 2000)
	Induced intercellular adhesion molecule-1 (ICAM-1) expression in keratinocytes.	(Dustin et al., 1988, Ackermann and Harvima, 1998)
	Induced CCL17 and CCL22 mRNA expression and CXCL10, CCL2, I-309 and CCL22 protein secretion in primary cultures of human keratinocytes.	(Horikawa et al., 2002, Albanesi et al., 2001)

Appendix I *In vitro* studies on principal cellular constituents orchestrating cutaneous inflammation in Atopic dermatitis (AD).		
TNF-α	Produced from T lymphocytes , mast cells, Langerhans cells, dermal dendritic cells and keratinocytes upon stimulation and induce expression of adhesion molecules [i.e. VACM-1, ICAM-1, E-selectin and P-selectin] in keratincoytes, fibrblasts or interstitial dermal dendritic cells that leads to the recruitment of inflammatory cells [e.g. T lymphocytes and eosinophils]. The extent of adhesion molecules expression was directly proportional to the number of TNF-α containing cells [i.e. chymase-containing mast cells and $CD68^+$ macrophages] in dermis of AD skin lesions.	(Walsh et al., 1991, Kock et al., 1990, Larrick et al., 1989, Nickoloff et al., 1991, Meng et al., 1995, Groves et al., 1995, Ackermann and Harvima, 1998, Numerof and Asadullah, 2006, de Vries et al., 1998, Kyan Aung et al., 1991, Weller et al., 1991)
	Induced maturation of dendritic cells i.e. decreasing their antigen uptaking ability and increasing their T lymphocytes stimulatory capacity.	(Sallusto and Lanzavecchia, 1994)
Appendix Ib B lymphocytes, Peripheral mononuclear cells		
IgE	Elevated serum IgE level in ~70-80% individuals with AD [i.e. extrinsic AD].	(Rho et al., 2004, Czech et al., 1992, Schmid Grendelmeier et al., 2001, Novak and Bieber, 2003)
	IgE production was induced by IL-4/IL-13 or lack of IFN-γ in PBMCs or purified B cells and was inhibited by IFN- γ/α, $_2PGE_2$, F(ab')2 fragments of an anti-CD23 monoclonal antibody, IL-4 antibodies or IL-12.	(Pene et al., 1988, Reinhold et al., 1990, Vercelli et al., 1990, Gascan et al., 1991, Jujo et al., 1992, Punnonen et al., 1993, Defrance et al., 1994, Rousset et al., 1991, Vollenweider et al., 1991)
Appendix Ic Dendritic cells (DCs)		
Increased number of $CD1a^+$ DCs in the epidermis of both lesional and nonlesional skin in extrinsic/intrinsic AD.		(Rho et al., 2004)

Appendix I *In vitro* studies on principal cellular constituents orchestrating cutaneous inflammation in Atopic dermatitis (AD).	
Immature DCs recruited to the site of inflammation; uptake and processing of antigens, are then migrated towards draining lymph nodes and become mature to stimulate T lymphocytes.	(Austyn, 1992)
Chemokines involved in the recruitment of immature DCs include CCL22, CCL3, CCL5 and CCL7.	(Sozzani et al., 1995, Godiska et al., 1997)
Myeloid DCs (mDCs) - Langerhans cells (LCs)	
Found in healthy and lesional AD skin.	(Wollenberg et al., 2002)
Secreted IL-12; a mediator for Th1 differentiation.	(Kang et al., 1996)
Epidermal LCs express surface receptors that are involved in the initiation of AD: high-affinity receptor for the Fc fragment of IgE (Fc epsilon RI) and thymic stromal lymphopoietin (TSLP)-receptor.	(Dubrac et al., 2010, Schmitt et al., 1990)
Fc epsilon RI on LCs has a trimetric structure, expressing IgE-binding α and γ-chain dimer, but lacking the classical β-chain. Expression of γ-chain was enhanced in DCs from individuals with AD, low or absent in DCs from normal individuals. Expression was dependent on the inflammatory environment in the skin and the serum IgE levels.	(Bieber et al. 1989; Bieber et al. 1992; Bieber 1997; Kraft et al. 1998; Novak et al. 2003
Maximize antigen uptake via specific IgE molecules bound to the Fc epsilon RI, subsequently present IgE-bound antigen to T cells and preferentially induce Th2 response.	(Bieber, 1997, Stingl and Maurer, 1997, Klechevsky et al., 2008, Novak et al., 2004b)
In vitro activation of monocyte-derived LCs-like dendritic cells (LCs-DCs) [i.e. generated by culturing peripheral blood monocytes of individuals with AD in the presence of IL-4, GM-CSF and TGF-β1] through Fc epsilon RI induced: 1) enhanced IL-16 secretion and mRNA expression, 2) enhanced [i.e.IL-8, CCL2 and IL-16] or decreased [i.e. IL-1α. TNF-α and CCL3] intracellular protein expression, 3) increased levels of CCL2 in the supernatant [i.e. accounted for the increased migration capacity of CCR2/CCR4/CCR6^{+} monocytes from the peripheral blood of individuals with AD *in vitro*].	(Reich et al., 2001, Novak et al., 2004c)

Appendix I *In vitro* studies on principal cellular constituents orchestrating cutaneous inflammation in Atopic dermatitis (AD).	
Myeloid Dendritic cells (mDCs) - Inflammatory dendritic epidermal cell (IDECs)	
Low or absent in healthy skin, increased amount in lesional AD skin.	(Wollenberg et al., 2002)
IDECs isolated from AD skin lesions produced higher amount of IL-12 after stimulation with lipopolysaccharide and released IL-12 and IL-18 after Fc epsilon RI ligation that promote Th1 response [i.e. IFN-γ predominant] as seen in chronic phase of AD.	(Novak et al., 2004c)
In vitro activation of monocyte-derived epidermal cell-like dendritic cells (IDEC-DCs) [i.e. generated by culturing peripheral blood monocytes of individuals with AD in the presence of IL-4, GM-CSF and agent 2-mercaptotethanol] through Fc epsilon RI enhanced intracellular protein expressions including IL-1α, CCL3, and IL-16; release of these soluble mediators might account for ability of IDEC-DCs to recruit T lymphocytes in migration assays.	(Novak et al., 2004c)
Epidermal cell suspension from lesional skin [i.e. containing IDEC-DCs] induced higher T lymphocytes proliferation than epidermal cell suspension from nonlesional skin [i.e. containing LCs-DCs] of individuals with AD; IDECs may serve as amplifiers in the inflammatory response.	(Novak et al., 2004c)
Plasmacytoid dendritic cells (pDCs)	
Anti-viral i.e. produce IFN-γ and IFN-β upon viral infection.	
The lack of pDCs in AD skin lesions may account for the increased susceptibility to viral infection e.g. eczema herpeticum in individuals with AD.	(Wollenberg et al., 2002)
pDCs derived from the peripheral blood of individuals with AD were different from those derived from healthy individual; expressing lower levels of cutaneous lymphocyte antigen (CLA) and L-selectin [i.e. reduced recruitment of pDCs into the lesional skin of AD].	(Novak et al., 2004a)
Appendix Id Eosinophils	

Appendix I *In vitro* studies on principal cellular constituents orchestrating cutaneous inflammation in Atopic dermatitis (AD).	
Elevated number of eosinophils in the peripheral blood and skin lesions [i.e. eosinophil granular proteins also increased] of individuals with AD; elevation maybe more prominent in individuals with positive skin prick tests [i.e. extrinsic AD] or other symptoms of atopic diseases.	(Jenerowicz et al., 2007, Uehara et al., 1990, Rho et al., 2004, Hamid et al., 1994, Akdis et al., 1999a, Jeong et al., 2003)
Number of serum eosinophils or eosinophil granular proteins maybe correlated with disease severity.	(Nishimoto et al., 1998, Uehara et al., 1990, Czech et al., 1992)
Superficially distributed; at depth of ~0.5-0.9 mm from the epidermis; <10% eosinophil granule protein deposition below a depth of 1.39mm from the epidermis.	(Kiehl et al., 2001)
Recruited to the tissue sites of inflammation possibly by specific binding of very late antigen-4 (VLA-4) to VCAM-1 or binding to E-selectin or ICAM-1; that were expressed on cytokine-stimulated [e.g. IL-4/TNF-α/IL-1] endothelial cells. The number of eosinophils and eosinophils-derived granule proteins was correlated to the extent of VACM-1 expression in AD skin lesions.	(Schleimer et al., 1992, Weller et al., 1991, Kyan Aung et al., 1991, Wakita et al., 1994, Dobrina et al., 1991)
Secreted IL-12 [i.e. a mediator for Th1 differentiation] after stimulating with Th2-type cytokines [i.e. IL-4, IL-5, GM-CSF, TNF-α and IL-1α].	(Grewe et al., 1998b)
IL-3/IL-5 prolonged esoinophil survival *in vitro*.	(Yamaguchi et al., 1991, Rothenberg et al., 1988, Akdis et al., 1999b)
Appedix Ie Keratinocytes (KCs)	
KCs of individuals with AD produced higher amount of certain cytokines [e.g. GM-CSF] and chemokines [i.e. Table 1.3] when compared to non-atopic control that maybe vital for the initiation and maintenance of cutaneous inflammation.	(Girolomoni et al., 2006, Pastore et al., 2000)

Appendix I *In vitro* studies on principal cellular constituents orchestrating cutaneous inflammation in Atopic dermatitis (AD).		
Increased expression of ICAM-1 in KCs in of AD skin lesions; levels of ICAM-1 expression were correlated witth degree of dermal inflammation and intra-epidermal lymphocytes and were reduced upon successful treatment. ICAM-1 expression in human keratinocytes was induced by IFN-γ, TNF-α, ultraviolet radiation or staphylococcal enterotoxin B.		(Grewe et al., 1994, Griffiths et al., 1989, Dustin et al., 1988, Krutmann et al., 1990, Wakita et al., 1995, Ackermann and Harvima, 1998)
Down-regulated expression of anti-microbial peptide e.g. human beta-defensin (HBD)-2 and human cathelicidin (LL-37) by IL-4, IL-13 and IL-10.		(Howell et al., 2005)
Increased susceptibility of KCs to apoptosis that contributed to acantholysis and spongiosis of the epidermis in eczematous skin lesions. This has been linked to the up-regulation of FasR on KCs by IFN-γ and the subsequent Fas ligation of FasR on KCs with Fas ligand expressed on infiltrated T lymphocytes in the epidermis.		(Wolff et al., 1993, Yamaguchi et al., 1991)
Primary cultures of human KCs stimulated with Th1-derived supernatant or IFN-γ plus TNF-α resulted in CXCL10, CCL2, CCL5, IL-8, I-309, CCL22 mRNA expression and protein secretion; similar was observed when KCs were stimulated with Th2-derived supernatant or IL-4 plus TNF-α, except for I-309 and CCL22 mRNA and protein secretion.		(Albanesi et al., 2001)
Keratinocytes-mediated effector mechanisms in AD		
GM-CSF	Elevated GM-CSF mRNA and protein expression in unstimulated cultures of KCs from individuals with AD and detected in the epidermal KCs of AD skin lesions by immunostaining. Elevation was much more prominent when AD KCs were stimulated by phorbol myristate acetate, IFN- γ, *Staphylococcus aureus* peptidoglycan or histamine. This elevated GM-CSF expression has been linked to the disregulated activation of the activator protein 1 (AP-1) family of transcription factors, including C-Jun, JunB and C-Fos and may contribute to chronicity of AD lesions: · Inhibited spontaneous monocyte apoptosis, hence increased survival of monocyte in chronic AD.	(Pastore et al., 1997, Pastore et al., 1998, Pastore et al., 2000, Kakinuma et al., 2001, Kanda and Watanabe, 2004, Matsubara et al., 2004, Bratton et al., 1995, Hancock et al., 1988, Heufler et al., 1988, Witmer Pack et al., 1987,

Appendix I *In vitro* studies on principal cellular constituents orchestrating cutaneous inflammation in Atopic dermatitis (AD).		
	· Stimulated KCs proliferation that maybe contributing to epidermal hyperplasia in chronic AD. · May support the activity, survival and migration of epidermal Langerhans cells at the cutaneous site of inflammation.	O'Sullivan et al., 1996, Rupec et al., 1996, Homey et al., 2006)
IL-12	Produced from keratinocytes/eosinophils/Langerhans cells/macrophages.	(Muller et al., 1994, Grewe et al., 1998b, Hsieh et al., 1993, Kang et al., 1996)
	Elevated IL-12 mRNA expression in chronic AD skin lesions when compared to uninvolved skin of individuals with AD and normal control.	(Hamid et al., 1996)
	Promoted differentiation of Th0 or Th2 [i.e. acute AD] to Th1 phenotype [i.e. chronic AD] via suppression of IL-4 production by Th2 lymphocytes and iindction of IFN-γ production.	(Hsieh et al., 1993, Manetti et al., 1993, Rissoan et al., 1999, Akdis et al., 2000b, Grewe et al., 1998b)
	Suppressed IgE mRNA and protein production in IL-4-stimulated peripheral blood mononuclear cell via inducing IFN-γ production or IFN-γ independent mechanisms.	(Chan et al., 1991, Kiniwa et al., 1992)
	Induced CLA expression on T cells.	(Akdis et al., 2000b)
TSLP	An epithelial-derived cytokine that promotes $CD4^+$ homeostasis; serving as a link between the KCs and immune responses.	(Al Shami et al., 2005, Izuhara et al., 2011)
	Highly expressed in KCs from skin lesions of individuals with AD, but not from normal skin or skin from individuals with Th1 polarized skin disease (e.g. nickel-induce allergic contact dermatitis or systemic lupus erythematosus).	(Soumelis et al., 2002)

Appendix I *In vitro* studies on principal cellular constituents orchestrating cutaneous inflammation in Atopic dermatitis (AD).		
	Released from KCs in response to clinically relevant stimuli (e.g. Th2 cytokines, scratching, bacteria or virus) i.e. Ø Tape stripping of skin lesions of individuals with AD showed that levels of TSLP expressed in stratum corneum (SC) correlated to the severity of AD, e.g. in terms of SC hydration, itch score and transepidermal water loss (TEWL). Ø In cultured skin explants and primary human epithelial cells, up-regulated expression of TSLP in KCs occurred when skin barrier was impaired or upon challenged by inflammatory cytokines (i.e. combination of TNF-α/IL-1α, IL4 and IL13), bacteria and viruses.	(Allakhverdi et al., 2007a, Bogiatzi et al., 2007, Angelova-Fischer et al., 2010, Sano et al., 2013)
	Plays a critical role in initiating, maintaining and skewing the development of immune response towards a proallergic (Th2 phenotype) state in AD through its effects on different cells types [e.g. dendritic cells, mast cells, T cells and natural killer cells)].	(Comeau and Ziegler, 2010)
	Activated DCs (i.e. primary human $CD11c^+$ myeloid DCs), characterized by the up-regulation of major histocompatibility complex class II and costimulatory molecules that subsequently cue naïve $CD4^+$ T cells to differentiate into a Th2 phenotype producing cytokines with profile similar to those found in skin lesions of individuals with AD (i.e. moderate to high levels of IL-4, IL-5, IL-13, TNF-α and down regulated levels of IL-10 and IFN-γ) through OX40 ligands.	(Soumelis et al., 2002, Reche et al., 2001, Seshasayee et al., 2007, Ito et al., 2005)
	TSLP-activated DCs produced high level of Th2-attracting chemokines including CCL17 and CCL22, both attract Th2 cells through CC chemokine receptor 4.	(Soumelis et al., 2002, Nickel et al., 1999)
	May contribute to the maturation and emigration of LCs from the epidermis to the lymph nodes where they prime naïve T lymphocytes to be proallergic Th2 phenotype; numerous LCs in the underlying dermis were observed to be at their mature state, expressing DC-LAMP/CD208.	(Soumelis et al., 2002)

Appendix I *In vitro* studies on principal cellular constituents orchestrating cutaneous inflammation in Atopic dermatitis (AD).		
	Promoted human $CD4^+$ T cells proliferation and differentiation towards the Th2 phenotype via induction of IL-4 production.	(Rochman et al., 2007, Omori and Ziegler, 2007)
	Prolonged survival of eosinophils and induced adhesion molecules, inflammatory cytokines [e.g. IL-6] and chemokines [e.g. IL-8, CXCL1 and CCL22] for the recruitment of eosinophils to stie of inflammation.	(Wong et al., 2010)
	Induced IL-4 and IL-13 production in human invariant natural killer T lymphocytes.	(Wu et al., 2010)
	In the presence of IL-1/TNF-α, induced production of cytokines (i.e. IL-5, IL-13, IL-6, IL-10, GM-CSF) and chemokines (CCL1 and CXCL8) in mast cells through the TSLP receptor complex. But unlike IgE, TSLP did not induce degranulation of pre-formed mediators (e.g. β-hexosaminidase, histamine, leukotriene C_4 and prostaglandin-D_2) or the release of lipid mediators from mast cells.	(Allakhverdi et al., 2007b)

Appendix II Secondary metabolites isolated from the root and rhizome of *Rheum tanguticum* Maxim. ex Balf. (RHE).		
Class	**Compound**	**Reference**
Anthraquinone	Aloe-emodin	(Jin et al., 2007, Jin et al., 2006a, Jin et al., 2006b, Komatsu et al., 2006, Choi et al., 2013, Chen et al., 2014b)
	Chrysophanol	(Jin et al., 2007, Jin et al., 2006a, Jin et al., 2006b, Ye et al., 2007, Komatsu et al., 2006, Jin et al., 2011, Choi et al., 2013, Chen et al., 2014b)
	Emodin	(Jin et al., 2007, Jin et al., 2006a, Jin et al., 2006b, Komatsu et al., 2006, Jin et al., 2011, Choi et al., 2013, Chen et al., 2014b)
	Physcion	(Jin et al., 2007, Jin et al., 2006a, Jin et al., 2006b, Komatsu et al., 2006, Jin et al., 2011, Choi et al., 2013, Chen et al., 2014b)
	Rhein	(Jin et al., 2007, Jin et al., 2006a, Jin et al., 2006b, Komatsu et al., 2006, Choi et al., 2013)
Anthraquinone glycoside	Aloe-emodin-1-O-β-D-glucoside	(Gao et al., 2014a)
	Aloe-emodin-8-O-β-D-glucoside	(Jin et al., 2007, Jin et al., 2006a, Jin et al., 2006b, Gao et al., 2014a, Komatsu et al., 2006)
	Aloe-emodin-8-O-β-D-(6'-O-galloyl)-glucoside	(Jin et al., 2007)
	Chrysophanol-1-O-β-D-glucoside	(Chen et al., 2016)
	Chrysophanol-8-O-β-D-glucoside	(Chen et al., 2016, Jin et al., 2007, Jin et al., 2006a, Jin et al., 2006b, Gao et al., 2014a, Ye et al., 2007, Komatsu et al., 2006, Jin et al., 2011)
	Chrysophanol-8-O-β-D-(6'-O-glucosyl)-glucoside	(Jin et al., 2007)
	Chrysophanol-8-O-β-D-(6'-O-galloyl)-glucoside	(Ye et al., 2007)
	Emodin-8-O-β-D-glucoside	(Jin et al., 2007, Ye et al., 2007, Komatsu et al., 2006)
	Emodin-8-O-(6'-O-malonyl)-glucoside	(Ye et al., 2007)
	Physcion-8-O-β-D-glucoside	(Chen et al., 2016, Jin et al., 2007, Komatsu et al., 2006)
	Rhein-1-O-β-D-glucoside	(Ye et al., 2007)
	Rhein-1-O-β-D-(O-acetyl)-glucoside	(Ye et al., 2007)
	Rhein 8-O-β-D-glucoside	(Jin et al., 2007, Gao et al., 2014a, Komatsu et al., 2006)
Dianthrone	Sennoside A	(Jin et al., 2007, Jin et al., 2006b)
	Sennoside B	(Jin et al., 2007, Jin et al., 2006b)

Appendix II Secondary metabolites isolated from the root and rhizome of *Rheum tanguticum* Maxim. ex Balf. (RHE).		
Class	**Compound**	**Reference**
	Sennoside C	(Jin et al., 2007)
	Sennoside D	(Jin et al., 2007)
Flavan-3-ol	(+)-Catechin	(Jin et al., 2007, Jin et al., 2006a, Jin et al., 2006b, Jin and Tu, 2005, Komatsu et al., 2006)
	(-)-Epicatechin-3-O-gallate	(Jin et al., 2007, Jin et al., 2006a, Jin et al., 2006b, Komatsu et al., 2006)
Galloylglucose	1-O-Galloyl-β-D-glucose	(Jin et al., 2007, Komatsu et al., 2006)
	6-O-Galloyl-β-D-glucose	(Komatsu et al., 2006)
	1,6-Di-O-Galloyl-β-D-glucose	(Komatsu et al., 2006)
	1,2,6-Tri-O-galloyl-β-D-glucose	(Jin et al., 2007, Komatsu et al., 2006)
	1-O-Galloyl-2-O-cinnamoyl-β-D-glucose	(Jin et al., 2007, Komatsu et al., 2006)
	1,2-Di-O-galloyl-6-O-cinnamoyl-β-D-glucose	(Komatsu et al., 2006)
	1,3-Di-O-galloyl-2-O-cinnamoyl-β-D-glucose	(Komatsu et al., 2006, Jin et al., 2007)
Naphthalene glycoside	6-Hydroxymusizin-8-O-β-D -glucoside	(Gao et al., 2012a, Jin et al., 2007)
	Torachrysone-8-O-ß-D-glucoside	(Gao et al., 2012a, Jin et al., 2007, Jin et al., 2006a, Jin et al., 2006b)
Phenolic acid	*trans*-Cinnamic acid	(Gao et al., 2012a)
	Gallic acid	(Jin et al., 2007, Komatsu et al., 2006)
Phenolic acid derivative	p-Coumaric acid glucoside	(Gao et al., 2012a)
	4-(ß-D-Glucopyranosyloxy)-3,5-dimethoxybenzoic acid	(Gao et al., 2014a)
	Gallic acid-3-O-β-D-glucoside	(Jin et al., 2007)
	Gallic acid-4-O-β-D-glucoside	(Jin et al., 2007)
	Gallic acid 3-O-β-D-(6'-O-galloyl)-glucoside	(Jin et al., 2007)
	Gallic acid 4-O-β-D-(6'-O-galloyl)-glucoside	(Jin et al., 2007)
	4-Hydroxybenzenepropanoic acid methyl ester	(Gao et al., 2012a)
Phenylbutanone derivative	4-[4-(β-D-Glucosyloxy)-3-methoxyphenyl]-2-butanone	(Gao et al., 2014a)
	4-(4'-O-β-D-Glucosyl-3',5',-dimethoxyphenyl)-2-butanone	(Gao et al., 2014a)
	4-(4'-Hydroxyphenyl)-2-butanone	(Jin et al., 2006a, Jin et al., 2006b)
	4-(4'-Hydroxylphenyl)-2-butanone 4'-O-β-D-glucoside	(Jin et al., 2007)
	4-(4'-Hydroxyphenyl)-2-butanone-4'-O-β-D-(2''-O-galloyl-6''-O-p-cinnamoyl)-glucoside	(Gao et al., 2012a, Jin et al., 2007, Jin et al., 2006a)

Appendix II Secondary metabolites isolated from the root and rhizome of *Rheum tanguticum* Maxim. ex Balf. (RHE).		
Class	**Compound**	**Reference**
	4-(4'-hydroxyphenyl)-2-butanone-4'-O-β-D-(6"-O-galloyl-2"-O-cinnamoyl)-glucoside	(Jin et al., 2006b)
	4-(4'-Hydroxyphenyl)-2-butanone-4'-O-β-D-(2"-O-galloyl-6"-O-p-coumaroyl)-glucoside	(Jin et al., 2007, Jin et al., 2006a, Jin et al., 2006b)
	4-(4'-Hydroxyphenyl)-2-butanone-4'-O-β-D-(2"-O-galloyl-6"-O-galloyl)-glucoside	(Jin et al., 2007)
	4-(4'-Hydroxyphenyl)-2-butanone-4'-O-ß-D-(6"-O-cinnamoyl)-glucoside	(Gao et al., 2012a)
	4-(4'-Hydroxyphenyl)-2-butanone-4'-O-ß-D-(6"-O-galloyl-2"-O-cinnamoyl)-glucoside	(Jin et al., 2007, Jin et al., 2006b)
	4-(4'-Hydroxyphenyl)-2-butanone-4'-O-ß-D-(6"-O-p-coumaroyl)-glucoside	(Jin et al., 2007, Gao et al., 2014a)
	Isolindleyin	(Jin et al., 2007, Jin et al., 2006a, Jin et al., 2006b, Komatsu et al., 2006)
	Lindleyin	(Jin et al., 2007, Jin et al., 2006a, Jin et al., 2006b, Komatsu et al., 2006)
Procyanidin	Procyanidin B	(Jin et al., 2007)
	Procyanidin B 2 3'-O-gallate	(Komatsu et al., 2006)
	Procyanidin B2 3,3'-di-O-gallate	(Komatsu et al., 2006)
Stilbene	Resveratrol	(Jin et al., 2007, Jin et al., 2006a, Jin et al., 2006b)
Stilbene glycoside	Desoxyrhaponticin	(Li et al., 2014, Zhao et al., 2013b)
	Resveratrol-4'-O-β-D-glucoside	(Jin et al., 2007, Jin et al., 2006a, Jin et al., 2006b, Jin and Tu, 2005, Komatsu et al., 2006)
	Resveratrol-4'-O-β-D-(2"-O-galloyl)-glucoside	(Jin et al., 2007, Jin et al., 2006a, Jin et al., 2006b)
	Resveratrol-4'-O-β-D-(6"-O-galloyl)-glucoside	(Jin et al., 2007, Jin et al., 2006a, Jin et al., 2006b, Komatsu et al., 2006)
	Rhaponticin	(Li et al., 2014, Zhao et al., 2013b)
Others	2,5-Dimethyl-7-hydroxychromone-7-O-β-D-glucoside	(Gao et al., 2014a)
	2,5-Dimethyl-8-hydroxynaphthopyrone-10-O-β-D-glucoside	(Gao et al., 2014a)
	6-Methoxy-2-acetyl-3-methyl-1,4-naphthoquinone-8-O-β-D-glucoside	(Gao et al., 2014a)
	Phlorizin	(Gao et al., 2014a)

Appendix II Secondary metabolites isolated from the root and rhizome of *Rheum tanguticum* Maxim. ex Balf. (RHE).		
Class	**Compound**	**Reference**
	β-Sitosterol	(Jin et al., 2006a)

Appendix III Immunomodulatory activity of the root and rhizome of *Rheum tanguticum* Maxim. ex Balf. (RHE).				
Preparation	**Activity**	**Method**	**Dose**	**Reference**
		In vivo		
Polysaccharide-enriched fraction	Attenuated 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced ulcerative colitis in Sprague-Dawley (SD) rats as indicated by:		200 mg/kg; given intragastrically 6 hrs. after TNBS stimulation	(Liu et al., 2003)
	1.Inhibited $CD4^+$ T cells expansion,	Colon; immunohistochemical analysis/ Luminal lymphoid node; western-blot analysis		
	2.Inhibited the elevation of myeloperoxidase (MPO) activity [i.e. marker of neutrophil infiltration in the tissue],	Colon ; chromatometry		
	3.Attenuated ulcerative area.	Colon mucosae; ulcerative areas		
Polysaccharide-enriched fraction	Attenuated TNBS/ethanol-induced ulcerative colitis in BALB/c mice and TNBS-induced Crohn's disease in SD rats as indicated by:		200 mg/kg/day; given intragastrically for 5 days after TNBS stimulation	(Liu et al., 2005)
	1.Attenuated ulcerative area,	Colon mucosae; ulcerative areas		
	2.Attenuated the elevation of colon oedema,	Distal colon; weight		
	3.Inhibited the elevation of MPO activity,	Colonic mucosa; MPO activity assay		
	4.Inhibited $CD4^+$ T cells expansion,	Colon; immunohistochemical analysis/ Peripheral blood from caudal vein; flow cytometry/ Luminal lymphoid node; western-blot analysis		

Appendix III Immunomodulatory activity of the root and rhizome of *Rheum tanguticum* Maxim. ex Balf. (RHE).				
Preparation	**Activity**	**Method**	**Dose**	**Reference**
	5.Improved the imbalance of Th1 [i.e. IFN-γ] and Th2 [i.e. IL-4] cells.	Culture medium of lymphocytes derived from lymph nodes; ELISA		
Polysaccharide-enriched fraction	Attenuated TNBS-induced ulcerative colitis in SD rats as indicated by:		200 mg/kg/day; given intraperitoneally/ orally for 5 days after TNBS stimulation	(Liu et al., 2008)
	1.Attenuated ulcerative area,	Colon mucosae; ulcerative areas		
	2.Attenuated the elevation of colon oedema,	Distal colon; weight		
	3.Inhibited the elevation of MPO activity,	Colonic mucosa; MPO activity assay		
	4.Inhibited the elevated IFN-γ secretion and enhanced the decreased IL-4 secretion in macrophages [derived from the peritoneal exudates of rats with colitis] via targeting the mannose receptor (MR) in macrophage,	ELISA		
	5.Restored the decreased MR-mediated ligand binding and endocytosis of macrophages,	Measurement of MR ligand [i.e mannosyl bovine serum albumin-fluorescein isothiocyanate (MAN-BSA-FITC)] binding to MR in macrophage [i.e. fluorescence intensity measured using ELISA reader]		
	6.Protective effects against colorectal damage.	Colon ; H&E staining		
70% Ethanol extract	Attenuated 2,4-dinitrochlorobenzen (DNCB)-induced dermatitis in NC/Nga mice as indicated by:		30-300 mg/kg/day; given	(Jin et al., 2011)

Appendix III Immunomodulatory activity of the root and rhizome of *Rheum tanguticum* Maxim. ex Balf. (RHE).				
Preparation	**Activity**	**Method**	**Dose**	**Reference**
	1.Reduced skin severity score, 2.Reduced serum IgE and neutrophils concentration.	Mice; observation Serum; ELISA	orally for 5 weeks after DNCB stimulation	
In vitro				
70% Ethanol extract	Inhibited 5-lipoxygenase (5-LOX)-catalyzed leukotriene (LT) production in A23187-treated basophilic leukemia (BRL-1) cells [i.e. leukotriene is a pathological molecule of AD].	ELISA	30μg/ml	(Jin et al., 2011)

Appendix IV Compounds isolated from the root of *Scutellaria baicalensis* Georgi (SCU).		
Class	**Compound**	**Reference**
Flavanone and its glycoside	Carthamidin [5,6,7,4'-Tetrahydroxyflavanone]	(Qiao et al., 2016)
	Carthamidin 7-O-glucuronide	(Qiao et al., 2016)
	Dihydrobaicalein [5,6,7-Trihydroxyflavanone]	(Liu et al., 2009)
	Dihydrobaicalin [5,6,7-Trihydroxyflavanone 7-O-glucuronide]	(Zhang et al., 2007b, Tomimori et al., 1983, Qiao et al., 2016, Liu et al., 2009, Han et al., 2007)
	Dihydrooroxylin A [5,7-Dihydroxy-6-methoxyflavanone]	(Qiao et al., 2016)
	Dihydroxy-dimethoxyflavanone O-glucuronide	(Qiao et al., 2016)
	Dihydroxyflavanone	(Qiao et al., 2016)
	Dihydroxyflavanone O-glucuronide	(Qiao et al., 2016)
	Dihydroxy-methoxyflavanone	(Qiao et al., 2016)
	5,7-Dihydroxy-6-methoxyflavanone 7-O-β-D-glucoside	(Miyaichi and Tomimori, 1995)
	5,7-Dihydroxy-6-methoxyflavanone 7-O-β-D-glucuronide	(Qiao et al., 2016)
	5,7-Dihydroxy-2'-methoxyflavanone 7-O-β-D-glucuronide	(Liu et al., 2009)
	(-)-Eriodictyol [(2S)-5,7,3',4'-Tetrahydroxyflavanone]	(Zhang et al., 1994)
	Ganhuangemin [(2R,3R)-3,5,7,2',6'-Pentahydroxyflavanone]	(Qiao et al., 2016, Liu et al., 2009, Zhang et al., 2007b, Takagi et al., 1981b)
	Isocarthamidin 7-O-β-D-glucuronide	(Qiao et al., 2016, Seo et al., 2013)
	Pentahydroxyflavanone	(Seo et al., 2013)
	3,6,7,2',6'-Pentahydroxyflavanone	(Qiao et al., 2016)
	Pinocembrin	(Qiao et al., 2016)
	Tetrahydroxyflavanone	(Qiao et al., 2016)
	5,7,2',6'-Tetrahydroxyflavanone	(Qiao et al., 2016, Zhang et al., 1994)
	5,7,2',6'-Tetrahydroxyflavanone 2'-O-β-D-glucoside	(Qiao et al., 2016)
	5,7,2',5'-Tetrahydroxy-6-methoxyflavanone	(Qiao et al., 2016)
	Trihydroxy-methoxyflavanone	(Qiao et al., 2016)
	7,2',6'-Trihydroxy-5-methoxyflavanone	(Tomimori et al., 1984a)
	5,7,4'-Trihydroxy-6-methoxyflavanone	(Takagi et al., 1980)
	Trihydroxy-methoxyflavanone O-glucuronide	(Liu et al., 2009)

Appendix IV Compounds isolated from the root of *Scutellaria baicalensis* Georgi (SCU).		
Class	**Compound**	**Reference**
	5,7,2'-Trihydroxy-6-methoxyflavanone 7-O-β-D-glucuronide	(Qiao et al., 2016)
Flavone	Baicalein [5,6,7-Trihydroxyflavone]	(Qiao et al., 2016, Liu et al., 2009, Han et al., 2007, Zhang et al., 2007b, Lu et al., 2011)
	8,8''-Bibaicalein [5,5'',6,6'',7,7''-Hexahydroxy-8-8''-biflavone]	(Qiao et al., 2016, Liu et al., 2009, Zhang et al., 2007b)
	Chrysin [5,7-Dihydroxyflavone]	(Qiao et al., 2016, Liu et al., 2009, Seo et al., 2013, Zhang et al., 2007b, Lu et al., 2011)
	Dihydroxy-dimethoxyflavone	(Qiao et al., 2016)
	5,7-Dihydroxy-6,8-dimethoxyflavone	(Liu et al., 2009)
	5,8-Dihydroxy-6,7-dimethoxyflavone	(Qiao et al., 2016, Tomimori et al., 1982)
	6,2'-Dihydroxy-5,7,8,6'-tetramethoxyflavone	(Wang et al., 2002)
	5,6'-Dihydroxy-6,7,8,2'-tetramethoxyflavone	(Qiao et al., 2016)
	5,7-Dihydroxy-8,2',3',6'-tetramethoxyflavone	(Long et al., 2015)
	5,2'-Dihydroxy-7,8,6'-trimethoxyflavone	(Liu et al., 2009)
	Dihydronorwogonin	(Qiao et al., 2016)
	5-Hydroxy-7,8-dimethoxyflavone	(Tomimori et al., 1983)
	Norwogonin [5,7,8-Trihydroxyflavone]	(Qiao et al., 2016, Seo et al., 2013, Liu et al., 2009, Zhang et al., 2007b, Han et al., 2007)
	Oroxylin A [5,7-Dihydroxy-6-methoxyflavone]	(Qiao et al., 2016, Wang et al., 2014d, Liu et al., 2009, Zhang et al., 2007b, Han et al., 2007)
	Pentahydroxyflavone	(Seo et al., 2013)
	Pentahydroxy-methoxyflavone	(Qiao et al., 2016)
	Scutellarein [5,6,7,4'-Tetrahydroxyflavone]	(Qiao et al., 2016)
	Scutevulin [5,7,2'-Trihydroxy-8-methoxyflavone]	(Tomimori et al., 1984a)
	Skullcapflavone [5,2'-Dihydroxy-7,8,6'-trimethoxyflavone]	(Liu et al., 2009, Qiao et al., 2016)
	Skullcapflavone I [5,2'-Dihydroxy-7,8-dimethoxyflavone]	(Takido et al., 1975)
	Skullcapflavone II [5,2'-Dihydroxy-6,7,8,6'-tetramethoxyflavone]	(Liu et al., 2009, Seo et al., 2013, Takido et al., 1975, Zhang et al., 1994, Han et al., 2007)
	Tenaxin I [5,2'-Dihydroxy-6,7,8-trimethoxyflavone]	(Qiao et al., 2016, Liu et al., 2009, Seo et al., 2013, Han et al., 2007, Tomimori et al., 1983)

Appendix IV Compounds isolated from the root of *Scutellaria baicalensis* Georgi (SCU).		
Class	**Compound**	**Reference**
	Tenaxin II [5,7,2'-trihydroxy-6-methoxyflavone]	(Tomimori et al., 1983, Qiao et al., 2016)
	Tetrahydroxyflavone	(Qiao et al., 2016)
	5,7,2',3'-Tetrahydroxyflavone	(Tomimori et al., 1984a)
	5,7,2',5'-Tetrahydroxyflavone	(Zhang et al., 1994)
	5,7,2',6'-Tetrahydroxyflavone	(Qiao et al., 2016, Tomimori et al., 1982, Zhang et al., 2007b)
	Tetrahydroxy-methoxyflavone	(Qiao et al., 2016)
	Tetrahydroxy-trimethoxyflavone	(Qiao et al., 2016)
	Trihydroxy-dimethoxyflavone	(Qiao et al., 2016)
	5,8,2'-Trihydroxy-6,7-dimethoxyflavone	(Qiao et al., 2016)
	5,7,6'-Trihydroxy-8,2'-dimethoxyflavone	(Qiao et al., 2016)
	5,8,2'-Trihydroxy-6,7-dimethoxyflavone	(Takagi et al., 1980)
	5,7,2'-Trihydroxy-8,6'-dimethoxyflavone	(Zhang et al., 1994, Tomimori et al., 1984b)
	5,7,2'-Trihydroxyflavone	(Qiao et al., 2016, Tomimori et al., 1984b)
	3,5,7-Trihydroxy-4'-methoxyflavone	(Han et al., 2007)
	5,7,2'-Trihydroxy-6'-methoxyflavone	(Tomimori et al., 1984a)
	5,7,4'-Trihydroxy-6-methoxyflavone	(Takagi et al., 1980)
	5,8,2'-Trihydroxy-7-methoxyflavone	(Takagi et al., 1980)
	5,7,4'-Trihydroxy-8-methoxyflavone	(Qiao et al., 2016, Tomimori et al., 1982, Han et al., 2007)
	Trihydroxy-methoxyflavone	(Qiao et al., 2016)
	Trihydroxy-tetramethoxyflavone	(Qiao et al., 2016)
	Trihydroxy-trimethoxyflavone	(Qiao et al., 2016)
	5,2',5'-Trihydroxy-6,7,8-trimethoxyflavone	(Qiao et al., 2016, Tomimori et al., 1984b)
	Wogonin [5,7-Dihydroxy-8-methoxyflavone]	(Qiao et al., 2016, Wang et al., 2014d, Seo et al., 2013, Liu et al., 2009, Lu et al., 2011, Zhang et al., 2007b, Han et al., 2007)
	Viscidulin I [3,5,7,2',6'-Pentahydroxyflavone]	(Tomimori et al., 1984a, Liu et al., 2009, Zhang et al., 2007b, Qiao et al., 2016, Zhang et al., 1994)
	Viscidulin II [5,2,'6'-trihydroxy-7,8-dimethoxyflavone]	(Qiao et al., 2016, Tomimori et al., 1984a, Zhang et al., 1994)
	Viscidulin III [5,7,2',5'-Tetrahydroxy-8,6'-dimethoxyflavone]	(Qiao et al., 2016, Zhang et al., 1994, Liu et al., 2009, Tomimori et al., 1984b)

Appendix IV Compounds isolated from the root of *Scutellaria baicalensis* Georgi (SCU).		
Class	**Compound**	**Reference**
Flavone C-glycoside	Chrysin-6-C-α-L-arabinoside-8-C-β-D-glucoside	(Qiao et al., 2016, Takagi et al., 1981a, Seo et al., 2013, Liu et al., 2009, Zhang et al., 2007b, Han et al., 2007)
	Chrysin-6-C-β-L-arabinoside-8-C-β-D-glucoside	(Qiao et al., 2016)
	Chrysin 6,8-di-C-glucoside	(Han et al., 2007)
	Chrysin-6-C-β-D-glucoside-8-C-α-L-arabinoside	(Qiao et al., 2016, Takagi et al., 1981a, Seo et al., 2013, Liu et al., 2009, Zhang et al., 2007b, Han et al., 2007)
	Chrysin-6-C-β-D-glucoside-8-C-β-L-arabinoside	(Qiao et al., 2016)
	Chrysin-6-C-β-D-glucoside	(Qiao et al., 2016, Miyaichi and Tomimori, 1994)
	Chrysin-8-C-β-D-glucoside	(Qiao et al., 2016, Zhang et al., 1997, Miyaichi and Tomimori, 1994, Seo et al., 2013)
	Chrysin 6-C-hex-8-C-pen	(Qiao et al., 2016)
	Chrysin 6-C-pen-8-C-hex	(Qiao et al., 2016)
	Schaftoside [Apigenin 8-C-α-L-arabinoside 6-C-β-D-glucoside]	(Qiao et al., 2016, Seo et al., 2013, Han et al., 2007)
	Isoschaftoside [Apigenin 6-C-α-L-arabinoside 8-C-β-D-glucoside]	(Qiao et al., 2016)
Flavone O-glycoside	Apigenin 7-O-β-D-glucuronide	(Seo et al., 2013, Zhang et al., 2007b)
	Apigenin 7,4'-di-O-rhamnoside	(Seo et al., 2013)
	Baicalein 6-O-β-D-glucuronide	(Qiao et al., 2016, Seo et al., 2013, Liu et al., 2009)
	Baicalein 7-O-β-D-glucoside	(Qiao et al., 2016, Liu et al., 2009, Tomimori et al., 1984b, Han et al., 2007)
	Baicalein 7-O-β-D-ethylglucuronide	(Wang et al., 2014d)
	Baicalin [Baicalein 7-O-β-D-glucuronide]	(Seo et al., 2013, Liu et al., 2009, Han et al., 2007, Zhang et al., 2007b, Lu et al., 2011, Qiao et al., 2016)
	Baicalin methyl ester	(Ishimaru et al., 1995, Qiao et al., 2016)
	Chrysin 7-O-β-D-glucuronide	(Qiao et al., 2016, Seo et al., 2013, Liu et al., 2009, Miyaichi and Tomimori, 1994)
	Cynaroside [5,7,3',4'-Tetrahydroxyflavone 7-O-β-D-glucoside]	(Zhang et al., 2007b)
	5,7-Dihydroxy-6,8-dimethoxyflavone 7-O-β-D-glucuronide	(Liu et al., 2009, Wang et al., 2013a)
	5,7-Dihydroxy-8,2'-dimethoxyflavone 7-O-β-D-glucuronide	(Qiao et al., 2016)
	Dihydroxy-dimethoxyflavone 2'-O-glucuronide	(Qiao et al., 2016)

Appendix IV Compounds isolated from the root of *Scutellaria baicalensis* Georgi (SCU).		
Class	**Compound**	**Reference**
	Isorhamnetin-7-O-rhamnosyl-glucoside	(Han et al., 2007)
	Norwogonin 7-O-β-D-glucuronide	(Qiao et al., 2016, Seo et al., 2013, Liu et al., 2009)
	Norwogonin 8-O-β-D-glucuronide	(Qiao et al., 2016)
	Oroxylin A 7-O-β-D-glucoside	(Qiao et al., 2016, Seo et al., 2013, Liu et al., 2009)
	Oroxyloside [Oroxylin A 7-O-β-D-glucuronide]	(Qiao et al., 2016, Seo et al., 2013, Liu et al., 2009, Wang et al., 2014d)
	Oroxylin A 7-O-β-D-methylglucuronide	(Tomimori et al., 1982)
	Scutellarin [Scutellarein-7-O-β-D-glucuronide]	(Qiao et al., 2016, Liu et al., 2009, Han et al., 2007, Zhang et al., 2007b)
	5,7,2',6'-Tetrahydroxyflavone 2'-O-β-D-glucoside	(Qiao et al., 2016)
	5,2',6'-Trihyroxy-6,7-dimethoxyflavone 2'-O-β-D-glucoside	(Qiao et al., 2016, Ishimaru et al., 1995)
	7,3',4'-Trihydroxy-5,6-dimethoxyflavone 7-O-β-D-glucoside	(Han et al., 2007)
	Trihydroxy-methoxyflavone O-glucoside	(Qiao et al., 2016)
	5,7,2'-Trihyroxy-6-methoxyflavone 7-O-β-D-glucoside	(Qiao et al., 2016)
	Trihydroxy-methoxyflavone O-glucosyl-glucuronide	(Qiao et al., 2016)
	Trihydroxy-methoxyflavone O-glucuronide	(Qiao et al., 2016)
	5,7,2'-Trihyroxy-6-methoxyflavone 7-O-β-D-glucuronide	(Qiao et al., 2016, Liu et al., 2009)
	5,7,2'-Trihyroxy-6'-methoxyflavone 7-O-β-D-glucuronide	(Han et al., 2007, Luo et al., 2012)
	5,7,8-Trihyroxy-6-methoxyflavone 7-O-β-D-glucuronide	(Liu et al., 2009)
	5,6,7-Trihyroxy-8-methoxyflavone 7-O-β-D-glucuronide	(Liu et al., 2009)
	5,2',6'-Trihydroxy-6,7,8-trimethoxyflavone-2'-O-β-D-glucoside	(Qiao et al., 2016, Ishimaru et al., 1995)
	Viscidulin I 2'-O-β-D-glucoside	(Miyaichi and Tomimori, 1995)
	Viscidulin II 2'-O-β-D-glucuronide	(Qiao et al., 2016)
	Viscidulin II 2'-O-β-D-glucoside	(Miyaichi and Tomimori, 1995, Qiao et al., 2016)
	Viscidulin III 2'-O-β-D-glucoside	(Qiao et al., 2016, Zhang et al., 2007b)
	Wogonin 7-O-β-D-ethylglucuronide	(Wang et al., 2014d)
	Wogonin 5-O-β-D-glucoside	(Qiao et al., 2016, Han et al., 2007, Takagi et al., 1981b)
	Wogonin 7-O-β-D-glucoside	(Liu et al., 2009)
	Wogonin O-acetyl-diarabinoside	(Seo et al., 2013)

Appendix IV Compounds isolated from the root of *Scutellaria baicalensis* Georgi (SCU).		
Class	**Compound**	**Reference**
	Wogonin O-glucosyl-glucuronide	(Qiao et al., 2016, Han et al., 2007)
	Wogonoside [Wogonin-7-O-glucuronide]	(Qiao et al., 2016, Wang et al., 2014d, Liu et al., 2009, Han et al., 2007, Zhang et al., 2007b, Lu et al., 2011, Seo et al., 2013)
Phenylethanoid glycoside	Acteoside	(Qiao et al., 2016, Zhang et al., 1997, Miyaichi and Tomimori, 1994, Seo et al., 2013)
	Acteoside isomer	(Qiao et al., 2016)
	Cistanoside C	(Qiao et al., 2016)
	Cistanoside D	(Qiao et al., 2016)
	Cistanoside D isomer	(Qiao et al., 2016)
	Darendoside A	(Miyaichi and Tomimori, 1995)
	Darendoside B	(Miyaichi and Tomimori, 1995)
	2-(3-hydroxy-4-methoxyphenyl)ethyl 1-O-α-L-rhamnosyl-(1 à 3)-β-D-(4-feruloyl)glucoside	(Takagi et al., 1981b)
	Isomartynoside	(Miyaichi and Tomimori, 1994)
	Leucosceptoside A	(Qiao et al., 2016, Miyaichi and Tomimori, 1994)
	Leucosceptoside A isomer	(Qiao et al., 2016)
	Salidroside	(Miyaichi and Tomimori, 1995)
Phenolic acid	Chlorogenic acid	(Lu et al., 2011)
	Ferulic acid	(Lu et al., 2011)
	4-Hydroxybenzoic acid	(Qiao et al., 2016)
	Protocatechuic acid	(Qiao et al., 2016)
Others	Benzyl O-β-D-apiofuranosyl-(1→2)-β-D-glucoside	(Miyaichi and Tomimori, 1995)
	Campesterol	(Takido et al., 1975)
	Chrysin-7-O-glucosyl-8-C-glucoside	(Han et al., 2007)
	(+)-5,5'-Dimethoxylariciresinol	(Miyaichi and Tomimori, 1994, Liu et al., 2009, Miyaichi and Tomimori, 1998)
	Eythro-guaiacylglycerol-β-syringaresinol ether 4"-O-β-D-glucoside	(Miyaichi and Tomimori, 1998)
	Hedyotol C-4"-O-β-D-glucoside	(Miyaichi and Tomimori, 1998)
	Hedyotol D-4"-O-β-D-glucoside	(Miyaichi and Tomimori, 1998)

Appendix IV Compounds isolated from the root of *Scutellaria baicalensis* Georgi (SCU).		
Class	**Compound**	**Reference**
	Rutin	(Alolga et al., 2015)
	β-Sitosterol	(Takido et al., 1975)
	Stigmasterol	(Takido et al., 1975)
	(+)-Syringaresinol O-β-D-glucooside	(Miyaichi and Tomimori, 1994)
	2,6,2',4'-Tetrahydroxy-6'-methoxychalcone	(Tomimori et al., 1984a)
	2',4',6'-Trihydroxydihydrochalcone 3'-C-β-D-glucoside-6'-O-β-D-glucoside	(Qiao et al., 2016)
	2',4',6'-Trihydroxydihydrochalcone 3'-C-β-D-glucoside-6'-O-β-D-glucoside isomer	(Qiao et al., 2016)
	5,7,6'-trihydroxy-2'-methoxyflavonol	(Long et al., 2015)

Appendix V Immunomodulatory activity of the root of *Scutellaria baicalensis* Georgi (SCU).				
Preparation	**Activity**	**Method**	**Dose**	**Reference**
		In vivo		
Butanol soluble fraction of decoction	Attenuated zymosan-induced inflammation in Balb/c mice (12-13 weeks old) as indicated by:		500 or 750 mg/kg/day; given orally for 10 days before induction of the air pouch and injection of zymosan into the air pouch	(Kim et al., 2009a)
	1.Reduced leukocytes infiltration,	Exudates; hemocytomer		
	2.Inhibited the induction of NO and iNOS mRNA expression,	Exudates; Griess reagent and RT-PCR		
	3.Inhibited the induction of PGE_2 production and COX-2 mRNA expression,	Exudates; PGE_2 assay kit and RT-PCR		
	4.Inhibited the induction of IL-1β, IL-2, IL-6, IL-12 and TNF-α protein and mRNA expression and IκBα and NF-κB mRNA expression.	Exudates; ELISA and RT-PCR		
30% Ethanol extract	Inhibited 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis in female C57BL/6 mice (6 weeks old) as indicated by:		25 mg/kg/day; given orally for 6 days after TNBS stimulation	(Jiang et al., 2015)
	1.Attenuated colon shortening,	Colon; length		
	2.Inhibited the induction of TNF-α and IL-1β mRNA expression,	Colon; RT-PCR		
	3.Inhibited the induction of COX-2 expression.	Colon; Immunohistochemical analysis		

Appendix V Immunomodulatory activity of the root of *Scutellaria baicalensis* Georgi (SCU).				
Preparation	**Activity**	**Method**	**Dose**	**Reference**
	Prevented dextran sulfate sodium (DSS)-induced colitis in mice as indicated by:		25 mg/kg/day; given orally for 4 days followed by co-administration with DSS for 6 days	
	1. Attenuated body weight loss,	Mice; body weight		
	2. Attenuated colon shortening,	Colon; colon length		
	3. Proliferation of epithelial cells.	Colon; BrdU in situ hybridization		
	Attenuated DSS-induced colitis in mice as indicated by:		25 mg/kg/day; given orally for 4 days after the 5 days DSS stimulation	
	1. Attenuated body weight loss,	Mice; body weight		
	2. Attenuated colon shortening.	Colon; colon length		
70% Ethanol extract	Attenuated ovalbumin (OVA)-induced food allergy symptoms in female BALB/mice (6 weeks old) as indicated by:		25 mg/kg/day; given orally for 18 days (with co-administration of OVA every 3 days) after the 17 days OVA plus alum stimulation	(Shin et al., 2014)
	1. Suppressed anaphylactic response,	Mice; symptoms		
	2. Suppresed the elevation of rectal temperature,	Mice; Thermalert TH5 monitoring thermometer		
	3. Inhibited the induction of Ig E,	Serum; ELISA		
	4. Inhibited the induction of IL-17, IL-4, IL-5, IL-10 and IL-13.	Splenocytes; cytokine assay kit		

Appendix V Immunomodulatory activity of the root of *Scutellaria baicalensis* Georgi (SCU).				
Preparation	**Activity**	**Method**	**Dose**	**Reference**
80% Ethanol extract	Inhibited anti-dintrophenyl (DNP) Ig E-induced Ig E dependent cutaneous reaction in female Sprague-Dawley (SD) rats (6 weeks old).	Dorsal skin; dye area after injection of DNP-human serum albumin (HAS) antigen	280 mg/kg; given orally for one hr after the 47 hrs anti-DNP Ig E stimulation	(Jung et al., 2012)
Methanol extract	Improved oxazolone-induced AD-like skin lesions in female mice (five weeks old) as indicated by:		250 and 500 mg/kg/day; given orally for 32 days after the 21 days oxazolone stimulation	(Song et al., 2012)
	1.Suppressed mast cell infiltration,	Dorsal skin; Stained with toluidine blue		
	2.Attenuated development of clinical symptoms.	Dorsal skin; Clinical severity scores [i.e. sum of erosion/excoriation/hemorrhage and dryness/scaling]		
		In vitro		
Butanol soluble fraction of decoction	Inhibited lipopolysaccharide (LPS)-induced inflammatory mediator NO, PGE_2, IL-1β, IL-2, IL-6, IL-12 and TNF-α production and iNOS and COX-2 mRNA expression in RAW 264.7 macrophages.	Griess reagent/ PGE_2 assay kit/ RT-PCR/ ELISA	300 μg/ml	(Kim et al., 2009a)
	Linked to the inhibition of c-Raf-1, MEK1/2, IκB kinase αβ, IκBα and JNK, ERK1/2 and p38 MAPKs phosphorylation, NF-κB and IκBα mRNA expression and NF-κB p65 and p50 translocation.	Immunoblotting		

Appendix V Immunomodulatory activity of the root of *Scutellaria baicalensis* Georgi (SCU).				
Preparation	**Activity**	**Method**	**Dose**	**Reference**
Decoction	Inhibited LPS-induced inflammatory mediator NO in RAW 264.7 macrophages.	ELISA	25, 50, 100, 200 μg/ml	(Yoon et al., 2009a)
	Inhibited LPS-induced inflammatory mediator IL-1α, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-12p40, IL-13, IL-17, IP-10, keratinocyte-derived chemokine and vascular endothelial growth factor (VEGF) in RAW 264.7 macrophages.	Multiplex bead array assay based on xMAP technology		
30% Ethanol extract	Attenuated TNF-α-induced COX-2 expression in HT029 cells.	Western blot analysis	10, 20 and 50 μg/ml	(Jiang et al., 2015)
	Linked to the inhibition of JNK1/2 and p38 MAPKs phosphorylation.			
80% Ethanol extract	1.Inhibited compound 48/80-induced histamine production in rat peritoneal mast cells,	O-phthalaldehyde spectrofluorometric procedure	1, 10, and 100 μg/ml	(Jung et al., 2012)
	2.Inhibited phorbol 12-myristate 13-acetate (PMA) plus calcium ionophore A23187-induced TNF-α and IL-8 production in human mast cells [HMC-1 cells];	ELISA		
	1 and 2 were linked to the inhibition of ERK, JNK and p38 MAPK phosphorylation in HMC-1 cells.	Western blot analysis		
	1. Inhibited LPS-induced IL-6 and TNF-α expression in murine macrophage RAW264.7 cells,	RT-PCR and ELSIA	40 (except IL-6),70 and 100 μg/ml	(Hong et al., 2013)

Appendix V Immunomodulatory activity of the root of *Scutellaria baicalensis* Georgi (SCU).				
Preparation	**Activity**	**Method**	**Dose**	**Reference**
70% Methanol extract	2.Inhibited LPS-induced COX-2 and iNOS expression in murine macrophage RAW264.7 cells;	RT-PCR and Western blot analysis	10,40,70 and 100 μg/ml	
	1 and 2 were linked to the inhibition of IκBα degradation, NF-κB p65 translocation and ERK, JNK and p38 MAPK phosphorylation.	Western blot analysis	10 (MAPK only), 40 (MAPK only), 70 (MAPK only) and 100 μg/ml	
Methanol extract	Inhibited ovalbumin-induced histamine and leukotriene production in mast cell obtained from female guinea pigs' lung.	Fluorometric method and ELISA	10, 30, or 60 μg/mL;	(Kim et al., 2010a)
Methanol soluble fraction of ethyl acetate extract	Inhibition of IL-1β-induced PGE_2 and LT B_4 production in human gingival fibroblasts.	EIA	1 μg/mL	(Chung et al., 1995)

Appendix VI Compounds isolated from the root bark of *Dictamnus dasycarpus* Turcz. (DIC).		
Class	**Compound**	**Reference**
Alkaloid	Dictamnin A	(Bai et al., 2014a)
	Dictamnin B	(Bai et al., 2014a)
	Dasycarine	(Du et al., 2005, Chen et al., 2000)
	Dictamnine	(Bai et al., 2014b, Zhao et al., 1998a, Xiang et al., 2008, Du et al., 2005, Chen et al., 2000, Jiang et al., 2006a, Yang et al., 2011a, Lv et al., 2015, Wu et al., 1994, Yoon et al., 2012)
	Dictangustine A	(Yoon et al., 2012)
	3-Chloro-8,9-dimethoxygeibalansine	(Yang et al., 2011a)
	1',2'-Didehydro-7,8-dimethoxyplatydesmine	(Yang et al., 2011a)
	5,9-Dimethoxy-2,2-dimethyl-[2H]-pyranol[2,3-b]quinoline	(Yang et al., 2011a)
	(3R)-(-)-8,9-Dimethoxygeibalansine	(Yang et al., 2011a)
	7,8-Dimethoxymyrtospine	(Yang et al., 2011a, Wu et al., 1994)
	7,8-Dimethoxyplatydesmine	(Wu et al., 1994)
	O-Ethylnordictamnine	(Lin and Shieh, 1986)
	O-Ethylnor- γ-fagarine	(Lin and Shieh, 1986)
	O-Ethylnorskimmianine	(Lin and Shieh, 1986)
	γ-Fagarine	(Xiang et al., 2008, Du et al., 2005, Lv et al., 2015, Wu et al., 1994, Yoon et al., 2012)
	Haplopine	(Zhao et al., 1998a, Yoon et al., 2012)
	5-Hydroxy-4,8-dimethoxy furoquinoline	(Lv et al., 2015)
	3-[1β-Hydroxy-2(β-D-glucosyloxy)-ethyl]-4-methoxy-2(1H)-quinolinone	(Yoon et al., 2012)
	Isodictamnine	(Lv et al., 2015)
	Iso-γ-fagarine	(Yoon et al., 2012)
	Isomaculosidine	(Yoon et al., 2012)
	Kokusaginin	(Lv et al., 2015)
	Maculosidin	(Lv et al., 2015)
	5 or 6 or 7-Methoxydictamnine	(Lv et al., 2015)
	8-Methoxy-N-methylflindersine	(Yoon et al., 2012)

Appendix VI Compounds isolated from the root bark of *Dictamnus dasycarpus* Turcz. (DIC).		
Class	**Compound**	**Reference**
	Platydesmine	(Wu et al., 1994)
	Preskimmianine	(Xiang et al., 2008, Yoon et al., 2012)
	Robustine	(Lv et al., 2015)
	Skimmianine	(Xiang et al., 2008, Du et al., 2005, Lv et al., 2015, Yoon et al., 2012)
Coumarin	Furocoumarin	(Komissarenko et al., 1983)
	Scopoletin	(Bai et al., 2014b)
Flavone	Luteolin	(Wang, 2006)
	Quercetin	(Bai et al., 2014b)
	Rutin	(Bai et al., 2014b)
	5,7,4'-Trihydroxy-3'-methoxyisoflavone	(Wang, 2006)
	Wogonin	(Du et al., 2005)
Limonoid	7α-Acetyldihydronomilin	(Zhao et al., 1998a)
	7α-Acetylobacunol	(Zhao et al., 1998a)
	Calodendrolide	(Zhao et al., 1998a, Lv et al., 2015, Yoon et al., 2008)
	Dasycarpol	(Zhao et al., 1998a, Yoon et al., 2008)
	Dihydroobacunone	(Chen et al., 2000)
	Dictamdiol	(Jiang et al., 2006a, Yoon et al., 2008)
	Dictamdiol A	(Yoon et al., 2008)
	Dictamdiol B	(Yoon et al., 2008)
	Dictamnusine	(Yoon et al., 2008)
	Dasylactone A	(Yang et al., 2011a, Wang et al., 2014c)
	Dasylactone B	(Yang et al., 2011a, Wang et al., 2014c)
	Fraxinellone	(Bai et al., 2014b, Zhao et al., 1998a, Xiang et al., 2008, Du et al., 2005, Chen et al., 2000, Jiang et al., 2006a, Yang et al., 2011a, Lv et al., 2015, Wu et al., 1994, Wang et al., 2014c, Yoon et al., 2008)
	Fraxinellonone	(Bai et al., 2014b, Du et al., 2005, Jiang et al., 2006a, Yang et al., 2011a, Yoon et al., 2008)
	6β-Hydroxyfraxinellone	(Zhao et al., 1998a, Yang et al., 2011a)
	9α-Hydroxyfraxinellone-9-O-β-D-glucoside	(Yoon et al., 2008)

Appendix VI Compounds isolated from the root bark of *Dictamnus dasycarpus* Turcz. (DIC).		
Class	**Compound**	**Reference**
	Isodictamdiol	(Lv et al., 2015)
	Isofraxinellone	(Zhao et al., 1998a, Yang et al., 2011a, Wang et al., 2014c)
	Kihadanin A	(Wang et al., 2014c)
	Kihadanin B	(Xiang et al., 2008, Du et al., 2005, Wang et al., 2014c)
	Kihadanin C	(Wang et al., 2014c)
	Limonin	(Bai et al., 2014b, Zhao et al., 1998a, Jiang et al., 2006a, Lv et al., 2015, Wu et al., 1994, Yoon et al., 2008)
	Limonin diosphenol	(Zhao et al., 1998a, Xiang et al., 2008, Du et al., 2005)
	Limonoic acid	(Yang et al., 2011a)
	23-Methoxydasylactone A	(Wang et al., 2014c)
	Obacunone	(Bai et al., 2014b, Zhao et al., 1998a, Xiang et al., 2008, Du et al., 2005, Chen et al., 2000, Jiang et al., 2006a, Yang et al., 2011a, Lv et al., 2015, Wu et al., 1994, Wang et al., 2014c, Yoon et al., 2008)
	Rutaevin	(Bai et al., 2014b, Xiang et al., 2008, Du et al., 2005, Yang et al., 2011a, Lv et al., 2015, Yoon et al., 2008)
	Rutaevin acetate	(Yang et al., 2011a)
Sesquiterpene and its glycoside	Dictamnadiol	(Guo et al., 2012a)
	Dictamnol	(Naoki et al., 1993, Zhao et al., 1998a, Xiang et al., 2008)
	Dictamnoside A	(Chang et al., 2001, Zhao et al., 1998b)
	Dictamnoside B	(Chang et al., 2001, Zhao et al., 1998b)
	Dictamnoside C	(Zhao et al., 1998b)
	Dictamnoside D	(Chang et al., 2001, Zhao et al., 1998b)
	Dictamnoside E	(Zhao et al., 1998b)
	Dictamnoside F	(Zhao et al., 1999)
	Dictamnoside G	(Chang et al., 2001, Zhao et al., 1999)
	Dictamnoside H-N	(Chang et al., 2001)
	β-Elemol	(Zhao et al., 1998a)
	Radicol	(Xiang et al., 2005, Xiang et al., 2008)
Others	Dasycarpusenester A	(Guo et al., 2012b)

Appendix VI Compounds isolated from the root bark of *Dictamnus dasycarpus* Turcz. (DIC).		
Class	**Compound**	**Reference**
	Dasycarpusenester B	(Guo et al., 2012b)
	Dasycarpuside A	(Chang et al., 2002)
	Dasycarpuside B	(Chang et al., 2002)
	Dasycarpusacid	(Guo et al., 2012b)
	Daucosterol	(Bai et al., 2014b, Xiang et al., 2008)
	Dictabretols A-D	(Kim et al., 2015)
	Dictamnaindiol	(Guo et al., 2012a)
	3β-Hydroxy-cholesta-5-ene	(Bai et al., 2014b)
	5-Hydroxymethylfuraldehyde	(Bai et al., 2014b)
	7α-Hydroxysitosterol	(Zhao et al., 1998a)
	6β-Hydroxystigmast-4-en-3-one	(Wu et al., 1994)
	2-Methoxy-4-hydroxymethylphenol 1-O-α-rhamnopyranosyl-(1" à 6')-β-glucoside	(Chang et al., 2002)
	2-Methoxy-4-acetylphenol 1-O-α-rhamnopyranosyl-(1" à 6')-β-glucoside	(Chang et al., 2002)
	2-Methoxy-4-(8-hydroxyethyl)-phenol 1-O-α-rhamnopyranosyl-(1" à 6')-β-glucoside	(Chang et al., 2002)
	3'-O-methyltaxifolin	(Wang, 2006)
	Pregnenolone	(Zhao et al., 1998a, Wu et al., 1994)
	Progesterone	(Wu et al., 1994)
	β-Sitosta-4,22-diene-3-one	(Wu et al., 1994)
	β-Sitosta-4-ene-3-one	(Wu et al., 1994)
	β-Sitosterol	(Bai et al., 2014b, Zhao et al., 1998a, Xiang et al., 2008, Du et al., 2005, Chen et al., 2000, Wu et al., 1994)
	Stigmasterol	(Wu et al., 1994)

Appendix VII Immunomodulatory activity of the root bark of *Dictamnus dasycarpus* Turcz. (DIC).				
Preparation	**Activity**	**Method**	**Dose**	**Reference**
		In vivo		
70% Ethanol extract	Inhibited compound 48/80-induced allergy in female ICR mice (6-10 weeks old) as indicated by:			(Jiang et al., 2008)
	1.Reduced mortality rate,	Mice; percentage of mortality	100, 200 and 500 mg/kg, given orally 1 hr before compound 48/80 stimulation	
	2.Reduced scratching behavior,	Mice; scratching behaviour per hr	500 mg/kg, given orally 1 hr before compound 48/80 stimulation	
	3.Inhibited elevation of vascular permeability.	Skin; dye area after injection of Evans blue solution intravenously		
	Inhibited histamine- or serotonin- induced scratching behavior in female ICR mice (6-10 weeks old).	Mice; scratching behaviour per hr	200mg/kg (serotonin only) and 500mg/kg given orally 1 hr before compound 48/80 stimulation	
Methanol extract	Inhibited 1-fluoro-2,4-dinitrofluorobenzene (DNFB)-induced contact dermatitis in male Balb/c mice (6 weeks old) as indicated by:			(Kim et al., 2013)
	1.Inhibited increases in ear weight and thickness,	Ear; thickness and weight	30 and 300 μg/ear; given topically every 2 days for 4 times (on day 8, 10, 12 and 14) after DNFB	
	2.Inhibited spongiosis, edema, hyperplasia and immune cell infiltration,	Ear; hematoxylin and eosin staining		

Appendix VII Immunomodulatory activity of the root bark of *Dictamnus dasycarpus* Turcz. (DIC).				
Preparation	**Activity**	**Method**	**Dose**	**Reference**
	3.Inhibited the induction of IFN-γ and TNF-α.	Ear; cytometric bead array kit	stimulation (on day 7, 9, 11 and 13) and sensitization (on day 1-6)	
Methanol extract	Inhibited DNFB-induced contact dermatitis in male Balb/c mice (6 weeks old) as indicated by:			(Han et al., 2015)
	1.Inhibited increases in ear thickness,	Ear; thickness	300 μg/ear; given topically every 2 days for 4 times after DNFB stimulation and sensitization	
	2.Inhibited the induction of ICAM-1 expression,	Ear; ICAM-1 expression score	30 and 300 μg/ear; given topically every 2 days for 4 times after DNFB stimulation and sensitization	
	3.Inhibited the infiltration of immune cells in skin lesion.	Ear ; H&E staining		
In vitro				
70% Ethanol extract	Inhibited compound 48/80-induced histamine release from rat peritoneal mast cells.	Flourometric assay	100 and 300 μg/ml	(Jiang et al., 2008)
Methanol extract	Inhibited phorbol 12-myristate 13-acetate (PMA)-plus calcium ionophore A23187-induced β-Hexosaminidase and histamine release in RBL-2H3 mast cell-like leukemia cells.	β-Hexosaminidase release assay/ EIA	50 (except histamine), 100, 200 and 400 μg/ml	(Kim et al., 2013)
	Linked to the inhibition of p38 MAPK phosphorylation.	Western blot analysis	25, 100 and 400 μg/ml	
	1.Inhibited TNF-α-induced ICAM-1 expression in	Flow cytometric analysis	200 mg/ml	

Appendix VII Immunomodulatory activity of the root bark of *Dictamnus dasycarpus* Turcz. (DIC).				
Preparation	**Activity**	**Method**	**Dose**	**Reference**
Methanol extract	HaCaT human keratinocyte cells,			(Han et al., 2015)
	2.Inhibited human monocytic cells (THP-1) binding to the HaCaT cells.	Fluorescence microscopy	25,50 and 100 μg/ml	
	3.Inhibited TNF-α-induced expression of IL-6, IL-8, CXCL9, CCL2 and CCL5 in HaCaT cells;	Cytometric bead array method (Moncunill et al., 2014)	For IL-6, IL-8 and CCL2: 25 (except CCL2), 50 and 100 μg/ml; For CXCL9 and CCL5: 100 μg/ml	
	1,2 and 3 were linked to the inhibition of TNF-α-induced NF-κB p65 and IκBα phosphorylation.	Western blot analysis	12.5,25,50 and 100 μg/ml	

Appendix VIII Compounds isolated from the root of *Sophora flavescens* Aiton (SOP).		
Class	**Compound**	**Reference**
Alkaloid (matridine skeleton)	(+)-Allomatrine	(Liu et al., 2010a)
	Aloperine	(Lin et al., 2011)
	(−)-9*α*-Hydroxy-7,11-dehydromatrine	(Liu et al., 2010a)
	(+)-9α-Hydroxymatrine	(Liu et al., 2011, Liu et al., 2010a)
	(−)-14β-Hydroxymatrine	(Liu et al., 2010a)
	9α-Hydroxysophocarpine	(Liu et al., 2010a, Liu et al., 2011)
	7α-Hydroxysophoramine	(Liu et al., 2011)
	9α-Hydroxysophoramine	(Liu et al., 2010a, Liu et al., 2011)
	(+)-Isomatrine	(Liu et al., 2010a, Liu et al., 2011)
	Isosophocarpine	(Liu et al., 2011)
	Leontalbinine [(+)-7,11-Dehydromatrine]	(Liu et al., 2010a, Liu et al., 2011)
	Leontalbinine N-oxide	(Liu et al., 2011)
	(+)-Matrine	(Liu et al., 2010a, Liu et al., 2011, Zhang and Chen, 2013)
	(+)-Oxymatrine	(Liu et al., 2010a, Liu et al., 2011)
	(+)-Oxysophocarpine	(Liu et al., 2011, Liu et al., 2010a)
	(−)-Sophocarpine	(Liu et al., 2010a, Liu et al., 2011)
	(+)-Sophoramine	(Liu et al., 2010a)
	(+)-Sophoranol [(+)-5α-Hydroxymatrine]	(Liu et al., 2011, Liu et al., 2010a)
	(−)-Sophoridine	(Liu et al., 2010a, Liu et al., 2011)
Alkaloid (non-matridine skeleton)	(-)-Anagyrine	(Liu et al., 2011)
	Baptifoline	(Liu et al., 2011)
	Cytisine	(Liu et al., 2011)
	Flavascensine	(Liu et al., 2010a)
	Isokuraramine	(Liu et al., 2011)
	Kuraramine	(Liu et al., 2011)
	Lamprolobine	(Liu et al., 2011)
	Lupanine	(Liu et al., 2011)
	Mamanine	(Liu et al., 2011)

Appendix VIII Compounds isolated from the root of *Sophora flavescens* Aiton (SOP).		
Class	**Compound**	**Reference**
	(−)-N-methylcytisine	(Liu et al., 2010a, Liu et al., 2011)
Coumarin	Umbelliferone	(Jung et al., 2005a, Zhang et al., 2000)
Chalcone	Demethylkuraridin	(Zhang et al., 2008)
	Demethylxanthohumol	(Zhang et al., 2008)
	Isokuraridin	(Zhang et al., 2008)
	Kuraridin	(Ryu et al., 1997, Zhang et al., 2008, Jung et al., 2005a, Kim et al., 2010b, Quang et al., 2012, Yang et al., 2011b, Zhang et al., 2007a, Woo et al., 1998)
	Kuraridinol	(Zhang et al., 2007a, Zhang et al., 2008, Jung et al., 2010, Woo et al., 1998)
	Kushenol D	(Zhang et al., 2008, Zhang et al., 2007a)
	7,9,2',4'-Tetrahydroxy-8-isopentenyl-5-methoxychalcone	(Choi et al., 2010, Lee et al., 2010)
	Xanthohumol	(Zhang et al., 2008, Zhang et al., 2007a, Jung et al., 2005a, Jung et al., 2010)
Flavanone	3β,7,4'-Trihydroxy-5-methoxy-8-(γ,γ-dimethylallyl)-flavanone	(Jung et al., 2005a, Quang et al., 2012)
	Isokurarinone	(Zhang et al., 2008, Zhang et al., 2007a)
	Isoxanthohumol	(Zhang et al., 2008, Zhang et al., 2007a, Quang et al., 2012)
	Kosamol Q	(Zhang et al., 2007a)
	Kosamol R	(Zhang et al., 2007a)
	Kurarinol	(Ryu et al., 1997, Zhang et al., 2008, Yang et al., 2011b, Woo et al., 1998)
	(−)-Kurarinone	(Ryu et al., 1997, Zhang et al., 2008, Kang et al., 2000b, Zhang et al., 2007a, Kim et al., 2010b, Quang et al., 2012, Yang et al., 2011b)
	Kushenol A	(Zhang et al., 2007a, Kim et al., 2010b, Yang et al., 2011b)
	Kushenol B	(Ryu et al., 1997)
	Kushenol E	(Ryu et al., 1997, Wu et al., 1985a)
	Kushenol F	(Zhang et al., 2008, Wu et al., 1985a)
	Kushenol P	(Yang et al., 2011b)
	Kushenol T	(Quang et al., 2012)

Appendix VIII Compounds isolated from the root of *Sophora flavescens* Aiton (SOP).		
Class	**Compound**	**Reference**
	Kushenol U	(Kim et al., 2010b)
	Leachianone G	(Jung et al., 2010)
	2'-Methoxykurarinone	(Zhang et al., 2008, Kang et al., 2000b, Zhang et al., 2007a, Jung et al., 2005a, Quang et al., 2012)
	Neokurarinol	(Yang et al., 2011b)
	Norkurarinol	(Quang et al., 2012, Zhang et al., 2007a)
	Sophoraflavanone B	(Zhang et al., 2008)
	Sophoraflavanone G / Norkurarinone	(Ryu et al., 1997, Kang et al., 2000b, Zhang et al., 2007a, Kim et al., 2010b, Zhang et al., 2008, Quang et al., 2012, Yang et al., 2011b)
Flavanonol	Kosamol A	(Ryu et al., 1997)
	Kushenol H	(Zhang et al., 2008, Ryu et al., 1997, Yang et al., 2011b, Woo et al., 1998, Wu et al., 1985a)
	Kushenol I	(Zhang et al., 2008, Zhang et al., 2007a, Yang et al., 2011b, Wu et al., 1985a)
	Kushenol J	(Wu et al., 1985b)
	Kushenol K	(Yang et al., 2011b, Woo et al., 1998, Wu et al., 1985b)
	Kushenol L	(Ryu et al., 1997, Zhang et al., 2008, Wu et al., 1985b)
	Kushenol M	(Ryu et al., 1997, Ryu et al., 1995, Wu et al., 1985b)
	Kushenol N	(Zhang et al., 2007a, Ryu et al., 1997, Wu et al., 1994, Yang et al., 2011b)
	Kushenol X	(Yang et al., 2011b)
	Kushenol Y	(Yang et al., 2011b)
Flavonol	Desmethylanhydroicaritin	(Jung et al., 2005a)
	Kushenol C	(Zhang et al., 2007a, Jung et al., 2010)
	Kushenol G	(Wu et al., 1985a)
	8-Lavandulylkaempferol	(Jung et al., 2010, Yang et al., 2011b, Jung et al., 2005b)
	Noranhydroicaritin	(Zhang et al., 2013a)
	Sophoflavescenol	(Woo et al., 1998)
Isoflavanone	Sophoraisoflavanone A	(Zhang et al., 2007a)

Appendix VIII Compounds isolated from the root of *Sophora flavescens* Aiton (SOP).		
Class	**Compound**	**Reference**
Isoflavone and its glycoside	3',7-Dihydroxy-4'-methoxy isoflavone	(Zhang et al., 2007a)
	Formononetin	(Ryu et al., 1997, Zhang et al., 2007a, Kang et al., 2000b, Jung et al., 2005a, Quang et al., 2012, Li et al., 2004)
	Kushenol O	(Zhang et al., 2007a, Wu et al., 1994)
	4'-methoxyisoflavone-7-O- β-D-apiofuranosyl-(1 à 6)- β-D-glucoside	(Zhang et al., 2013a)
	6"-β-D-Xylopyranosylgenistin	(Zhang et al., 2013a)
Pterocarpan	(−)-4-Hydroxy-3-methoxy-(6aR,11aR)-8,9-methylenedioxypterocarpan	(Jung et al., 2005a)
	Kushecarpins A	(Zhang et al., 2007a)
	(−)-Maackiain	(Zhang et al., 2007a, Kang et al., 2000b, Jung et al., 2005a, Li et al., 2004)
	Trifolirhizin	(Zhang et al., 2007a, Jung et al., 2005a, Ryu et al., 1997, Woo et al., 1998)
	Trifolirhizin 6"-malonate	(Zhang et al., 2007a, Li et al., 2004)
	Trifolirhizin 6'-monoacetate	(Zhang et al., 2013a)
Triterpenoid and its saponin	Lupeol	(Zheng et al., 2014)
	Sophoraflavoside I	(Yoshikawa et al., 1985)
	Soyasaponin I	(Yoshikawa et al., 1985)
Others	2,4-Dihydroxy benzoic acid	(Li et al., 2004)
	trans-Hexadecyl ferulic acid	(Jung et al., 2005a)
	trans-Hexadecyl sinapic acid	(Jung et al., 2005a)
	Kushequinone A	(Wu et al., 1986)
	Lignoceric acid	(Zhang et al., 2000)
	cis-Octadecyl ferulic acid	(Jung et al., 2005a)
	β-Sitosterol	(Zhang et al., 2000, Zhang et al., 2010b, Li et al., 2004)
	Sucrose	(Zhang et al., 2000)

Appendix IX Immunomodulatory activity of the root of *Sophora flavescens* Aiton (SOP).				
Preparation	**Activity**	**Method**	**Dose**	**Reference**
		In vivo		
Alkaloid-free flavonoid enriched fraction of the ethanol extract	Attenuated adjuvant-induced arthritic inflammation in Wister rats (4-6 weeks old) as indicated by:			(Jin et al., 2010)
	1.Reduced erosion and infiltration of inflammatory cells,	Rats; hematoxylin and eosin (H&E) staining	100mg/kg/day; given orally for 18-20 days before adjuvant stimulation	
	2.Inhibited increases in paw volume, body weight, thymus weight and spleen weight.	Rats; paw volume and body, thymus and spleen weights		
	Suppressed acetic acid-induced writhing in male ICR mice.	Mice; writhing number	50, 100 and 400 mg/kg; given orally 1 hour before acetic acid stimulation	
95% ethanol extract	Decreased mortality due to *Streptococus agalactiae* infection in Tilapia via: 1. Stimulating activity of some immunity factors i.e.:		0%. 025%, 0.05%, 0.1%, 0.2%, 0.4% g/kg; given orally for 30 days with bacterial suspension of *Streptococus agalactiae* stimulation on day 10	(Wu et al., 2013a)
	a. leucocytes' myeloperoxidase,	Peripheral blood leucocytes; leucocyte myeloperoxidase assay		
	b. serum lysozyme,	Serum; Lysozyme activity assay		
	c. anti-proteases activities,	Serum; Antiprotease activity assay		

Appendix IX Immunomodulatory activity of the root of *Sophora flavescens* Aiton (SOP).				
Preparation	**Activity**	**Method**	**Dose**	**Reference**
	d. hemolytic complement activities,	Serum; Natural hemolytic complement activity assay		
	2. Increased reactive oxygen species production,	Serum; Respiratory burst assay		
	3. Increased reactive nitrogen species production.	Serum; Griess reagent assay		
Methanol extract	Attenuated 1-fluoro-2,4-dinitrofluorobenzene (DNFB)-induced-contact dermatitis in male Balb/c mice (6 weeks old) as indicated by:			(Kim et al., 2012)
	1.Suppressed ear swelling,	Ear; thickness and weight	1 and 10 mg/ml/ear; given topically every 2 days for 4 times (on day 8, 10, 12 and 14) after DNFB stimulation (on day 7, 9, 11 and 13) and sensitization (on day 1-3)	
	2.Inhibitied inflammatory mononuclear cell infiltration, hyperplasia, spongiosis and edema,	Ear; H&E staining		
	3.Inhibited IFN-γ and TNF- α expression	Ear; cytometeric bead array kit		
Nanoparticles	Inhibited lipopolysaccharide (LPS)-induced uveitis in male adult Wistar rat (2 months old) as indicated by:		75 mg/kg/day; given orally after LPS stimulation	(Han and Wang, 2012)

Appendix IX Immunomodulatory activity of the root of *Sophora flavescens* Aiton (SOP).				
Preparation	**Activity**	**Method**	**Dose**	**Reference**
	1.Reduced infiltration of polymorphonuclear cells,	Rat ear vein blood; myeloperoxidase (MPO) assay		
	2.Inhibited the induction of ICAM-1, COX-2 and iNOS expression.	Rat ear vein blood; immunohistochemical analysis		
Water extract	Inhibited LPS induced uveitis in male adult Wistar rat (2 months old) as indicated by:		75mg/kg/day; given orally for 1 day after LPS stimulation	(Han et al., 2011)
	1.Attenuated infiltration of polymorphonuclear cells,	Eye humor; MPO and thiobarbituric acid assay		
	2.Inhibitied the induction of ICAM-1, COX-2, iNOS, IL-1β, TNF-α and NF-κB expessions.	Eye humor; immunohistochemical analysis		
In vitro				
Alkaloid-free flavonoid enriched fraction of the ethanol extract	Inhibited LPS-induced PGE_2, NO, IL-6 and TNF-α protein production and COX-2 and iNOS protein expression in murine macrophage-like RAW 264.7 cells.	ELISA/ Western blot analysis	2, 10, 20and 50 μg/ml	(Jin et al., 2010)

Appendix IX Immunomodulatory activity of the root of *Sophora flavescens* Aiton (SOP).				
Preparation	**Activity**	**Method**	**Dose**	**Reference**
Polysaccharide-enriched fraction	Enhanced NO production, iNOS activity and phagocytosis activity against H22 hepatocarcinoma cells in peritoneal macrophages.	Macrophage phagocytosis assay/ Griess reagent assay/ Colorimetric method	25,50and 100 μg/ml	(Bai et al., 2012)
Methanol extract	Suppressed RBL-2H3 mast cell-like leukemia cells migration.	Cell migration assay	25-400 μg/ml	(Kim et al., 2012)
	Inhibited phorbol 12-myristate 13-acetate (PMA)- plus calcium ionophore A23187-induced β-hexosaminidase and histamine release in RBL-2H3 mast cell-like leukemia cell.	Histamine detection kit/ β-hexosaminidase release assay	50, 100, 200 μg/ml	

Appendix X Compounds isolated from the fruit of *Kochia scoparia* (L.) Schrad (KOC).		
Class	**Compound**	**Reference**
Flavonoid and its glycoside	5,2'-Dihydroxy-6,7-methylenedioxyisoflavone	(Zhang et al., 2013c)
	5-Hydroxy-6,7-methylenedioxyflavone	(Zhang et al., 2013c)
	Hyperoside	(Xu et al., 2012)
	Iriflogenin	(Zhang et al., 2013c)
	Isorhamnetin	(Lu et al., 2012)
	Isorhamnetin-3-O-β-D-glucoside	(Lu et al., 2012)
	Isorhamnetin-3-O-β-D-galactoside	(Xu et al., 2012)
	Quercetin	(Lu et al., 2012, Xu et al., 2012)
	Rutin	(Lu et al., 2012)
	5,7,4'-Trihydroxy-6,3'-dimethoxyflavone	(Lu et al., 2012)
	5,7,4'-Trihydroxy-6-methoxyflavone	(Lu et al., 2012)
Triterpenoid saponin	2'-O-β-D-Glucosylmomordin Ic	(Yoshikawa et al., 1997a, Yoshikawa et al., 1997b, Han et al., 2006, Xu et al., 2012, Wang et al., 2003)
	2'-O-β-D-Glucosylmomordin IIc	(Yoshikawa et al., 1997a, Han et al., 2006, Lu et al., 2012)
	3-O-β-D-Glucosyl-oleanolic acid 28-O-β-D-glucoside	(Lu et al., 2012)
	Kochianoside I	(Yoshikawa et al., 1997a)
	Kochianoside II	(Yoshikawa et al., 1997a)
	Kochianoside III	(Yoshikawa et al., 1997a)
	Kochianoside IV	(Yoshikawa et al., 1997a)
	Momordin I	(Yoshikawa et al., 1997a)
	Momordin Ic	(Yoshikawa et al., 1997a, Yoshikawa et al., 1997b, Han et al., 2006, Choi et al., 2002, Lu et al., 2012, Wang et al., 2003)
	Momordin Ic 6'-methyl ester	(Yoshikawa et al., 1997a, Lu et al., 2012, Xu et al., 2012, Wang et al., 2003)
	Momordin IIc	(Yoshikawa et al., 1997a, Xu et al., 2012, Wang et al., 2003)
	Momordin IIc 6'-methyl ester	(Yoshikawa et al., 1997a)
	Scoparianoside A	(Yoshikawa et al., 1997b)
	Scoparianoside B	(Yoshikawa et al., 1997b)

Appendix X Compounds isolated from the fruit of *Kochia scoparia* (L.) Schrad (KOC).		
Class	**Compound**	**Reference**
	Scoparianoside C	(Yoshikawa et al., 1997b)
	Oleanolic acid 3-O-β-D-glucuronide-6-O-methyl ester	(Wang et al., 2003, Choi et al., 2002)
	Olenolic acid 3-O-β-D-glucuronide	(Yoshikawa et al., 1997a, Lu et al., 2012, Choi et al., 2002)
Others	Daucosterol	(Zhang et al., 2013c, Lu et al., 2012, Xu et al., 2012, Wang et al., 2003)
	N-*trans*-Feruloylmethoxytyramine	(Zhang et al., 2013c)
	N-*trans*-Feruloyltyramine	(Zhang et al., 2013c)
	Ferulic acid	(Zhang et al., 2013c)
	Oleanolic acid	(Choi et al., 2002, Zhang et al., 2013c, Lu et al., 2012, Wang et al., 2003)
	Stearic acid	(Lu et al., 2012)
	Stigmasterol	(Zhang et al., 2013c)
	β-Sitosterol	(Lu et al., 2012, Xu et al., 2012)

Appendix XI Immunomodulatory activity of the fruit of *Kochia scoparia* (L.) Schrad. (KOC).				
Preparation	**Activity**	**Method**	**Dose**	**Reference**
		In vivo		
Decoction	Inhibited 1-chloro-2,4-dinitrobenzene (DNCB)-induced skin inflammation in female BALB/c mice (7 weeks old) as indicated by:		1%; given topically for 10 days with DNCB during sensitization and for 9 days after stimulation with DNCB	(Choi et al., 2014b)
	1.Inhibited skin thickening and hyperplasia,	Dorsal skin; H&E staining		
	2.Inhibted the induction of IL-1β and TNF-α expression;	Dorsal skin; RT-PCR		
	1 and 2 were linked to the inhibition NF-κB expression and ERK1/2, JNK and p38 MAPK phosphorylation.	Dorsal skin; Western blot analysis		
70% Ethanol extract	Attenuated carrageenan-/histamine-/serortonin-/bradykinin-induced paw edema in ddY strain mice or Wistar strain rats.	Mice/rats; hind paw volume	50,200 and 500 mg/kg; given orally 1 hr before stimulation	(Matsuda et al., 1997a)
	Attenuated arachidonic acid-induced ear swelling in ddY strain mice.	Mice; ear thickness	500 mg/kg; given orally 1 hr before arachidonic acid stimulation	
70% Ethanol extract	Inhibited ovalbumin (OVA)-induced allergic airway inflammation in female BLB/c mice (6 weeks old) as indicated by:		100 and 200 mg/kg/day; given orally on day 18 to 23 after OVA stimulation (on day 21, 22, 23 and 25)	(Lee et al., 2011a)
	1.Inhibitied inflammatory cell infiltration,	Lung; H&E staining		

Appendix XI Immunomodulatory activity of the fruit of *Kochia scoparia* (L.) Schrad. (KOC).				
Preparation	**Activity**	**Method**	**Dose**	**Reference**
	2.Inhibitied the increases levels of IL-4 and IL-5, OVA-specific IgE and IgG1,	Plasma; ELISAs	and immunization (on day 0 and 14)	
	3.Inhibited the induction of matrix metalloproteinase (MMP)-9 expression,	Lung; gelatin zymography		
	4.Inhibited the induction of ICAM-1 and VCAM-1 expression.	Lung; western blot analysis		
		In vitro		
Methanol extract	Inhibited lipopolysaccharide (LPS)-induced NO, PGE_2 and TNF-α production in macrophage cell line RAW 264.7.	Griess reaction/ EIA kit	7.5, 15, 30 μg/ml	(Shin et al., 2004)
	Linked to the inhibition of iNOS and COX-2 mRNA and protein expression and NF-κB DNA binding activity.	Western blot analysis/ RT-PCR EMSA		

Appendix XII Compounds isolated from the bark of *Phellodendron chinensis* C. K. Schneid. (PHE).		
Class	**Compound**	**Reference**
Alkaloid	Berberine	(Alolga et al., 2015, Yan et al., 2015, Hu et al., 2010, Qin and Wang, 2003, Liu et al., 2010b)
	Candicine	(Alolga et al., 2015, Yan et al., 2015)
	Canthin-6-one	(Li et al., 2012c, Liu et al., 2010b)
	Chilenine	(Liu et al., 2010b)
	Columbamine	(Hu et al., 2010)
	Dehydroheliamine	(Yan et al., 2015)
	8,13-Dioxo-14-butoxycanadine	(Li et al., 2011a)
	Epiberberine	(Alolga et al., 2015)
	Evoeuropine	(Yan et al., 2015)
	γ-Fagarine	(Li et al., 2012c)
	Isoplatydesmine	(Li et al., 2012c)
	Jatrorrhizine	(Alolga et al., 2015, Yan et al., 2015, Hu et al., 2010)
	Lotusine	(Alolga et al., 2015, Hu et al., 2010)
	Magnoflorine	(Alolga et al., 2015, Hu et al., 2010)
	Magnoflorine isomer	(Hu et al., 2010)
	Menisperine	(Alolga et al., 2015, Hu et al., 2010)
	N-Methyltetrahydrocolumbamine	(Alolga et al., 2015)
	Noroxyhydastinine	(Yan et al., 2015, Liu et al., 2010b)
	(−)-Oblongine	(Hu et al., 2010)
	Oxyberberine	(Yan et al., 2015)
	Palmatine	(Alolga et al., 2015, Yan et al., 2015, Hu et al., 2010, Qin and Wang, 2003)
	Phellodendrine	(Hu et al., 2010)
	(−)-(R)-Platydesmine	(Liu et al., 2010b)
	Pteleine	(Liu et al., 2010b)
	Skimmianine	(Li et al., 2012c, Liu et al., 2010b)

Appendix XII Compounds isolated from the bark of *Phellodendron chinensis* C. K. Schneid. (PHE).		
Class	**Compound**	**Reference**
	Tembetarine	(Alolga et al., 2015)
	Tetrahydrocoptisine	(Yan et al., 2015)
	Tetrahydrojatrorrhizine	(Alolga et al., 2015, Hu et al., 2010)
	Tetrahydropalmatine	(Alolga et al., 2015, Yan et al., 2015)
Coumarin	3-Acetyl-3,4-dihydro-5,6-dimethoxy-1H-2-benzopyran-1-one	(Cui et al., 2003)
	Hymercromone	(Yan et al., 2015)
Iridoid	Pikuroside	(Yan et al., 2015)
Limonoid	Obacunone	(Alolga et al., 2015, Yan et al., 2015, Qin and Wang, 2003)
	Obaculactone	(Alolga et al., 2015, Yan et al., 2015, Qin and Wang, 2003)
Others	2-Amino-N-(3-amino-2-hydroxypropyl)adenosine	(Yan et al., 2015)
	Benzoic acid, 3,5-dimethoxy-,2-[4-(2,3,6,7-tetrahydro-1,3-dimethyl-2,6-dioxo-1H-purin-8-yl)-1-piperazinyl]ethyl ester	(Yan et al., 2015)
	2-{3,3-Bis[(2-hydroxyethyl)amino]-2-nitroprop-2en-1-ylidene}-5,5-dimethylcyclohexane-1,3-dione	(Yan et al., 2015)
	3,11-Bis(4-hydroxy-3-methoxyphenyl)-2,4,10,12-tetradispiro-hexadecan-7-one	(Yan et al., 2015)
	[4,6-Bis(dimethylamino)-1,3,5-triazin-2-yl](2-phenoxyethyl)cyanamide	(Yan et al., 2015)
	Chlorogenic acid	(Hu et al., 2010)
	Daucosterol	(Qin and Wang, 2003)
	5,7-Diamino[1,2,5]oxadiazolo[3,4-b]pyridine-6-carbonitrile	(Yan et al., 2015)
	8-[(Dibenzylamino)methyl]-7-hydroxy-3-phenyl-4H-chromen-4-one	(Yan et al., 2015)
	3,5-Dihydroxybenzoicacid O-xlosyl-glucoside	(Hu et al., 2010)

Appendix XII Compounds isolated from the bark of *Phellodendron chinensis* C. K. Schneid. (PHE).		
Class	**Compound**	**Reference**
	5-[1,2-Dihydroxy-2-methyl-3-(4-morpholinyl)propyl]-2,4-imidazolidinedione	(Yan et al., 2015)
	2-[3,4-Dihydroxyphenyl]ethyl-3-O-β-D-glucosyl-β-D-glucoside	(Yan et al., 2015)
	5,5'-Dimethoxylariciresinol-4-O-glucoside	(Hu et al., 2010)
	1,3-Dimethyl-5-[(2H-tetrazol-5-ylamino)methyl]-1,3-dihydro-2H-benzimidazol-2-one	(Yan et al., 2015)
	5-[(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)hydrazono]pyrimidine-2,4,6(1H,3H,5H)-trione	(Yan et al., 2015)
	Dodecahydrodibenzo-octaoxacyclotetracosine-2,17-dicarbaldehyde	(Yan et al., 2015)
	Ethyl{5-[ethyl(phenyl)amino][1,2,5]oxadiazolo[3,4-e][1,2,4]triazolo[4,3-α]pyrazin-8-yl}acetate	(Yan et al., 2015)
	(+)-Ethyl 5-O-feruloylquinate	(Qin and Wang, 2003)
	Ferulic acid	(Yan et al., 2015, Hu et al., 2010, Li et al., 2012c)
	3-O-Feruloyquinic acid	(Yan et al., 2015, Hu et al., 2010)
	5-O-Feruloylquinic acid	(Hu et al., 2010, Li et al., 2012c)
	Hobt	(Yan et al., 2015)
	4-Hydroxy-5-(pentyloxy)pentanehydrazide	(Yan et al., 2015)
	2-(p-Hydroxyphenyl)-ethanol-1-O-β-D-apiofuranosyl (1-6)-O-β-D-glucoside	(Hu et al., 2010)
	Methyl-N-{[(2-methyl-2-propanyl)oxy]carbonyl}glycylprolylglycinate	(Yan et al., 2015)
	Methyl-3,6-dideoxy-α-D-xylo-hexopyra-nosyl-(1→3)-[α-D-galactopyranosyl-(1→2)]-α-D-mannopyranoside	(Yan et al., 2015)
	Neo-chlorogenic acid	(Hu et al., 2010)

Appendix XII Compounds isolated from the bark of *Phellodendron chinensis* C. K. Schneid. (PHE).		
Class	**Compound**	**Reference**
	Phellolactone	(Li et al., 2009)
	Sanleng acid	(Yan et al., 2015)
	Shikimic acid	(Yan et al., 2015)
	Syringin	(Yin et al., 2012)
	6,7,12,13-Tetrahydro-5H-indolo[2,3-α]pyrrolo[3,4-c]carbazol-5-one	(Yan et al., 2015)

Appendix XIII Immunomodulatory activity of the bark of *Phellodendron chinensis* C.K. Schneid. (PHE).				
Preparation	**Activity**	**Method**	**Dose**	**Reference**
Immunomodulatory activity				
In vivo				
Decoction	Attenuated xylene-induced ear oedema in Kunming mice.	Ear; thickness	0.096 , 0.192 and 0.385, g/kg/day; given intragastrically for 7 days before xylene stimulation	(Yang et al., 2014b)
	Attenuated plastic ring-induced granuloma in male SD rat.	Granuloma; weight	0.086 , 0.173 and 0.346, g/kg/day; given intragastrically for 7 days after stimulation	
Decoction	Attenuated DNFB-induced delayed-type hypersensitivity in male NIH mice as indicated by:		20 or 100%; given orally for 7 days	(Lu, 1999)
	1. Suppressed ear swelling	Ear: thickness		
	2. Inhibited increases in IFN-γ levels,	Serum: macrophage derived NO_2 production		
	3.Inhibited IL-2 production in splenocytes and IL-1 and TNF-α production in peritoneal macrophage isolated from DTH mice.	NA		
Ethanol extract	Attenuated 12-O-tetradecanoyl-phorbol-13-acetate (TPA)-induced inflammation in male ICR mice as indicated by:		200 and 400 mg/kg; given intragastrically for 3 days after TPA stimulation	(Xian et al., 2011)
	1.Suppressed ear oedema	Ear; thickness		
	2.Decreased myeloperoxidase (MPO) activity,	Ear; MPO colorimetric assay		

Appendix XIII Immunomodulatory activity of the bark of *Phellodendron chinensis* C.K. Schneid. (PHE).				
Preparation	**Activity**	**Method**	**Dose**	**Reference**
	3.Decreased reactive oxygen species (ROS) level,	Ear; 2'-7'-Dichlorodihydrofluorescein diacetate (DCFH-DA) assay		
	4.Inhibited the induction of PGE_2 production,	Ear; PGE_2 EIA		
	5.Inhibited the induction of IL-6, TNF-α and IL-1β protein expression,	Ear; ELISA		
	6.Inhibited the induction of IL-6, TNF-α, IL-1β and COX-2 mRNA expression.	Ear; RT-PCR		

Appendix XIV List of compounds isolated from botanical drugs making up the hexa-herbal formula (HHCF).

DIC= root bark of *Dictamnus dasycarpus* Turcz.; KOC= fruit *of Kochia scoparia* (L.) Schrad.; P= bark of *Phellodendron chinense* C.K. Schneid. or *Phellodendron amurense* Rupr. ;PA= bark of *Phellodendron amurense* Rupr.; PHE= bark of *Phellodendron chinense* C.K. Schneid.; R= rootstock of *Rheum* species; RHE= rootstock of *Rheum tanguticum* Maxim. ex Balf.; RO= rootstock of *Rheum officinale* Baill.; RP= rootstock of *Rheum palmatum* L.; SCU= rootstock of *Scutellaria baicalensis* Georgi; SOP= rootstock of *Sophora flavescens* Aiton

Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
60.05	$C_2H_4O_2$	64-19-7	Acetic acid	R	NA	NA (Blundstone and Dickinson, 1964)
90.03	$C_2H_2O_4$	144-62-7	Oxalic acid	R	NA	NA (Blundstone and Dickinson, 1964)
90.08	$C_3H_6O_3$	50-21-5	Lactic acid	R	NA	NA (Blundstone and Dickinson, 1964)
118.09	$C_4H_6O_4$	110-15-6	Succinic acid	R	NA	NA (Blundstone and Dickinson, 1964)
126.11	$C_6H_6O_3$	67-47-0	5-Hydroxymethylfuraldehyde	DIC	129 $[M+H]^+$ 151 $[M+Na]^+$	NA (Bai et al., 2014b)
132.16	C_9H_8O	104-55-2	Cinnamic aldehyde	RP	NA	NA (Miyazawa et al., 1996)
135.12	$C_6H_5N_3O$	2592-95-2	Hobt	P	134 $[M-H]^-$	MS^2 [134]: 134, 109, 108, 96, 75 (Yan et al., 2015)
138.12	$C_7H_6O_3$	29656-58-4	Hydroxybenzoic acid	R	137 $[M-H]^-$	MS^2 [137]: 121, 93 (Yang et al., 2015a)
138.12	$C_7H_6O_3$	99-96-7	4-Hydroxybenzoic acid	SCU	137 $[M-H]^-$	MS^2 [137]: 93 (Qiao et al., 2016)
148.16	$C_9H_8O_2$	140-10-3	*trans*-Cinnamic acid	RHE	NA	NA (Gao et al., 2012a)
152.15	$C_8H_8O_3$	621-59-0	Isovanillin	PHE	NA	NA (Wang et al., 2009)
154.12	$C_7H_6O_4$	89-86-1	2,4-Dihydroxy benzoic acid	SOP	NA	NA (Li et al., 2004)
154.12	$C_7H_6O_4$	99-50-3	Protocatechuic acid	SCU	153 $[M-H]^-$	MS^2 [153]: 109 (Qiao et al., 2016)
162.14	$C_9H_6O_3$	93-35-6	7-Hydroxycoumarin [Umbelliferone]	SOP	NA	NA (Jung et al., 2005a, Zhang et al., 2000)
164.16	$C_9H_8O_3$	7400-08-0	*p*-Coumaric acid	R	163 $[M-H]^-$	MS^2 [163]: 147, 119 (Yang et al., 2015a)
164.20	$C_{10}H_{12}O_2$	5471-51-2	4-(4'-Hydroxyphenyl)-2-butanone	RP	163 $[M-H]^-$	MS^2 [163]: 163 (Liu et al., 2016)

Appendix XIV List of compounds isolated from botanical drugs making up the hexa-herbal formula (HHCF).

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
				RHE	165 $[M+H]^+$	NA (Jin et al., 2006a)
					182 $[M+NH_4]^+$	
					187 $[M+Na]^+$	
					NA	NA (Jin et al., 2006b)
166.17	$C_9H_{10}O_3$	552-41-0	Paeonol	RP	NA	NA (Miyazawa et al., 1996)
168.15	$C_8H_8O_4$	168899-47-6/ 127531-40-2/ 28026-96-2/ 5981-39-5/ 4780-64-7/ 4780-63-6/ 4707-49-7/ 3929-89-3/ 480-67-1/ 480-64-8	Dihydroxy methylbenzoic acid	R	167 $[M-H]^-$	MS^2 [167]: 123(Yang et al., 2015a)
170.12	$C_7H_6O_5$	149-91-7	Gallic acid	R	169 $[M-H]^-$	MS^2 [169]: 125, 107 (Yang et al., 2015a)
				RO	NA	NA (Komatsu et al., 2006)
				RP	169 $[M-H]^-$	MS^2 [169]: 169 (Liu et al., 2016)
						MS^2 [169]: 125 (Han et al., 2008, Wang et al., 2011a, Alolga et al., 2015)
					NA	NA (Komatsu et al., 2006)
				RHE	169 $[M-H]^-$	MS^2 [169]: 125 (Jin et al., 2007)
					NA	NA (Komatsu et al., 2006)

Appendix XIV List of compounds isolated from botanical drugs making up the hexa-herbal formula (HHCF).

DIC= root bark of *Dictamnus dasycarpus* Turcz.; KOC= fruit *of Kochia scoparia* (L.) Schrad.; P= bark of *Phellodendron chinense* C.K. Schneid. or *Phellodendron amurense* Rupr. ;PA= bark of *Phellodendron amurense* Rupr.; PHE= bark of *Phellodendron chinense* C.K. Schneid.; R= rootstock of *Rheum* species; RHE= rootstock of *Rheum tanguticum* Maxim. ex Balf.; RO= rootstock of *Rheum officinale* Baill.; RP= rootstock of *Rheum palmatum* L.; SCU= rootstock of *Scutellaria baicalensis* Georgi; SOP= rootstock of *Sophora flavescens* Aiton

Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
174.15	$C_7H_{10}O_5$	138-59-0	Shikimic acid	PHE	173 $[M-H]^-$	MS^2 [173]: 157, 137, 111, 94, 71, 67 (Yan et al., 2015)
176.14	$C_6H_4N_6O$	728887-91-0	5,7-Diamino[1,2,5]oxadiazolo[3,4-b]pyridine-6-carbonitrile	PHE	177 $[M+H]^+$	MS^2 [177]: 149, 133, 145, 117 (Yan et al., 2015)
176.17	$C_{10}H_8O_3$	90-33-5	Hymecromone	PHE	177 $[M+H]^+$	MS^2 [177]: 163, 151, 147, 145, 121, 118, 109, 89 (Yan et al., 2015)
178.14	$C_9H_6O_4$	305-01-1	Aesculetin	P	177 $[M-H]^-$	MS^2 [177]: 133, 105, 75 (Yun et al., 2012)
178.23	$C_{11}H_{14}O_2$	93-15-2	Methyl eugenol	RP	NA	NA (Miyazawa et al., 1996)
178.27	$C_{12}H_{18}O$	151201-77-3	Dictamnol	DIC	NA	NA (Naoki et al., 1993, Zhao et al., 1998a, Xiang et al., 2008)
180.20	$C_{10}H_{12}O_3$	5597-50-2	4-Hydroxybenzenepropanoic acid methyl ester	RHE	NA	NA (Gao et al., 2012a)
180.27	$C_{11}H_{18}NO$	6656-13-9	Candicine	PHE	180 $[M]^+$	MS^2 [180]: 180, 121 (Alolga et al., 2015)
						MS^2 [180]: 150, 133, 122, 119, 70 (Yan et al., 2015)
				PA	216 $[M+Cl+H]^+$	MS^2 [216]: 192, 180, 121 (Hu et al., 2010)
182.17	$C_9H_{10}O_4$	570-10-5	4-Methoxy-6-methylsallicylic acid	R	181 $[M-H]^-$	MS^2 [181]: 163, 151, 137 (Yang et al., 2015a)
184.15	$C_8H_8O_5$	99-24-1	Methyl gallate	R	183 $[M-H]^-$	MS^2 [183]: 168, 124 (Yang et al., 2015a)
186.16	$C_{11}H_6O_3$	66-97-7	Furocoumarin	DIC	NA	NA (Komissarenko et al., 1983)

Appendix XIV List of compounds isolated from botanical drugs making up the hexa-herbal formula (HHCF).

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
190.19	$C_{11}H_{10}O_3$	58045-41-3/39966-61-5/7560-50-1	Methyl formyl cinnamate	R	189 $[M-H]^-$	MS^2 [189]: 174,159, 147, 133 (Yang et al., 2015a)
190.20	$C_{11}H_{10}O_3$	38412-47-4	2,5-Dimethyl-7-hydroxychromone	RP	NA	NA (Kashiwada et al., 1984)
190.24	$C_{11}H_{14}N_2O$	485-35-8	Cytisine	SOP	191 $[M+H]^+$	MS^2[191]:148 (Liu et al., 2011)
191.18	$C_{10}H_9NO_3$	21796-14-5	Noroxyhydrastinine	PHE	192 $[M+H]^+$	MS^2[192]: 163, 160, 151, 60 (Yan et al., 2015)
					NA	NA (Liu et al., 2010b)
191.23	$C_{11}H_{13}NO_2$	3382-18-1	Dehydroheliamine	PHE	192 $[M+H]^+$	MS^2[192]: 175, 151, 122, 109, 88 (Yan et al., 2015)
192.12	$C_6H_8O_7$	77-92-9	Citric acid	R	NA	NA (Blundstone and Dickinson, 1964)
192.17	$C_{10}H_8O_4$	92-61-5	Scopoletin	DIC	193 $[M+H]^+$	NA (Bai et al., 2014b)
					NA	NA (Komissarenko et al., 1983)
192.21	$C_{11}H_{12}O_3$	2373-79-7	*p*-Ethoxycinnamic acid	R	191 $[M-H]^-$	MS^2 [191]: 175, 147, 131 (Yang et al., 2015a)
194.18	$C_{10}H_{10}O_4$	1135-24-6	Ferulic acid	KOC	NA	NA (Zhang et al., 2013c)
				PHE	NA	NA (Li et al., 2012c, Wang et al., 2009)
					193 $[M-H]^-$	MS^2 [193]: 179, 166, 149, 135, 117, 59 (Yan et al., 2015)
						MS^2 [193]: 191, 179, 149 (Hu et al., 2010)
				PA		MS^2 [193]: 191, 179, 149 (Hu et al., 2010)
				SCU	NA	NA (Lu et al., 2011)
194.18	$C_7H_{14}O_6$	97-30-3	Methyl α-D-glucoside	R	193 $[M-H]^-$	MS^2 [193]: 271, 211, 169, 125 (Yang et al., 2015a)
196.20	$C_{10}H_{12}O_4$	4707-47-5	Atraric acid/Methyl β-orsellinate	PHE	NA	NA (Wang et al., 2009)

Appendix XIV List of compounds isolated from botanical drugs making up the hexa-herbal formula (HHCF).

DIC= root bark of *Dictamnus dasycarpus* Turcz.; KOC= fruit *of Kochia scoparia* (L.) Schrad.; P= bark of *Phellodendron chinense* C.K. Schneid. or *Phellodendron amurense* Rupr. ;PA= bark of *Phellodendron amurense* Rupr.; PHE= bark of *Phellodendron chinense* C.K. Schneid.; R= rootstock of *Rheum* species; RHE= rootstock of *Rheum tanguticum* Maxim. ex Balf.; RO= rootstock of *Rheum officinale* Baill.; RP= rootstock of *Rheum palmatum* L.; SCU= rootstock of *Scutellaria baicalensis* Georgi; SOP= rootstock of *Sophora flavescens* Aiton

Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
196.29	$C_{12}H_{20}O_2$	849693-04-5	Radicol	DIC	NA	NA (Xiang et al., 2008, Xiang et al., 2005)
199.21	$C_{12}H_9NO_2$	484-29-7	Dictamnine	DIC	200 $[M+H]^+$	MS^2 [247]: 231, 216, 188 (Lv et al., 2015)
						MS^2 [200]: 129 (Wang et al., 2013d)
						NA (Bai et al., 2014b)
					222 $[M+Na]^+$	NA (Bai et al., 2014b)
					NA	NA (Bai et al., 2014b, Wu et al., 1994, Zhao et al., 1998a, Chen et al., 2000, Du et al., 2005, Jiang et al., 2006a, Xiang et al., 2008, Yang et al., 2011a, Yang et al., 2010, Wang et al., 2012, Wang et al., 2013d)
199.21	$C_{12}H_9NO_2$	484-74-2	Isodictamnine	DIC	200 $[M+H]^+$	MS^2 [200]: 185, 128, 77 (Lv et al., 2015)
204.27	$C_5H_7N_3O$	6220-47-9	N-Methylcytisine	SOP	205 $[M+H]^+$	MS^2 [205]: 146, 108 (Liu et al., 2011, Liu et al., 2010a)
204.35	$C_{15}H_{24}$	24406-05-1	α-Candinene	RP	NA	NA (Miyazawa et al., 1996)
204.35	$C_{15}H_{24}$	3856-25-5	α-Copaene	RP	NA	NA (Miyazawa et al., 1996)
204.35	$C_{15}H_{24}$	10208-80-7	α-Muurolene	RP	NA	NA (Miyazawa et al., 1996)
208.21	$C_{11}H_{12}O_4$	102-37-4	Caffeic acid ethyl ester	PHE	NA	NA (Wang et al., 2009)
208.30	$C_{12}H_{16}N_2O$	1257392-35-0	Flavascensine	SOP	NA	NA (Liu et al., 2010a)
213.23	$C_{13}H_{11}NO_2$	95874-16-1	O-Ethylnordictamnine	DIC	NA	NA (Lin and Shieh, 1986)
215.20	$C_{12}H_9NO_3$	221457-19-8	Dictangustine A	DIC	NA	NA (Yoon et al., 2012)
215.20	$C_{12}H_9NO_3$	2255-50-7	Robustine	DIC	216 $[M+H]^+$	MS^2 [216]: 201, 145, 117, 90, 59 (Lv et al., 2015)
218.21	$C_{12}H_{10}O_4$	94356-33-9	2-Methyl-5-acetyl-7-hydroxychromone	RP	NA	NA (Kashiwada et al., 1984)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
218.29	$C_{10}H_{22}N_2O_3$	372088-61-4	4-Hydroxy-5-(pentyloxy)pentanehydrazide	PHE	219 $[M+H]^+$	MS^2 [219]: 205, 202, 175, 161, 147, 81 (Yan et al., 2015)
220.23	$C_{14}H_8N_2O$	479-43-6	Canthin-6-one	PHE	NA	NA (Li et al., 2012c)
222.37	$C_{15}H_{26}O$	32142-08-8	β-Elemol	DIC	NA	NA (Zhao et al., 1998a)
228.24	$C_{14}H_{12}O_3$	501-36-0	Resveratrol	R	227 $[M-H]^-$	MS^2 [227]: 185, 143 (Yang et al., 2014a, Yang et al., 2015a)
				RP		MS^2 [227]: 185, 159, 143 (Liu et al., 2016)
				RHE	NA	NA (Jin et al., 2007, Jin et al., 2006b)
228.28	$C_{12}H_{18}N_2O_2$	79659-61-3	Kuraramine	SOP	223 $[M+H]^+$	MS^2[223]:191, 162 (Liu et al., 2011)
228.28	$C_{12}H_{18}N_2O_2$	85799-36-6	Isokuraramine	SOP	223 $[M+H]^+$	MS^2[223]:191, 162 (Liu et al., 2011)
229.23	$C_{13}H_{11}NO_3$	524-15-2	□-Fagarine	DIC	230 $[M+H]^+$	MS^2 [230]: 215, 200, 187 (Lv et al., 2015)
					NA	NA (Lv et al., 2015, Xiang et al., 2008, Wu et al., 1994, Du et al., 2005)
				PHE	NA	NA (Li et al., 2012c, Wang et al., 2009)
				PA	230 $[M+H]^+$	MS^2 [230]: 215, 200 (Xian et al., 2014)
229.23	$C_{13}H_{11}NO_3$	569-02-8	Iso-□-Fagarine	DIC	NA	NA (Yoon et al., 2012)
229.23	$C_{13}H_{11}NO_3$	119708-35-9/2221-41-2/ 523-66-0	Methoxydictamnine	DIC	230 $[M+H]^+$	MS^2[230]: 215, 200, 187 (Lv et al., 2015)
229.23	$C_{13}H_{11}NO_3$	2221-41-2	Pteleine	PHE	NA	NA (Liu et al., 2010b)
230.26	$C_{11}H_{18}O_5$	1419709-70-8	Dasycarpus acid	DIC	NA	NA (Guo et al., 2012b)
232.23	$C_{13}H_{12}O_4$	NA	Acetyl methyl formyl cinnamate	R	231 $[M-H]^-$	MS^2 [231]: 189, 174, 159, 147, 133 (Yang et al., 2015a)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
232.27	$C_{14}H_{16}O_3$	28808-62-0	Fraxinellone	DIC	233 $[M+H]^+$	MS^2 [233]: 215, 187, 123, 95 (Lv et al., 2015)
						NA (Bai et al., 2014b)
					255 $[M+Na]^+$	NA (Bai et al., 2014b)
					+	MS [232, 136, 108, 94, 80, 66] (Du et al., 2005)
					NA	NA (Wu et al., 1994, Zhao et al., 1998a, Chen et al., 2000, Du et al., 2005, Jiang et al., 2006a, Xiang et al., 2008, Yoon et al., 2008, Zhao et al., 2008, Yang et al., 2010, Yang et al., 2011a, Wang et al., 2012, Bai et al., 2014a, Lv et al., 2015)
232.27	$C_{14}H_{16}O_3$	92481-63-5	Isofraxinellone	DIC	NA	NA (Miyazawa et al., 1995, Zhao et al., 1998a, Yang et al., 2011a, Wang et al., 2014c)
232.36	$C_{15}H_{24}N_2$	56293-29-9	Aloperine	SOP	NA	NA (Lin et al., 2011)
234.20	$C_{12}H_{10}O_5$	NA	(5Z)-6-Hydroxy-3,4-dioxo-6-phenyl-5-hexenoic acid	R	233 $[M-H]^-$	MS^2 [233]: 189, 175, 147 (Yang et al., 2015a)
234.20	$C_{12}H_{10}O_5$	94356-34-0	2-Methyl-5-carboxymethyl-7-hydroxychromone	RP	NA	NA (Kashiwada et al., 1984)
234.25	$C_{13}H_{14}O_4$	94356-35-1	2-(2'-Hydroxypropyl)-5-methyl-7-hydroxychromone	RP	NA	NA (Kashiwada et al., 1984)
241.29	$C_{15}H_{15}NO_2$	50333-13-6	N-Methylflindersine	PA	242 $[M+H]^+$	MS^2 [242]: 226, 211 (Xian et al., 2014)
242.27	$C_{12}H_{18}O_5$	1419709-60-6	Dasycarpusenester A	DIC	NA	NA (Guo et al., 2012b)
243.26	$C_{14}H_{13}NO_3$	105988-99-6	O-Ethylnor-γ-fagarine	DIC	NA	NA (Lin and Shieh, 1986)
244.20	$C_{10}H_{12}O_7$	NA	Galloylglycerol	R	243 $[M-H]^-$	MS^2 [243]: 169, 125, 124, 107 (Yang et al., 2015a)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
244.20	$C_{10}H_{12}O_7$	87087-60-3	(+)-1-O-Galloylglycerol	R	NA	NA (Nonaka and Nishioka, 1983, Zhou et al., 2011a)
244.28	$C_{12}H_{20}O_5$	1419709-65-1	Dasycarpusester B	DIC	NA	NA (Guo et al., 2012b)
244.33	$C_{15}H_{20}N_2O$	486-89-5	(-)-Anagyrine	SOP	245 $[M+H]^+$	MS^2[245]:148, 98 (Liu et al., 2011)
244.33	$C_{15}H_{20}N_2O$	6882-66-2	(+)-Sophoramine	SOP	NA	NA (Liu et al., 2010a)
245.23	$C_{13}H_{11}NO_4$	5876-17-5	Haplopine	DIC	NA	NA (Zhao et al., 1998a)
245.23	$C_{13}H_{11}NO_4$	128508-21-4	5-Hydoxy-4,8-dimethoxy furoquinoline	DIC	246 $[M+H]^+$	MS^2 [246]: 231, 216, 188 (Lv et al., 2015)
246.26	$C_{14}H_{14}O_4$	128475-17-2	Fraxinellonone	DIC	247 $[M+H]^+$	NA (Bai et al., 2014b)
					269 $[M+Na]^+$	NA (Bai et al., 2014b)
					NA	NA (Du et al., 2005, Jiang et al., 2006a, Yoon et al., 2008, Zhao et al., 2008, Yang et al., 2011a, Bai et al., 2014a)
246.26	$C_{14}H_{14}O_4$	22649-04-3	Torachrysone	R	245 $[M-H]^-$	MS^2 [245]: 230, 215, 187 (Yang et al., 2015a)
				RP		NA (Wang et al., 2014f)
246.35	$C_{15}H_{22}N_2O$	46862-63-9	(+)-7,11-Dehydromatrine [leontalbinie]	SOP	247 $[M+H]^+$	MS^2[247]: 176, 148 (Liu et al., 2011)
					+	MS [246, 245, 218, 204, 190, 176, 175] (Murakoshi et al., 1982)
					NA	NA (Liu et al., 2010a)
246.35	$C_{15}H_{22}N_2O$	68398-59-4	Isosophocarpine	SOP	247 $[M+H]^+$	MS^2[247]: 179, 150, 148, 136 (Liu et al., 2011)
246.35	$C_{15}H_{22}N_2O$	6483-15-4	(-)-Sophocarpine	SOP	247 $[M+H]^+$	MS^2[247]: 227, 179, 150, 148, 136 (Liu et al., 2011)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
					NA	NA (Liu et al., 2010a, Lin et al., 2011)
248.27	$C_{14}H_{16}O_4$	202343-57-5	6β-Hydroxyfraxinellone/9β-Hydroxyfraxinellone/Dasycarpol	DIC	NA	NA (Zhao et al., 1998a, Yoon et al., 2008, Yang et al., 2011a)
248.36	$C_{15}H_{24}N_2O$	641-39-4	Allomatrine	SOP	NA	NA (Liu et al., 2010a)
248.36	$C_{15}H_{24}N_2O$	17801-36-4	(+)-Isomatrine	SOP	249 $[M+H]^+$	MS^2 [249]: 176, 150, 148 (Liu et al., 2011)
					NA	NA (Liu et al., 2010a)
248.36	$C_{15}H_{24}N_2O$	550-90-3	Lupanine	SOP	249 $[M+H]^+$	MS^2 [249]: 206, 166, 136 (Liu et al., 2011)
248.36	$C_{15}H_{24}N_2O$	519-02-8	(+)-Matrine	SOP	249 $[M+H]^+$	MS^2 [249]: 176], 148, 112 (Zhang and Chen, 2013)
						MS^2 [249]: 176, 150, 148 (Liu et al., 2011)
					NA	NA (Liu et al., 2010a, Lin et al., 2011)
248.36	$C_{15}H_{24}N_2O$	6882-68-4	(-)-Sophoridine	SOP	249 $[M+H]^+$	MS^2 [249]: 176, 150, 148 (Liu et al., 2011)
					NA	NA (Liu et al., 2010a, Lin et al., 2011)
252.35	$C_{15}H_{24}O_3$	1415932-41-0	Dictamnadiol	DIC	275 $[M+NA]^+$	NA (Guo et al., 2012b)
254.24	$C_{15}H_{10}O_4$	481-74-3	Chrysophanol	R	253 $[M-H]^-$	NA (Lin et al., 2006)
						MS^2 [253]: 225 (Yang et al., 2015a)
				RP		MS^2 [253]: 253, 225 (Alolga et al., 2015)
						MS^2 [253]: 225, 210 MS^3 [253 à 225]: 182 (Zhao et al., 2013a)
						MS^2 [253]: 225 (Han et al., 2008)
				RHE		MS^2 [253]: 225, 210, 182 (Jin et al., 2007)
					NA	NA (Jin et al., 2006b)
254.24	$C_{15}H_{10}O_4$	480-40-0	5,7-Dihydroxyflavone [Chrysin]	SCU	253 $[M-H]^-$	MS^2 [253]: 209, 143, 107 (Qiao et al., 2016)
						MS^2 [253]: 253, 209, 185, 181, 165, 143 (Seo et al., 2013)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
						MS^2 [253]: 143 (Luo et al., 2012)
						MS^2 [253]: 225 (Zhang et al., 2007b)
					255 $[M+H]^+$	MS^2 [255]: 231, 213, 209, 187, 171, 153, 129 (Liu et al., 2009)
					NA	NA (Lu et al., 2011, Zhang et al., 1994, Takagi et al., 1980, Kimuya et al., 1981)
256.21	$C_{11}H_{12}O_7$	35388-57-9	Piscidic acid	SOP	255 $[M-H]^-$	NA (Zhang et al., 2013a)
					279 $[M+NA]^+$	
256.25	$C_{15}H_{12}O_4$	NA	Dihydroxyflavanone	SCU	255 $[M-H]^-$	MS^2 [255]: 211, 169 (Qiao et al., 2016)
256.25	$C_{15}H_{12}O_4$	480-39-7	Pinocembrin	SCU	255 $[M-H]^-$	MS^2 [255]: 211, 169 (Qiao et al., 2016)
256.42	$C_{16}H_{32}O_2$	57-10-3	Palmitic acid	RP	NA	NA (Miyazawa et al., 1996)
258.27	$C_{15}H_{14}O_4$	500-65-2	Rhapontigenin	RO	NA	NA (Zhou et al., 2011b)
259.26	$C_{14}H_{13}NO_4$	518-96-7	Isomaculosidine	DIC	NA	NA (Lin and Shieh, 1986)
259.26	$C_{14}H_{13}NO_4$	484-08-2	Kokusaginin	DIC	260 $[M+H]^+$	MS^2 [260]: 245, 227, 216 (Lv et al., 2015)
259.26	$C_{14}H_{13}NO_4$	522-19-0	Maculosidin	DIC	260 $[M+H]^+$	MS^2 [260]: 245, 227, 216 (Lv et al., 2015)
259.26	$C_{14}H_{13}NO_4$	83-95-4	Skimmianine	DIC	260 $[M+H]^+$	MS^2 [260]: 245, 216 (Lv et al., 2015)
						MS^2 [260]: 227 (Wang et al., 2013d)
					+	MS [259, 244, 229, 214, 200] (Du et al., 2005)
				PHE	NA	NA (Li et al., 2012c)
				PA	260 $[M+H]^+$	MS^2 [260]: 245, 228 (Xian et al., 2014)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
259.27	$C_{11}H_{13}N_7O$	878424-66-9	1,3-Dimethyl-5-[(2H-tetrazol-5-ylamino)methyl]-1,3-dihydro-2H-benzimidazol-2-one	PHE	260 $[M+H]^+$	MS^2 [260]: 243, 188, 177, 163, 161, 120 105 (Yan et al., 2015)
259.30	$C_{15}H_{17}NO_3$	27495-37-0	Isoplatydesmine	PHE	NA	NA (Li et al., 2012c)
259.30	$C_{15}H_{17}NO_3$	318465-89-3	Platydesmine	DIC	NA	NA (Wu et al., 1994)
				PHE	NA	NA (Liu et al., 2010b)
260.29	$C_{15}H_{16}O_4$	35986-56-2	Calodendrolide	DIC	261 $[M+H]^+$	MS^2 [261]: 243, 225, 215, 187, 119, 95 (Lv et al., 2015)
					NA	NA (Zhao et al., 1998a, Yoon et al., 2008)
260.33	$C_{15}H_{20}N_2O_2$	732-50-3	Baptifoline	SOP	261 $[M+H]^+$	MS^2 [261]: 243, 164, 114 (Liu et al., 2011)
260.33	$C_{15}H_{20}N_2O_2$	259860-46-3	7α-Hydroxysophoramine	SOP	261 $[M+H]^+$	MS^2 [261]: 243, 136 (Liu et al., 2011)
260.33	$C_{15}H_{20}N_2O_2$	85769-34-2	9α-Hydroxysophoramine	SOP	261 $[M+H]^+$	MS^2 [261]: 243, 150 (Liu et al., 2011)
					NA	NA (Liu et al., 2010a)
262.30	$C_{12}H_{22}O_6$	1707-77-3	1,2:5,6-Bis-O-(1-methylethylidene)-D-mannitol	PHE	261 $[M-H]^-$	MS^2 [261]: 247, 243, 223 (Yan et al., 2015)
262.35	$C_{15}H_{22}N_2O_2$	1257392-34-9	(-)-9α-Hydroxy-7,11-dehydromatrine	SOP	NA	NA (Liu et al., 2010a)
262.35	$C_{15}H_{22}N_2O_2$	907607-58-3	9α-Hydroxysophocarpine	SOP	263 $[M+H]^+$	MS^2 [263]: 245, 164 (Liu et al., 2011)
					NA	NA (Liu et al., 2010a)
262.35	$C_{15}H_{22}N_2O_2$	147731-96-2	Leontalbinine N-oxide	SOP	263 $[M+H]^+$	MS^2 [263]: 245, 195, 166 (Liu et al., 2011)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
262.35	$C_{15}H_{22}N_2O_2$	60394-92-5	Mamanine	SOP	263 $[M+H]^+$	MS^2[263]: 231 (Liu et al., 2011)
262.35	$C_{15}H_{22}N_2O_2$	26904-64-3	(+)-Oxysophocarpine	SOP	263 $[M+H]^+$	MS^2 [263]: 263, 245, 150, 138 (Liu et al., 2011)
264.27	$C_{14}H_{16}O_5$	1344115-48-5	Dasylactone A	DIC	NA	NA (Wang et al., 2014c, Yang et al., 2011a)
264.27	$C_{14}H_{16}O_5$	1344115-49-6	Dasylactone B	DIC	NA	NA (Wang et al., 2014c, Yang et al., 2011a)
264.36	$C_{15}H_{24}N_2O_2$	3411-37-8	(+)-5α-Hydroxymatrine [Sophoranol]	SOP	265 $[M+H]^+$	MS^2 [265]: 247, 205 (Liu et al., 2011)
264.36	$C_{15}H_{24}N_2O_2$	88509-92-6	(+)-9α-Hydroxymatrine	SOP	265 $[M+H]^+$	MS^2 [265]: 247, 150, 148, 112 (Liu et al., 2011)
					NA	NA (Liu et al., 2010a)
264.36	$C_{15}H_{24}N_2O_2$	183074-18-2	(-)-14β-Hydroxymatrine	SOP	NA	NA (Liu et al., 2010a)
264.36	$C_{15}H_{24}N_2O_2$	18688-40-9	Lamprolobine	SOP	265 $[M+H]^+$	MS^2 [265]: 150 (Liu et al., 2011)
264.36	$C_{15}H_{24}N_2O_2$	16837-52-8	(+)-Oxymatrine	SOP	265 $[M+H]^+$	MS^2 [265]: 247, 205, 148 (Zhang and Chen, 2013)
						MS^2 [265]: 265, 247, 205, 148 (Liu et al., 2011)
					NA	NA (Liu et al., 2010a)
264.36	$C_{15}H_{24}N_2O_2$	1217501-78-4	Oxysophoridine	SOP	NA	NA (Sun et al., 2009a)
267.37	$C_{18}H_{21}NO$	82992-78-7	4-Dimethylamino-4'-isopropylbenzophenone	PA	268 $[M+H]^+$	MS^2 [268]: 253, 147 (Xian et al., 2014)
268.26	$C_{16}H_{12}O_4$	485-72-3	Formononetin	SOP	269 $[M+H]^+$	MS^2 [269]: 254, 213, 159, 137, 118 (Zhang et al., 2007a)
					291 $[M+Na]^+$	NA (Zhang et al., 2007a)

Appendix XIV List of compounds isolated from botanical drugs making up the hexa-herbal formula (HHCF).

DIC= root bark of *Dictamnus dasycarpus* Turcz.; KOC= fruit *of Kochia scoparia* (L.) Schrad.; P= bark of *Phellodendron chinense* C.K. Schneid. or *Phellodendron amurense* Rupr. ;PA= bark of *Phellodendron amurense* Rupr.; PHE= bark of *Phellodendron chinense* C.K. Schneid.; R= rootstock of *Rheum* species; RHE= rootstock of *Rheum tanguticum* Maxim. ex Balf.; RO= rootstock of *Rheum officinale* Baill.; RP= rootstock of *Rheum palmatum* L.; SCU= rootstock of *Scutellaria baicalensis* Georgi; SOP= rootstock of *Sophora flavescens* Aiton

Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
					NA	NA (Ryu et al., 1997, Li et al., 2004, Kang et al., 2000b, Quang et al., 2012)
268.35	$C_{17}H_{20}N_2O$	90-94-8	Bis-[4-(dimethylamino)phenyl]methanone	PA	269 $[M+H]^+$	MS^2 [269]: 254, 148 (Xian et al., 2014)
						MS^2 [269]: 254, 224, 210, 148, 120 (Xian et al., 2014)
270.24	$C_{15}H_{10}O_5$	481-72-1	Aloe-emodin	R	269 $[M-H]^-$	MS^2 [269]: 255, 240 (Yang et al., 2015a)
						MS^2 [269]:240 MS^3 [240]: 211 (Yang et al., 2014a)
						MS^2 [269]: 240 (Lin et al., 2006)
				RP		MS^2 [269]: 239 (Liu et al., 2016)
						MS^2 [269]: 269, 240, 211 (Alolga et al., 2015)
						NA (Wang et al., 2014f)
						MS^2 [269]: 269,240 MS^3 [269 à 240]: 211 (Zhao et al., 2013a)
						MS^2 [269]: 241, 240 (Han et al., 2008)
				RHE		MS^2 [269]: 239, 211, 183(Jin et al., 2007)
					NA	NA (Jin et al., 2006b)
270.24	$C_{15}H_{10}O_5$	18499-83-7	Deoxyerythrolaccin	RP	269 $[M-H]^-$	MS^2 [269]: 225 (Han et al., 2008)
270.24	$C_{15}H_{10}O_5$	518-82-1	Emodin	R	269 $[M-H]^-$	MS^2 [269]: 241, 215 (Yang et al., 2015a)
						MS^2 [269]: 241, 225 MS^3 [225]: 210, 182 (Yang et al., 2014a)
						NA (Lin et al., 2006)
				RP		MS^2 [269]: 225 (Liu et al., 2016)
						MS^2 [269]: 269, 240, 211, 167 (Alolga et al., 2015)
						NA (Wang et al., 2014f)
						MS^2 [269]: 241,225,211 MS^3 [269 à 225]: 197 (Zhao et al., 2013a)
						MS^2 [269]: 241, 225 (Han et al., 2008)
				RHE		MS^2 [269]: 241, 225, 210, 182 (Jin et al., 2007)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
					NA	NA (Jin et al., 2006b, Jin et al., 2006a)
270.24	$C_{15}H_{10}O_5$	28013-27-6	Trihydroxyflavone	SCU	269 $[M-H]^-$	MS^2 [269]: 225, 151, 117/ MS^2 [269]: 269, 169 (Qiao et al., 2016)
270.24	$C_{15}H_{10}O_5$	491-67-8	5,6,7-Trihydroxyflavone [Baicalein]	SCU	269 $[M-H]^-$	MS^2 [269]: 241, 223 (Qiao et al., 2016)
						MS^2 [269]: 269, 167 (Alolga et al., 2015)
						MS^n [269]: 251, 241, 223 (Wang et al., 2014b)
						MS^2 [269]: 251, 195, 169, 223 (Wang et al., 2013a)
						MS^2 [269]: 251, 241 (Luo et al., 2012)
						MS^2 [269]: 251, 241 (Zhang et al., 2007b)
						MS^2 [269]: 251, 241, 225, 223 MS^3 [251]: 223 (Han et al., 2007)
					271 $[M+H]^+$	MS^2 [271]: 253, 123, 169, 225 (Wang et al., 2013a)
						MS^2 [271]: 254, 137 (Chen et al., 2010)
						MS^2 [271]: 253, 229, 225, 197, 169, 123 (Liu et al., 2009)
					NA	NA (Kimuya et al., 1981, Takido et al., 1975, Kubo et al., 1981, Zhang et al., 1994, Lu et al., 2011)
270.24	$C_{15}H_{10}O_5$	4443-09-8	5,7,8-Trihydroxyflavone [Norwogonin]	SCU	269 $[M-H]^-$	MS^2 [269]: 241, 223 (Qiao et al., 2016)
						MS^2 [269]: 269, 241, 225 (Alolga et al., 2015)
						MS^2 [269]: 251, 241, 223, 197, 195, 179, 169, 167, 151, 137, 123, 117 (Seo et al., 2013)
						MS^2 [269]: 251, 241 (Luo et al., 2012)
						MS^2 [269]: 251, 241, 169 (Han et al., 2007)
						MS^2 [269]: 251, 241, 225 (Zhang et al., 2007b)
					270 $[M^+]$	NA (Tomimori et al., 1983)
					271 $[M+H]^+$	MS^2 [271]: 253, 229, 225, 215, 201, 197, 187, 173, 169, 123 (Liu et al., 2009)
270.24	$C_{15}H_{10}O_5$	73046-40-9	5,7,2'-Trihydroxyflavone	SCU	269 $[M-H]^-$	MS^2 [269]: 225, 197, 171 (Qiao et al., 2016)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
					NA	NA (Tomimori et al., 1984b)
271.31	$C_{16}H_{17}NO_3$	1162079-21-1	5,9-Dimethoxy-2,2-dimethyl-[2H]-pyranol[2,3-b]quinoline	DIC	NA	NA (Yang et al., 2011a)
271.31	$C_{16}H_{17}NO_3$	64190-94-9	8-MethoxyN-methylflindersine	DIC	NA	NA (Yoon et al., 2012)
272.25	$C_{15}H_{12}O_5$	NA	Dihydronorwogonin	SCU	271 $[M-H]^-$	MS^2 [271]: 243, 225, 152, 139 (Qiao et al., 2016)
273.28	$C_{15}H_{15}NO_4$	106006-02-4	O-Ethylnorskimmianine	DIC	NA	NA (Lin and Shieh, 1986)
273.29	$C_{11}H_{19}N_3O_5$	153789-69-6	5-[1,2-Dihydroxy-2-methyl-3-(4-morpholinyl)propyl]-2,4-imidazolidinedione	PHE	274 $[M+H]^+$	MS^2 [274]: 257, 217, 189, 179, 127, 95 (Yan et al., 2015)
278.30	$C_{15}H_{18}O_5$	126655-23-0	Dictamdiol	DIC	301 $[M+Na]^+$	NA (Lv et al., 2015, Jiang et al., 2006b)
					296 $[M+NH_4]^+$	NA (Jiang et al., 2006b)
					NA	NA (Jiang et al., 2006a, Zhao et al., 2008, Yoon et al., 2008, Lv et al., 2015)
278.30	$C_{15}H_{18}O_5$	1009320-61-9	Dictamdiol A	DIC	NA	NA (Yoon et al., 2008)
278.30	$C_{15}H_{18}O_5$	1009320-62-0	Dictamdiol B	DIC	NA	NA (Yoon et al., 2008)
278.30	$C_{15}H_{18}O_5$	959142-59-7	Isodictamdiol	DIC	301 $[M+Na]^+$	NA (Lv et al., 2015)
					296 $[M+NH_4]^+$	NA (Zhao et al., 2008)
278.30	$C_{15}H_{18}O_5$	1632410-42-4	23-Methoxydasylactone A	DIC	NA	NA (Wang et al., 2014c)
282.25	$C_{16}H_{10}O_5$	110204-45-0	5-Hydroxy-6,7-methylenedioxyflavone	KOC	NA	NA (Zhang et al., 2013c)
282.29	$C_{17}H_{14}O_4$	71013-35-9	Chrysophanol dimethyl ether	RP	281	NA (Wang et al., 2014f)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
					$[M-H]^-$	
283.32	$C_{17}H_{17}NO_3$	20375-37-5	N-*p*-Coumaroyltyramine	PHE	NA	NA (Lian et al., 2013)
284.22	$C_{15}H_8O_6$	478-43-3	Rhein	R	283 $[M-H]^-$	MS^2 [283]: 239, 211, 183 (Yang et al., 2015a)
				RP		MS^2 [283]: 239 (Liu et al., 2016)
						MS^2 [283]: 283, 239, 211, 183 (Alolga et al., 2015)
						MS^2 [283]: 257,241,239 MS^3 [283 à 257]: 257, 241, 239 MS^4 [283 à 257 à 239]: 257, 229, 212, 195 (Zhao et al., 2013a)
						MS^2 [283]: 257, 239 MS^3 [257]: 239 (Han et al., 2008)
				RHE		MS^2 [283]: 239, 211, 183 (Jin et al., 2007)
284.48	$C_{18}H_{36}O_2$	57-11-4	Stearic acid	KOC	NA	NA (Zhang et al., 2013c)
286.24	$C_{15}H_{10}O_6$	491-70-3	Luteolin	DIC	NA	NA (Wang, 2006)
284.26	$C_{16}H_{12}O_5$	480-11-5	5,7-Dihydroxy-6-methoxyflavone [Oroxylin A]	SCU	283 $[M-H]^-$	MS^2 [283]: 268, 239, 184 (Qiao et al., 2016)
						MS^n [283]: 268, 239, 163 (Wang et al., 2014b)
						MS^2 [283]: 268 (Luo et al., 2012)
						MS^2 [283]: 268 MS^2 [268]: 239, 212, 163 (Han et al., 2007)
						MS^2 [283]: 268 (Zhang et al., 2007b)
						NA (Wang et al., 2013a)
					285 $[M+H]^+$	MS^2 [285]: 270, 239, 168 MS^3 [270]: 168, 252 (Wang et al., 2013a)
						MS^2 [285]: 270 (Chen et al., 2010)
						MS^2 [285]: 270 (Liu et al., 2009)
					NA	NA (Kimuya et al., 1981, Takido et al., 1975, Zhang et al., 1994)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
284.26	$C_{16}H_{12}O_5$	632-85-9	5,7-Dihydroxy-8-methoxyflavone [Wogonin]	DIC	+	MS [284, 269, 241, 102] (Du et al., 2005)
				SCU	283 $[M-H]^-$	MS^2 [283]: 268, 239, 211, 184 (Qiao et al., 2016)
						MS^n [283]: 268, 239, 163 (Wang et al., 2014b)
						MS^2 [283]: 283, 268 (Seo et al., 2013)
						MS^2 [283]: 268 (Luo et al., 2012)
						MS^2 [283]: 268 MS^3 [268]: 240, 239, 223, 212, 196, 163 (Han et al., 2007)
						MS^2 [283]: 268 (Zhang et al., 2007b)
						NA (Wang et al., 2013a, Chen et al., 2010)
					285 $[M+H]^+$	MS^2 [285]: 270, 252 MS^3 [270]: 252 (Wang et al., 2013a)
						MS^2 [285]: 270 (Chen et al., 2010, Alolga et al., 2015)
						MS^2 [285]: 270 (Liu et al., 2009)
					NA	NA (Takido et al., 1975, Kimuya et al., 1981, Kubo et al., 1981, Zhang et al., 1994, Lu et al., 2011)
284.26	$C_{16}H_{12}O_5$	20575-57-9	3',7-Dihydroxy-4'-methoxy-isoflavone	SOP	285 $[M+H]^+$	MS^2 [285]: 270. 239, 211, 137 (Zhang et al., 2007a)
					307 $[M+Na]^+$	NA (Zhang et al., 2007a)
284.26	$C_{16}H_{12}O_5$	2035-15-6	(-)-Maackiain	SOP	285 $[M+H]^+$	MS^2[285]: 175, 151, 123 (Zhang et al., 2007a)
					NA	NA (Li et al., 2004, Kang et al., 2000b)
284.26	$C_{16}H_{12}O_5$	521-61-9	Physcion	R	283 $[M-H]^-$	MS^2 [283]: 269 (Yang et al., 2015a)
						MS^2 [283]: 268, 240 MS^3 [268]: 240 MS^3 [240]: 212, 184 (Yang et al., 2014a)
						NA (Lin et al., 2006)
				RP		MS^2 [283]: 283, 268, 240 (Alolga et al., 2015)
						MS^2 [283]: 268, 240 (Zhao et al., 2013a)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
						MS^2 [283]: 267, 241, 240 (Han et al., 2008)
				RHE		MS^2 [283]: 253, 225, 210, 182 (Jin et al., 2007)
					NA	NA (Jin et al., 2006b)
286.24	$C_{15}H_{10}O_6$	481-73-2	ω-Hydroxy-emodin	R	285 $[M-H]^-$	MS^2 [285]: 255, 239 (Yang et al., 2015a)
						NA (Lin et al., 2006)
286.24	$C_{15}H_{10}O_6$	520-18-3	Kaempferol	RP	NA	NA (Kashiwada et al., 1984)
286.24	$C_{15}H_{10}O_6$	314255-80-6	Lunatin	R	285 $[M-H]^-$	MS^2 [285]: 257, 241 (Yang et al., 2015a)
286.24	$C_{15}H_{10}O_6$	NA	Tetrahydroxyflavone	SCU	285 $[M-H]^-$	MS^2 [285]: 268, 175, 113/ MS^2 [285]: 267, 239, 171, 137 (Qiao et al., 2016)
286.24	$C_{15}H_{10}O_6$	529-53-3	5,6,7,4'-Tetrahydroxyflavone [Scutellarein]	SCU	285 $[M-H]^-$	MS^2 [285]: 267, 167, 137, 117 (Qiao et al., 2016)
						NA (Chen et al., 2010)
					287 $[M+H]^+$	MS^2 [287]: 183 (Chen et al., 2010)
286.24	$C_{15}H_{10}O_6$	74805-70-2	5,7,2',3'-Tetrahydroxyflavone	SCU	NA	NA (Tomimori et al., 1984a)
286.24	$C_{15}H_{10}O_6$	74805-72-4	5,7,2',5'-Tetrahydroxyflavone	SCU	286 $[M]^+$	MS^1: 286, 269, 258, 153, 134 (Zhang et al., 1994)
286.24	$C_{15}H_{10}O_6$	82475-00-1	5,7,2',6'-Tetrahydroxyflavone	SCU	285 $[M-H]^-$	MS^2 [285]: 241, 199, 151, 133 (Qiao et al., 2016)
						MS^2 [285]: 241, 217, 151 (Zhang et al., 2007b)
					NA	NA (Wang et al., 2013a, Tomimori et al., 1982, Ishimaru et al., 1995)
286.28	$C_{16}H_{14}O_5$	97660-90-7	Dihydroxymethoxyflavanone	SCU	285 $[M-H]^-$	NA (Qiao et al., 2016)
286.28	$C_{16}H_{14}O_5$	18956-18-8	5,7-Dihydroxy-6-methoxyflavanone [Dihydrooroxylin A]	SCU	285 $[M-H]^-$	MS^2 [285]: 139, 124, 119 (Qiao et al., 2016)
					NA	NA (Takagi et al., 1980)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
286.34	$C_{17}H_{20}NO_3$	NA	3,4-Dihydro-1-[(4-hydroxyphenyl)methyl]-7-methoxy-2-methyl-6-isoquinolinol	PA	286 $[M]^+$	MS^2 [286]: 283, 255, 191 (Xian et al., 2014)
286.34	$C_{17}H_{20}NO_3$	NA	3,4-Dihydro-1-[(4-hydroxyphenyl)methyl]-7-methoxy-2-methyl-8-isoquinolinol	PA	286 $[M]^+$	MS^2 [286]: 283, 255, 191 (Xian et al., 2014)
287.32	$C_{18}H_{13}N_3O_6$	84-26-4	Rutaecarpine	PA	287 $[M]^+$	MS^2 [287]: 144, 128 (Xian et al., 2014)
288.25	$C_{15}H_{12}O_6$	NA	Tetrahydroxyflavanone	SCU	287 $[M-H]^-$	MS^2 [287]: 161, 125 (Qiao et al., 2016)
288.25	$C_{15}H_{12}O_6$	479-54-9	5,6,7,4'-Tetrahydroxyflavanone [Carthamidin]	SCU	287 $[M-H]^-$	MS^2 [287]: 181, 167, 153, 139, 119 (Qiao et al., 2016)
288.25	$C_{15}H_{12}O_6$	80604-16-6	(2S)-5,7,2',6'-Tetrahydroxyflavanone	SCU	287 $[M-H]^-$	MS^2 [287]: 161, 125 (Qiao et al., 2016)
					NA	NA (Zhang et al., 1994, Kubo et al., 1981)
288.25	$C_{15}H_{12}O_6$	116301-03-2	(2S)-5,7,3',4'-Tetrahydroxyflavanone [(-)-Eriodictyol]	SCU	NA	NA (Zhang et al., 1994)
290.27	$C_{15}H_{14}O_6$	154-23-4	(+)-Catechin	R	289 $[M-H]^-$	MS^2 [289]: 271, 245, 125, 109 (Yang et al., 2015a)
						MS^2 [289]: 245, 205, 179, 165 MS^3 [245]: 227, 203, 187, 161 (Yang et al., 2014a)
						MS^2 [289]: 123, 152, 109 (Dong et al., 2011a)
				RO	NA	NA (Komatsu et al., 2006)
				RP	289 $[M-H]^-$	MS^2 [289]: 289 (Liu et al., 2016)
						NA (Wang et al., 2014f)
					NA	NA (Komatsu et al., 2006)
				RHE	289 $[M-H]^-$	MS^2 [289]: 109, 152, 123 (Jin et al., 2007)

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					NA	NA (Komatsu et al., 2006, Jin et al., 2006b, Jin et al., 2006a)
290.27	$C_{15}H_{14}O_6$	490-46-0	(-)-Epicatechin	R	289 $[M-H]^-$	MS^2 [289]: 245, 125, 109 (Yang et al., 2015a)
290.35	$C_{17}H_{22}O_4$	102390-90-9	Kushequinone A	SOP	NA	NA (Wu et al., 1986)
298.25	$C_{14}H_{10}N_4O_4$	330215-97-9	1H-Benzotriazol-1-yl(4-methoxy-3-nitrophenyl)methanone	PHE	297 $[M-H]^-$	MS^2 [297]: 205, 193, 179, 93, 59 (Yan et al., 2015)
298.25	$C_{16}H_{10}O_6$	NA	6-Dehydroxylaccaic acid D	R	297 $[M-H]^-$	MS^2 [297]: 253 MS^3 [253]: 255 (Han et al., 2008)
298.25	$C_{16}H_{10}O_6$	401621-27-0	4,5-Dihydroxy-7-methyl-9,10-dioxo-9,10-dihydro-2-anthracenecarboxylic acid	R	297 $[M-H]^-$	MS^2 [297]: 253, 225 (Yang et al., 2015a)
298.25	$C_{16}H_{10}O_6$	97359-75-6	5,2'-Dihydroxy-6,7-methylenedioxyisoflavone	KOC	NA	NA (Zhang et al., 2013c)
298.29	$C_{17}H_{14}O_5$	3570-62-5	5-Hydroxy-7,8-dimethoxyflavone	SCU	298 $[M^+]$	MS^1: 298, 283, 102 (Tomimori et al., 1983)
298.50	$C_{19}H_{38}O_2$	112-61-8	Methyl octadecanoate	RP	NA	NA (Miyazawa et al., 1996)
300.22	$C_{15}H_8O_7$	478-45-5	Emodic acid	R	299 $[M-H]^-$	MS^2 [299]: 255, 239 (Yang et al., 2015a)
300.26	$C_{16}H_{12}O_6$	NA	Trihydroxy-methoxyflavone	SCU	299 $[M-H]^-$	MS^2 [299]: 284, 136/ MS^2 [299]: 284, 151, 107/ MS^2 [299]: 284, 267, 154/ MS^2 [299]: 284, 166, 138, 110 (Qiao et al., 2016)
300.26	$C_{16}H_{12}O_6$	491-54-3	3,5,7-Trihydroxy-4'-methoxyflavone	SCU	299 $[M-H]^-$	MS^2 [299]: 284 MS^3 [284]: 256, 228, 137 (Han et al., 2007)
300.26	$C_{16}H_{12}O_6$	86926-51-4	5,7,2'-Trihydroxy-6-methoxyflavone [Tenaxin II]	SCU	299 $[M-H]^-$	284, 154 (Qiao et al., 2016)
					300	MS^1: 300, 285, 118 (Tomimori et al., 1983)

Appendix XIV List of compounds isolated from botanical drugs making up the hexa-herbal formula (HHCF).

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
					$[M^+]$	
300.26	$C_{16}H_{12}O_6$	92519-94-3	5,7,2'-Trihydroxy-6'-methoxyflavone	SCU	NA	NA (Tomimori et al., 1984a)
300.26	$C_{16}H_{12}O_6$	80713-32-2	5,7,2'-Trihydroxy-8-methoxyflavone [Scutevulin]	SCU	NA	NA (Tomimori et al., 1984a)
300.26	$C_{16}H_{12}O_6$	2284-31-3	5,7,3'-Trihydroxy-4'-methoxy-isoflavone [Pratensein]	KOC	NA	NA (Zhang et al., 2013c)
300.26	$C_{16}H_{12}O_6$	1447-88-7	5,7,4'-Trihydroxy-6-methoxyflavone	KOC	NA	NA (Lu et al., 2012)
300.26	$C_{16}H_{12}O_6$	548-77-6	5,7,4'-Trihydroxy-6-methoxy-isoflavone [Tectorigenin]	KOC	NA	NA (Zhang et al., 2013c)
300.26	$C_{16}H_{12}O_6$	57096-02-3	5,7,4'-Trihydroxy-8-methoxyflavone	SCU	299 $[M-H]^-$	MS^2 [299]: 284, 256, 137 (Qiao et al., 2016)
						MS^2 [299]: 284 (Luo et al., 2012)
						MS^2 [299]: 284 MS^3 [284]: 267, 256, 166, 138 (Han et al., 2007)
					NA	NA (Tomimori et al., 1982)
300.26	$C_{16}H_{12}O_6$	36190-95-1	5,7,4'-Trihydroxy-3'-methoxyisoflavone	DIC	NA	NA (Wang, 2006)
300.26	$C_{16}H_{12}O_6$	1447-88-7	5,7,4'-Trihydroxy-6'-methoxyflavone	SCU	NA	NA (Takagi et al., 1980)
300.26	$C_{16}H_{12}O_6$	77056-20-3	5,8,2'-Trihydroxy-7-methoxyflavone	SCU	300 $[M^+]$	MS^1: 300, 118 (Takagi et al., 1980)
300.30	$C_{14}H_{20}O_7$	10338-51-9	Salidroside	PA	NA	NA (Ida et al., 1993)
				SCU	NA	NA (Miyaichi and Tomimori, 1995)
301.34	$C_{17}H_{19}NO_4$	1344115-47-4	1',2'-Didehydro-7,8-dimethoxyplatydesmine	DIC	302 $[M+H]^+$	NA (Yang et al., 2011a)
302.24	$C_{15}H_{10}O_7$	NA	Pentahydroxyflavone	SCU	303 $[M+H]^+$	MS^2 [303]: 303, 285, 257, 247, 235, 229, 179, 165, 153, 149, 137, 127 (Seo et al., 2013)

Appendix XIV List of compounds isolated from botanical drugs making up the hexa-herbal formula (HHCF).

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
302.24	$C_{15}H_{10}O_7$	92519-95-4	3,5,7,2',6'-Pentahydroxyflavone [Viscidulin I]	SCU	301 $[M-H]^-$	MS^2 [301]: 283, 257, 193, 151, 125 (Qiao et al., 2016)
						MS^2 [301]: 283 (Wang et al., 2013a)
						MS^2 [301]: 283, 273, 257, 229, 151 (Zhang et al., 2007b)
					303 $[M+H]^+$	MS^2 [303]: 257 (Wang et al., 2013a)
					NA	NA (Tomimori et al., 1984a)
302.24	$C_{15}H_{10}O_7$	117-39-5	Quercetin	DIC	303 $[M+H]^+$	NA (Bai et al., 2014b)
					325 $[M+Na]^+$	
				KOC	NA	NA (Lu et al., 2012, Xu et al., 2012)
302.28	$C_{16}H_{14}O_6$	92519-97-6	2,6,2',4'-Tetrahydroxy-6'-methoxychalcone	SCU	NA	NA (Tomimori et al., 1984a)
302.28	$C_{16}H_{14}O_6$	NA	Trihydroxy-methoxyflavanone	SCU	301 $[M-H]^-$	MS^2 [301]: 161, 139 (Qiao et al., 2016)
302.28	$C_{16}H_{14}O_6$	NA	5,7, 4'-Trihydroxy-6-methoxyflavanone	SCU	302 $[M]^+$	302$[M]^+$, 120 (Takagi et al., 1980)
302.28	$C_{16}H_{14}O$	92519-96-5	(2S)-7,2',6'-Trihydroxy-5-methoxyflavanone	SCU	NA	NA (Tomimori et al., 1984a)
303.35	$C_{17}H_{21}NO_4$	304909-68-0	Dasycarine	DIC	+	MS [303, 288, 272, 260, 248, 234 218] (Du et al., 2005, Chen et al., 2000)
303.35	$C_{17}H_{21}NO_4$	1437691-40-1	Dasycarpamin	PA	304 $[M+H]^+$	MS^2 [304]: 286, 256, 232, 201 (Wang et al., 2013c)
303.35	$C_{17}H_{21}NO_4$	38695-41-9	Preskimmianine	DIC	NA	NA (Xiang et al., 2008, Yoon et al., 2012)
303.36	$C_{19}H_{17}N_3O$	518-17-2	Evodiamine	PA	304 $[M+H]^+$	MS^2 [304]: 144, 128 (Xian et al., 2014)
304.25	$C_{15}H_{12}O_7$	NA	Pentahydroxyflavanone	SCU	303 $[M-H]^-$	MS^2 [303]: 257, 219, 167, 141, 129, 113 (Seo et al., 2013)
304.25	$C_{15}H_{12}O_7$	1402054-86-7/80366-15-0		SCU	303 $[M-H]^-$	MS^2 [303]: 285, 259, 177, 149, 125 (Qiao et al., 2016)
						NA (Liu et al., 2009, Wang et al., 2014b)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
			3,5,7,2',6'-Pentahydroxy flavanone [Ganhuangemin]			MS^2 [303]: 125, 149, 177, 217, 259, 285 (Wang et al., 2013a)
						MS^2 [303]: 285, 275, 259, 217, 177 (Zhang et al., 2007b)
					305 $[M+H]^+$	MS^2 [305]: 287, 259, 153 (Wang et al., 2013a)
					NA	NA (Takagi et al., 1981b, Ishimaru et al., 1995)
304.25	$C_{15}H_{12}O_7$	NA	3,6,7,2',6'-Pentahydroxy flavanone	SCU	303 $[M-H]^-$	MS^2 [303]: 285, 177, 125 (Qiao et al., 2016)
310.30	$C_{15}H1_8O_7$	40004-96-4	Cinnamoyl glucose	R	309 $[M-H]^-$	MS^2 [309]: 147, 131, 103 (Yang et al., 2015a)
311.34	$C_{20}H_{13}N_3O$	85753-43-1	6,7,12,13-Tetrahydro-5H-indolo[2,3-α]pyrrolo[3,4-c]carbazol-5-one	PHE	312 $[M+H]^+$	MS^2 [312]: 297, 290 (Yan et al., 2015)
312.27	$C_{17}H_{12}O_6$	94574-56-8	(1,3-Dihydroxy-9,10-dioxo-9,10-dihydro-2-anthracenyl)methyl acetate	R	311 $[M-H]^-$	MS^2 [311]: 269, 241, 225 (Yang et al., 2015a)
312.27	$C_{17}H_{12}O_6$	114309-82-9	(4,5-Dihydroxy-9,10-dioxo-9,10-dihydro-2-anthracenyl)methyl acetate	R	311 $[M-H]^-$	MS^2 [311]: 269, 240 (Yang et al., 2015a)
313.35	$C_{18}H_{19}NO_4$	66648-43-9	N-*trans*-Feruloyltyramine	KOC	NA	NA (Zhang et al., 2013c)
313.39	$C_{19}H_{23}NO_3$	524-20-9	Evoeuropine	PHE	312 $[M-H]^-$	MS^2 [312]: 297, 296, 293, 271, 268, 245, 233, 215, 206 (Yan et al., 2015)
					314 $[M+H]^+$	MS^2 [314]: 281, 189, 161, 150, 146, 121, 107 (Yan et al., 2015)
314.25	$C_{16}H_{10}O_7$	481-70-9	Endocrocin	R	313 $[M-H]^-$	MS^2 [313]: 269, 241, 225(Yang et al., 2015a)
314.29	$C_{17}H_{14}O_6$	31395-74-1	Dihydroxy-dimethoxyflavone	SCU	313 $[M-H]^-$	MS^2 [313]: 298, 283, 165 (Qiao et al., 2016)
314.29	$C_{17}H_{14}O_6$	41060-16-6	5,2'-Dihydroxy-7,8-dimethoxyflavone [Skullcapflavone I]	SCU	NA	NA (Takido et al., 1975)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
314.29	$C_{17}H_{14}O_6$	3162-45-6	5,7-Dihydroxy-6,8-dimethoxyflavone	SCU	313 $[M-H]^-$	MS^2 [313]: 298, 283 MS^3 [298]: 180, 283 (Wang et al., 2013a)
					315 $[M+H]^+$	MS^2 [315]: 271, 300 MS^3 [300]: 271 (Wang et al., 2013a)
						MS^2 [315]: 300(100), 285, 267 (Liu et al., 2009)
314.29	$C_{17}H_{14}O_6$	73202-52-5	5,8-Dihydroxy-6,7-dimethoxyflavone	SCU	313 $[M-H]^-$	MS^2 [313]: 298, 283, 211, 173 (Qiao et al., 2016)
					NA	NA (Tomimori et al., 1982)
314.29	$C_{17}H_{14}O_6$	69626-65-9	(-)-4-Hydroxy-3-methoxy-(6aR,11aR)-8,9-methylenedioxypterocarpan	SOP	314 $[M]^+$	NA (Jung et al., 2005a)
314.40	$C_{19}H_{24}NO_3$	6871-67-6	Lotusine	PHE	314 $[M]^+$	MS^2 [314]: 314, 269, 237, 192, 143 (Alolga et al., 2015)
						MS^2 [314]: 298, 270, 269 (Hu et al., 2010)
				PA		MS^2 [314]: 299, 269, 237, 192, 143, 107 (Wang et al., 2013c)
						MS^2 [314]: 298, 282, 269 (Xian et al., 2014)
						MS^2 [314]: 298, 270, 269 (Hu et al., 2010)
314.40	$C_{19}H_{24}NO_3$	6801-40-7	Magnocurarine	PA	314 $[M]^+$	MS^2 [314]: 298, 282, 269 (Xian et al., 2014)
314.40	$C_{19}H_{24}NO_3$	152230-57-4	(-)-Oblongine	PHE	314 $[M]^+$	MS^2 [314]: 298, 283, 269, 192 (Hu et al., 2010)
						MS^2 [314]: 270, 269, 191 (Xian et al., 2014)
				PA		MS^2 [314]: 314, 298, 269, 237, 192, 175 (Wang et al., 2013c)
						MS^2 [314]: 298, 283, 269, 192 (Hu et al., 2010)
314.46	$C_{21}H_{30}O_2$	57-83-0	Progesterone	DIC	NA	NA (Wu et al., 1994)
316.26	$C_{16}H_{12}O_7$	480-19-3	Isorhamnetin	KOC	NA	NA (Lu et al., 2012)
316.26	$C_{16}H_{12}O_7$	NA	Tetrahyroxy-methoxyflavone	SCU	315 $[M-H]^-$	MS^2 [315]: 300, 181/ MS^2 [315]: 300, 153

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
						MS^2 [315]: 300, 137 (Qiao et al., 2016)
316.26	$C_{16}H_{12}O_7$	1890982-85-0	5,7,6'-Trihydroxy-2'-methoxyflavonol	SCU	317 $[M+H]^+$	NA (Long et al., 2015)
					339 $[M+Na]^+$	
316.30	$C_{14}H_{20}O_8$	74950-96-2	Vanilloloside	PA	315 $[M-H]^-$	MS^2 [315]: 284, 285, 153, 152, 136, 106 (Hu et al., 2010)
					NA	NA (Ida et al., 1993)
316.48	$C_{21}H_{32}O_2$	145-13-1	Pregnenolone	DIC	NA	NA (Wu et al., 1994, Zhao et al., 1998a, Xiang et al., 2008, Naoki et al., 1993)
318.28	$C_{16}H_{14}O_7$	55812-91-4	3'-O-Methyltaxifolin	DIC	NA	NA (Wang, 2006)
318.28	$C_{16}H_{14}O_7$	81524-09-6	5,7, 2',5'-Tetrahydroxy-6-methoxyflavanone	SCU	317 $[M-H]^-$	MS^2 [317]: 191, 125 (Qiao et al., 2016)
318.32	$C_{17}H_{18}O_6$	254886-78-7	Kushecarpin A	SOP	319 $[M+H]^+$	MS^2[319]: 301 (Zhang et al., 2007a)
319.31	$C_{18}H_{13}N_3O_4$	472965-96-1	7,8-Dihydroxyrutaecarpine	PA	320 $[M+H]^+$	MS^2[320]: 301, 273 (Xian et al., 2014)
319.35	$C_{17}H_{21}NO_5$	366490-63-3	(3R)-(-)-8,9-Dimethoxygeibalansine	DIC	NA	NA (Yang et al., 2011a)
319.35	$C_{17}H_{21}NO_5$	142741-27-3	7,8-Dimethoxyplatydesmine	DIC	NA	NA (Wu et al., 1994)
323.34	$C_{19}H_{17}NO_4$	4312-32-7	Tetrahydrocoptisine	PHE	324 $[M+H]^+$	MS^2[324]: 296, 283, 202, 147, 145, 89, 81 (Yan et al., 2015)
326.30	$C_{15}H_{28}O_8$	14364-05-7	*p*-Coumaric acid glucoside	RHE	NA	NA (Gao et al., 2012a)
326.34	$C_{16}H_{22}O_7$	38963-94-9	4-(4'-Hydroxylphenyl)-2-butanone 4'-O-β-D-glucoside	RP	325 $[M-H]^-$	MS^2 [325]: 161 (Liu et al., 2016)
				RHE		MS^2 [325]: 163, 57 (Jin et al., 2007)
327.38	$C_{16}H_{21}N_7O$	300718-25-6	[4,6-Bis(dimethylamino)-1,3,5-triazin-2-yl](2-phenoxyethyl)cyanamide	PHE	328 $[M+H]^+$	MS^2 [328]: 326, 313 (Yan et al., 2015)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
328.27	$C_{17}H_{12}O_7$	52591-11-4	Iriflogenin	KOC	NA	NA (Zhang et al., 2013c)
328.38	$C_{19}H_{22}NO_4$	172924-22-0	Litcubine	PA	328 $[M]^+$	MS^2 [328]: 310, 282, 280, 192, 153, 136 (Hu et al., 2010)
329.39	$C_{19}H_{23}NO_4$	485-19-8	Reticuline	PA	328 $[M-H]^+$	MS^2 [328]: 326, 274, 253, 192, 191 (Hu et al., 2010)
330.29	$C_{17}H_{14}O_7$	97661-05-7	Trihydroxy-methoxyflavone	SCU	329 $[M-H]^-$	MS^2 [229]: 284, 151, 107 (Qiao et al., 2016)
330.29	$C_{17}H_{14}O_7$	NA	Trihydroxy-dimethoxyflavone	SCU	329 $[M-H]^-$	MS^2 [229]: 314, 299, 165/ MS^2 [229]: 314, 299, 271 (Qiao et al., 2016)
330.29	$C_{17}H_{14}O_7$	92519-93-2	5, 2',6'-Trihydroxy-7,8-dimethoxyflavone [Viscidulin II]	SCU	329 $[M-H]^-$	MS^2 [229]: 314, 299, 165 (Qiao et al., 2016)
330.29	$C_{17}H_{14}O_7$	92519-90-9	5,7,2'-Trihydroxy-8,6'-dimethoxyflavone	SCU	NA	NA (Tomimori et al., 1984b)
330.29	$C_{17}H_{14}O_7$	18085-97-7	5,7,4'-Trihydroxy-6,3'-dimethoxyflavone	KOC	NA	NA (Lu et al., 2012)
330.29	$C_{17}H_{14}O_7$	NA	5,7,6'-Trihydroxy-8,2'-dimethoxyflavone	SCU	329 $[M-H]^-$	MS^2 [229]: 314, 166, 110 (Qiao et al., 2016)
330.29	$C_{17}H_{14}O_7$	77056-21-4	5,8,2'-Trihydroxy-6,7-dimethoxyflavone	SCU	329 $[M-H]^-$	MS^2 [329]: 314, 299, 271 (Qiao et al., 2016)
					330 $[M]^+$	MS^1: 330, 118 (Takagi et al., 1980)
330.46	$C_{18}H_{34}O_5$	163860-24-0	Sanleng acid	PHE	331 $[M+H]^+$	MS^2 [331]: 317, 293, 278, 229, 182, 157, 109, 81 (Yan et al., 2015)
					329 $[M-H]^-$	MS^2 [329]: 251, 225, 171 (Yan et al., 2015)
				PA	329 $[M-H]^-$	MS^2 [329]: 329, 311, 293, 229, 211, 171 (Wang et al., 2013c)
331.32	$C_{19}H_{13}N_3O_3$	1621341-55-6	7-Hydroxy-8-methoxydedihydrorutaecarpine	PA	331 $[M]^+$	MS^2 [331]: 313, 287, 255 (Xian et al., 2014)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
332.26	$C_{13}H_{16}O_{10}$	NA	Gallic acid-O-β-D-glucoside	R	331 $[M-H]^-$	MS^2 [331]: 271, 211, 169, 125 (Yang et al., 2015a)
332.26	$C_{13}H_{16}O_{10}$	91984-84-8	Gallic acid-3-O-β-D-glucoside	R	331 $[M-H]^-$	MS^2 [331]: 169, 125 (Dong et al., 2011a)
						MS^2 [331]: 169 (Lin et al., 2006)
				RP		MS^2 [331]: 331, 271, 211, 169 (Alolga et al., 2015)
						NA (Wang et al., 2014f)
				RHE		MS^2 [331]: 169 (Jin et al., 2007)
332.26	$C_{13}H_{16}O_{10}$	84274-52-2	Gallic acid-4-O-β-D-glucoside	RP	331 $[M-H]^-$	MS^1 [331]: 169 (Lin et al., 2006)
				RHE		MS^2 [331]: 169 (Jin et al., 2007)
332.26	$C_{13}H_{16}O_{10}$	261510-23-0/33040-89-0	Galloylglucose	RP	331 $[M-H]^-$	MS^2 [331]: 331 (Liu et al., 2016)
						MS^2 [331]: 169, 125 (Wang et al., 2011a)
						MS^2 [331]: 271, 241, 169, 125 MS^3 [169]: 125 (Han et al., 2008)
332.26	$C_{13}H_{16}O_{10}$	13405-60-2	1-O-Galloylglucose	RO	NA	NA (Komatsu et al., 2006)
				RP	NA	NA (Komatsu et al., 2006)
				RHE	331 $[M-H]^-$	MS^2 [331]: 169 (Jin et al., 2007)
					NA	NA (Komatsu et al., 2006)
332.26	$C_{13}H_{16}O_{10}$	34781-46-9	6-Galloylglucose	RO	NA	NA (Komatsu et al., 2006)
				RHE		
				RHE		
332.26	$C_{16}H_{12}O_8$	1409991-64-5	Pentahydroxy-methoxyflavone	SCU	331 $[M-H]^-$	MS^2 [331]: 316, 181, 153, 125 (Qiao et al., 2016)
335.35	$C_{17}H_{21}NO_6$	934402-65-0	7,8-Dimethoxymyrtopsine	DIC	NA	NA (Wu et al., 1994, Yang et al., 2011a)
336.36	$C_{20}H_{18}NO_4$	2086-83-1	Berberine	PHE	336 $[M]^+$	MS^2 [336]: 336, 334, 306, 292 (Alolga et al., 2015)
						MS^2 [336]: 145, 133, 88 (Yan et al., 2015)
						MS^2 [336]: 321, 292, 306, 275, 242, 186 (Hu et al., 2010)
					NA	NA (Qin and Wang, 2003, Liu et al., 2010b)
				PA	336	MS^2 [336]: 321, 306, 292 (Xian et al., 2014)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
					$[M]^+$	MS^2 [336]: 321, 292, 275 (Xian et al., 2014)
						MS^2 [336]: 336, 321, 320, 306, 292, 278, 276 (Wang et al., 2013c)
						MS^2 [336]: 320, 292 (Li et al., 2010)
						MS^2 [336]: 321, 292, 306, 275, 242, 186 (Hu et al., 2010)
					NA	NA (Zhang et al., 2015b)
336.36	$C_{20}H_{18}NO_4$	2086-83-1DP	Berberine isomer	PA	336 $[M]^+$	MS^2 [336]: 334, 306, 292, 268, 186 (Hu et al., 2010)
336.36	$C_{20}H_{18}NO_4$	6873-09-2	Epiberberine	PHE	+	MS^2 [320, 292] (Alolga et al., 2015)
				PA	336 $[M]^+$	MS^2 [336]: 321, 268, 242, 101 (Hu et al., 2010)
337.80	$C_{17}H_{20}ClNO_4$	1340494-35-0	3-Chloro-8,9-dimethoxygeibalansine	DIC	338 $[M+H]^+$	NA (Yang et al., 2011a)
338.38	$C_{20}H_{20}NO_4$	3621-36-1	Columbamine	PHE	338 $[M]^+$	MS^2 [338]: 336, 323, 149, 141, 135 (Hu et al., 2010)
					NA	NA (Lian et al., 2013)
				PA	338 $[M]^+$	MS^2 [338]: 323, 294 (Xian et al., 2014)
						MS^2 [338]: 324, 323, 315, 294, 277 (Xian et al., 2014)
						MS^2 [338]: 336, 323, 221, 148 (Hu et al., 2010)
338.38	$C_{20}H_{20}NO_4$	3621-38-3	Jatrorrhizine	PHE	338 $[M]^+$	MS^2 [338]: 338, 322, 308, 294, 280 (Alolga et al., 2015)
						MS^2 [338]: 209, 167, 88 (Yan et al., 2015)
						MS^2 [338]: 336, 323, 221, 148 (Hu et al., 2010)
						MS^2 [338]: 323, 294 (Li et al., 2010)
				PA		MS^2 [338]: 323, 294 (Xian et al., 2014)
						MS^2 [338]: 329, 323, 315, 294, 277 (Xian et al., 2014)
						MS^2 [338]: 336, 323, 221, 148 (Hu et al., 2010)
					NA	NA (Zhang et al., 2015b)
339.39	$C_{20}H_{21}NO_4$	522-97-4	Tetrahydroberberine	PA		
340.37	$C_{20}H_{20}O_5$	115063-39-3		SOP	339	MS^2[339]: 339, 219

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
			Demethylxanthohumol		$[M-H]^-$	MS^3[219]: 219, 191, 176, 175, 151, 150, 149, 133 MS^4[175]: 175, 148, 145, 133, 132, 131, 65 (Zhang et al., 2008)
					341 $[M+H]^+$	MS^2[341]: 341, 285, 221 MS^3[221]: 221, 197, 183, 165 MS^3[285]: 285, 197, 191, 183, 179, 165, 121 (Zhang et al., 2008)
340.37	$C_{20}H_{20}O_5$	53846-50-7	Sophoraflavanone B	SOP	339 $[M-H]^-$	MS^2 [339]: 339, 219 MS^3[219]: 219, 175, 151, 150, 149, 133 MS^4[175] : 175, 148, 133, 132, 131, 65 (Zhang et al., 2008)
341.36	$C_{15}H_{23}N_3O_6$	255845-85-3	2-{3,3-Bis[(2-hydroxyethyl)amino]-2-nitroprop-2en-1-ylidene}-5,5-dimethylcyclohexane-1,3-dione	PHE	342 $[M+H]^+$	MS^2 [342]: 325, 313, 311, 298, 293, 290, 287 (Yan et al., 2015)
341.40	$C_{20}H_{23}NO_4$	1415932-40-9	Dictamnaindiol	DIC	364 $[M+Na]^+$	NA (Guo et al., 2012b)
341.40	$C_{20}H_{23}NO_4$	27313-86-6	Tetrahydrojatrorrhizine	PHE	342 $[M]^+$	MS^2 [342]: 342, 297, 265 (Alolga et al., 2015)
						MS^2 [342]: 342, 298, 249, 192, 177, 145 (Yan et al., 2015)
						MS^2 [342]: 314, 269, 191, 150, 135 MS^2 [314]: 269, 150, 135 (Hu et al., 2010)
						MS^2 [342]: 297, 265 (Li et al., 2010)
				PA		MS^2 [342]: 314, 298, 269, 268, 192, 177 (Xian et al., 2014)
						MS^2 [342]: 342, 297 269, 150, 135 (Wang et al., 2013c)
342.30	$C_{12}H_{22}O_{11}$	57-50-1	Sucrose	R	341 $[M-H]^-$	MS^2 [341]: 179, 161, 113 (Yang et al., 2015a)
				SOP	NA	NA (Zhang et al., 2000)
342.30	$C_{12}H_{22}O_{11}$	133-99-3	β -Maltose	R	341 $[M-H]^-$	MS^2 [341]: 179, 161, 113 (Yang et al., 2015a)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
342.31	$C_{15}H_{14}N_6O_4$	303126-79-6	5-[(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)hydrazono]pyrimidine-2,4,6(1H,3H,5H)-trione	PHE	341 $[M-H]^-$	MS^2 [341]: 293, 207, 173, 145, 128, 113, 85 (Yan et al., 2015)
342.34	$C_{16}H_{22}O_8$	531-29-3	Coniferin	PA	341 $[M-H]^-$	MS^2 [341]: 293, 179, 149, 110, 79 (Hu et al., 2010)
					NA	NA (Ida et al., 1993)
342.34	$C_{19}H_{18}O_6$	1168-42-9	Tetramethyl-O-scutellarin	PA	341 $[M-H]^-$	MS^2 [341]: 387, 341, 179, 161, 119 (Wang et al., 2013c)
342.41	$C_{20}H_{24}NO_4$	2141-09-5	Magnoflorine	PHE	342 $[M]^+$	MS^2 [342]: 342, 297, 265 (Alolga et al., 2015)
						MS^2 [342]: 297, 282, 237, 191, 58 (Wang et al., 2014a)
						MS^2 [342]: 297, 265 (Li et al., 2010)
						MS^2 [342]: 312, 297, 265, 192 (Hu et al., 2010)
				PA		MS^2 [342]: 297, 265, 237 (Xian et al., 2014)
						MS^2 [342]: 313, 299, 297, 279, 265, 237, 226, 192 (Xian et al., 2014)
						MS^2 [342]: 342, 297, 265, 192 (Wang et al., 2013c)
						MS^2 [342]: 312, 297, 265, 192 (Hu et al., 2010)
						NA (Zhang et al., 2015b)
342.41	$C_{20}H_{24}NO_4$	2141-09-5DP	Magnoflorine isomer	PHE	342 $[M]^+$	MS^2 [342]: 312, 297, 265, 192 (Hu et al., 2010)
				PA		MS^2 [342]: 297, 265, 237 (Xian et al., 2014)
						MS^2 [342]: 312, 297, 265, 192 (Hu et al., 2010)
342.41	$C_{20}H_{24}NO_4$	6873-13-8	Phellodendrine	PHE	342 $[M]^+$	MS^2 [342]: 342, 192 (Alolga et al., 2015)
						MS^2 [342]: 192, 177, 149 (Wang et al., 2014a)
						MS^2 [342]: 312, 297, 265, 191, 190, 150 (Hu et al., 2010)
						MS^2 [342]: 192 (Li et al., 2010)
				PA		MS^2 [342]: 297, 265, 192, 177 (Wang et al., 2013c)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
						MS^2 [342]: 312, 297, 265, 192, 177 (Xian et al., 2014)
						MS^2 [342]: 312, 279, 241, 226, 192, 177, 149 (Xian et al., 2014)
						MS^2 [342]: 312, 297, 265, 191, 190, 150 (Hu et al., 2010)
					NA	NA (Zhang et al., 2015b)
343.37	$C_{19}H_{21}NO_5$	78510-19-7	N-trans-Feruloyl-3-methoxytyramine	KOC	NA	NA (Zhang et al., 2013c)
343.38	$C_{15}H_{25}N_3O_6$	857437-12-8	Methyl-N-{[(2-methyl-2-propanyl)oxy]carbonyl}glycylprolylglycinate	PHE	344 $[M+H]^+$	MS^2 [344]: 343, 222, 209, 192, 163, 95 (Yan et al., 2015)
344.32	$C_{18}H_{16}O_7$	70028-59-0	5,2'-Dihydroxy-7,8,6'-trimethoxyflavone [Skullcapflavone]	SCU	343 $[M-H]^-$	MS^2 [343]: 328, 313, 298, 285 (Qiao et al., 2016)
						MS^2 [343]: 328, 313 MS^3 [328]: 313, 273 MS^4 [313]: 298, 285, 269, 165 (Han et al., 2007)
					345 $[M+H]^+$	MS^2 [345]: 312, 300, 284 (Liu et al., 2009)
344.32	$C_{18}H_{16}O_7$	86926-52-5	5,2'-Dihydroxy-6,7,8-trimethoxyflavone [Tenaxin I]	SCU	343 $[M-H]^-$	MS^2 [343]: 328, 313, 298 (Qiao et al., 2016)
						MS^2 [343]: 328,313,298 (Seo et al., 2013)
						MS^2 [343]: 328 MS^3 [328]: 313 (Wang et al., 2013a)
						MS^2 [343]: 328 MS^3 [328]: 313 MS^4 [313]: 298, 285, 270 (Han et al., 2007)
					344 $[M]^+$	MS: 344, 188 (Tomimori et al., 1983)
					345 $[M+H]^+$	MS^2 [345]: 315 MS^3 [315]: 197 (Wang et al., 2013a)
						MS^2 [345]: 330, 315, 312, 297 (Liu et al., 2009)

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344.38	$C_{19}H_{22}NO_5$	NA	5,8,13,13a-Tetrahydro-2,9,10,11-tetrahydroxy-3-methoxy-7-methyl-6H-dibenzo[a,g]quinolizinium	PA	344 $[M]^+$	MS^2 [344]: 314, 192, 177 (Xian et al., 2014)
344.42	$C_{20}H_{26}NO_4$	18446-73-6	Tembetarine	PHE	344 $[M]^+$	MS^2 [344]: 344, 299, 207, 175, 137 (Alolga et al., 2015)
				PA		MS^2 [344]: 299. 235, 207, 175, 137 (Wang et al., 2013c)
						MS^2 [344]: 298, 267, 192, 177 (Xian et al., 2014)
346.29	$C_{17}H_{14}O_8$	92519-91-0	Viscidulin III	SCU	345 $[M-H]^-$	MS^2 [345]: 330, 315, 287 (Qiao et al., 2016)
						MS^n [345]: 330, 315 (Wang et al., 2014b)
						MS^2 [345]: 330, 315 (Liu et al., 2009)
					347 $[M+H]^+$	MS^2 [347]: 332 (Wang et al., 2013a)
351.35	$C_{20}H_{17}NO_5$	549-21-3	Oxyberberine	PHE	352 $[M+H]^+$	MS^2 [352]: 309, 217, 163, 147 (Yan et al., 2015)
				PA		MS^2 [352]: 352, 336, 322, 230, 308 (Wang et al., 2013c)
						MS^2 [352]: 337, 308 (Xian et al., 2014)
351.35	$C_{20}H_{17}NO_5$	19716-60-0	8-Oxoepiberberine	PA	352 $[M+H]^+$	MS^2 [352]: 337, 309 (Xian et al., 2014)
						MS^2 [352]: 337, 324, 309, 291, 280, 259 (Xian et al., 2014)
352.34	$C_{17}H_{20}O_8$	1251459-63-8	2,5-Dimethyl-7-hydroxychromone-7-O-β-D-gluocoside	RHE	NA	NA (Gao et al., 2014a)
352.40	$C_{21}H_{22}NO_4$	3486-67-7	Palmatine	PHE	352 $[M]^+$	MS^2[352]: 352, 336, 322, 308, 294 (Alolga et al., 2015)
						MS^2[352]: 338, 324, 169, 161, 147, 121, 93 (Yan et al., 2015)
						MS^2[352]: 337, 322, 308, 291, 190 (Hu et al., 2010)
					NA	NA (Qin and Wang, 2003)
				PA	352 $[M]^+$	MS^2[352]: 337, 308 (Xian et al., 2014)
						MS^2[352]: 337, 308, 291 (Xian et al., 2014)
						MS^2[352]: 352, 337, 336, 320, 308, 292, 278, 254 (Wang et al., 2013c)

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						MS^2[352]: 337, 322, 308, 291, 190 (Hu et al., 2010)
						MS^2[352]: 336, 308 (Li et al., 2010)
					NA	NA (Zhang et al., 2015b)
352.40	$C_{21}H_{22}NO_4$	NA	Palmatine isomer	PA	352 $[M]^+$	MS^2[352]: 337, 242, 141 (Hu et al., 2010)
354.31	$C_{16}H_{18}O_9$	327-97-9	Chlorogenic acid	PHE	353 $[M-H]^-$	MS^2[353]: 191, 179, 135 (Hu et al., 2010)
				PA	355 $[M+H]^+$	MS^2[355]: 193, 181, 137 (Xian et al., 2014)
					353 $[M-H]^-$	MS^2[353]: 191, 179, 135 (Hu et al., 2010)
					NA	NA (Zhang et al., 2015b)
				SCU	NA	NA (Lu et al., 2011)
354.31	$C_{16}H_{18}O_9$	906-33-2	Neo chlorogenic acid	PHE	353 $[M-H]^-$	MS^2 [355]: 191, 179, 173 (Hu et al., 2010)
				PA		
354.35	$C_{20}H_{18}O_6$	28610-31-3	Desmethylanhydroicaritin/ Noranhydroicaritin	SOP	353 $[M-H]^-$	NA (Zhang et al., 2013a)
					377 $[M+Na]^+$	
					393 $[M+K]^+$	
					NA	NA (Jung et al., 2005a, Zhang et al., 2010b)
354.40	$C_{21}H_{22}O_5$	70872-29-6	7,4'-dihydroxy-5-methoxy-8-(γ,γ,-dimethylallyl)-flavanone [Isoxanthohumol]	SOP	353 $[M-H]^-$	MS^2 [353]: 353, 251, 247, 233, 218, 119 MS^3 [233]: 233, 218, 205, 201, 190, 189, 174, 173, 165, 159, 145, 133 (Zhang et al., 2008)
						NA (Zhang et al., 2013a)
					707 $[2M-H]^-$	NA (Zhang et al., 2013a)
					355	MS^2 [355]: 355, 299, 235, 179

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					$[M+H]^+$	MS^3 [179]: 211, 197, 179, 151 MS^3 [235]: 235, 197, 179 MS^3 [299]: 257, 197, 193, 179 (Zhang et al., 2008)
						MS^2 [335]: 299, 256, 235, 179 (Zhang et al., 2007a)
						NA (Zhang et al., 2013a)
					377 $[M+Na]^+$	NA (Zhang et al., 2007a)
					731 $[2M+Na]^+$	NA (Zhang et al., 2013a)
					Na	NA (Kang et al., 2000a)
354.40	$C_{21}H_{22}O_5$	6754-58-1	Xanthohumol	SOP	355 $[M+H]^+$	MS^2 [355]: 355, 299, 253 MS^3 [235]: 235, 234, 211, 197, 179 MS^3 [299]: 299, 257, 211, 197, 179 (Zhang et al., 2008)
						MS^2 [355]: 299, 235, 179 (Zhang et al., 2007a)
354.42	$C_{21}H_{24}N_4O_4$	26297-11-0	N-Methyl canadine	PA	354 $[M]^+$	MS^2 [354]: 354, 340, 322, 190 (Wang et al., 2013c)
355.35	$C_{13}H_{21}N_7O_5$	313476-83-4	2-Amino-N-(3-amino-2-hydroxypropyl)adenosine	PHE	356 $[M+H]^+$	MS^2 [356]: 261, 260, 242, 177
355.43	$C_{21}H_{25}NO_4$	2934-97-6	Tetrahydropalmatine	PHE	356 $[M+H]^+$	MS^2 [356]: 356, 192 (Alolga et al., 2015)
						MS^2 [356]: 192 (Li et al., 2010)
						MS^2 [356]: 324, 147, 130 (Yan et al., 2015)
				PA		MS^2 [356]: 328, 312, 192, 177 (Xian et al., 2014)
						MS^2 [356]: 339, 308, 293, 264, 205, 192, 191, 177 (Xian et al., 2014)
						MS^2 [356]: 352, 192, 191, 164, 149 (Hu et al., 2010)
356.37	$C_{17}H_{24}O_8$	64703-96-4	4-[4-(β-D-Glucosyloxy)-3-methoxyphenyl]-2-butanone	RHE	NA	NA (Gao et al., 2014a)
356.37	$C_{20}H_{20}O_6$	152464-78-3	Leachianone G	SOP	NA	NA (Jung et al., 2010)
356.43	$C_{21}H_{26}NO_4$	7224-60-4		PA	356	MS^2 [356]: 311, 279, 251 (Xian et al., 2014)

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DIC= root bark of *Dictamnus dasycarpus* Turcz.; KOC= fruit *of Kochia scoparia* (L.) Schrad.; P= bark of *Phellodendron chinense* C.K. Schneid. or *Phellodendron amurense* Rupr. ;PA= bark of *Phellodendron amurense* Rupr.; PHE= bark of *Phellodendron chinense* C.K. Schneid.; R= rootstock of *Rheum* species; RHE= rootstock of *Rheum tanguticum* Maxim. ex Balf.; RO= rootstock of *Rheum officinale* Baill.; RP= rootstock of *Rheum palmatum* L.; SCU= rootstock of *Scutellaria baicalensis* Georgi; SOP= rootstock of *Sophora flavescens* Aiton

Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
			N-Methylcorydine		$[M]^+$	MS^2 [356]: 328, 311, 304, 279, 265, 192, 135 (Hu et al., 2010)
356.43	$C_{21}H_{26}NO_4$	25342-82-9	Menisperine	PHE	356 $[M]^+$	MS^2 [356]: 356, 311, 279 (Alolga et al., 2015)
						MS^2 [356]: 352, 311, 279, 193, 192 (Hu et al., 2010)
						MS^2 [356]: 311, 279, 248 (Li et al., 2010)
				PA		MS^2 [356]: 311, 279, 251 (Xian et al., 2014)
						MS^2 [356]: 311, 296, 279, 191, 178, 165 (Wang et al., 2013c)
						MS^2 [356]: 352, 311, 279, 193, 192 (Hu et al., 2010)
356.43	$C_{21}H_{26}NO_4$	747366-57-0	N-Methyltetrahydrocolumbamine	PHE	356 $[M]^+$	MS^2 [356]: 356, 297, 192, 177, 148 (Alolga et al., 2015)
				PA	356 $[M]^+$	MS^2 [356]: 192, 177, 149 (Wang et al., 2013c)
356.43	$C_{21}H_{26}NO_4$	6872-88-4	Xanthoplanine	PA	356 $[M]^+$	MS^2 [356]: 352, 342, 312, 279, 192, 121 (Hu et al., 2010)
360.31	$C_{15}H_{20}O_{10}$	33228-65-8	4-(β-D-Glucosyloxy)-3,5-dimethoxybenzoic acid	RHE	NA	NA (Gao et al., 2014a)
360.31	$C_{18}H_{16}O_8$	NA	Trihydroxy-trimethoxyflavone	SCU	359 $[M-H]^-$	MS^2 [359]: 344, 329, 314 (Qiao et al., 2016)
360.31	$C_{18}H_{16}O_8$	92519-92-1	5,2',5-Trihydroxy-6,7,8-trimethoxyflavone	SCU	359 $[M-H]^-$	MS^2 [359]: 344, 329, 314, 195 (Qiao et al., 2016)
					NA	NA (Tomimori et al., 1984b)
367.36	$C_{17}H_{17}N_7O_3$	299970-67-5	Ethyl{5-[ethyl(phenyl)amino][1,2,5]oxadiazolo[3,4-e][1,2,4]triazolo[4,3-α]pyrazin-8-yl}acetate	PHE	368 $[M+H]^+$	MS^2 [368]: 354, 352, 337 (Yan et al., 2015)
367.40	$C_{21}H_{21}NO_5$	19716-59-7	8-Oxypalmatine	PA	368 $[M+H]^+$	MS^2 [368]: 353, 324 (Xian et al., 2014)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
367.40	$C_{21}H_{21}NO_5$	19716-59-7 or 779267-72-0	8-Oxypalmatine or 13-Hydroxypalmatine	PA	368 $[M+H]^+$	MS^2 [368]: 368, 353, 338, 310, 294 (Wang et al., 2013c)
367.40	$C_{21}H_{21}NO_5$	779267-72-0	13-Hydroxypalmatine	PA	368 $[M]^+$	MS^2 [368]: 353, 338, 324, 177, 145 (Xian et al., 2014)
368.34	$C_{17}H_{20}O_9$	1899-29-2	3-O-Feruloylquinic acid	PHE	367 $[M-H]^-$	MS^2 [367]: 325, 195, 135, 134 (Yan et al., 2015)
						MS^2 [367]: 193, 191, 173 (Hu et al., 2010)
				PA		MS^2 [367]: 191, 173, 194, 149, 134, 117, 111/ MS^2 [367]: 367, 191, 173, 134, 111 (Wang et al., 2013c)
						MS^2 [367]: 193, 191, 173 (Hu et al., 2010)
					369 $[M+H]^+$	MS^2 [369]: 353, 177 (Xian et al., 2014)
368.34	$C_{17}H_{20}O_9$	40242-06-6	5-O-Feruloylquinic acid	PHE	NA	NA (Li et al., 2012c)
					367 $[M-H]^*$	MS^2 [367]: 367, 193, 191, 176, 173, 147 (Hu et al., 2010)
				PA	368 $[M]^+$	MS^2 [368]: 353, 177 (Xian et al., 2014)
					NA	NA (Ida et al., 1993)
368.38	$C_{21}H_{20}O_6$	216450-65-6	Sophoflavescenol	SOP	NA	NA (Woo et al., 1998)
368.40	$C_{17}H_{27}N_3O_6$	1105047-98-0	Hydroxypalmatine	PA	368 $[M]^+$	MS^2 [368]: 368, 352, 312, 304, 141(Hu et al., 2010)
368.40	$C_{21}H_{22}NO_5$	76144-80-4	11-Hydroxypalmatine	PA	368 $[M]^+$	MS^2 [368]: 353, 324, 194 (Xian et al., 2014)
368.40	$C_{21}H_{22}NO_5$	NA	13-Methoxyjatrorrhizine	PA	368 $[M]^+$	MS^2 [368]: 353, 324 (Xian et al., 2014)
368.64	$C_{24}H_{48}O_2$	557-59-5	Lignoceric acid	SOP	NA	NA (Zhang et al., 2000)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
369.41	$C_{17}H_{27}N_3O_6$	415703-25-2	2-{2-[4-(4,5-Dimethoxy-2-nitrobenzyl)-1-piperazinyl]ethoxy}ethanol	PHE	370 $[M+H]^+$	MS^2 [370]: 343, 328, 261, 177, 114, 81 (Yan et al., 2015)
370.35	$C_{17}H_{22}O_9$	154461-65-1	Sinapic aldehyde 4-O-β-D-glucoside	PA	NA	NA (Ida et al., 1993)
370.38	$C_{20}H_{20}NO_6$	1105048-07-4	Dihydroxyl-jatrorrhizine	PA	370 $[M]^+$	MS^2 [370]: 368, 356, 338, 312, 304, 206 (Hu et al., 2010)
370.39	$C_{21}H_{22}O_6$	69573-59-7	Sophoraisoflavanone A	SOP	371 $[M+H]^+$	MS^2 [371]: 353, 325, 315, 285, 269, 235, 179, 153 (Zhang et al., 2007a)
					393 $[M+Na]^+$	NA (Zhang et al., 2007a)
370.39	$C_{21}H_{22}O_6$	943988-18-9	7,9,2',4'-Tetrahydroxy-8-isopentenyl-5-methoxychalcone	SOP	NA	NA (Choi et al., 2010)
370.39	$C_{21}H_{22}O_6$	204935-85-3	3β,7,4'-Trihydroxy-5-methoxy-8-(γ,γ-dimethylallyl)flavanone	SOP	NA	NA (Jung et al., 2005a, Quang et al., 2012)
370.46	$C_{22}H_{28}NO_4$	47528-98-3	N-Methyltetrahydropalmatine	PA	370 $[M]^+$	MS^2 [370]: 340. 293, 206, 191 (Xian et al., 2014)
372.37	$C_{17}H_{24}O_9$	118-34-3	Syringin	PA	NA	NA (Ida et al., 1993, Li et al., 2012b)
374.34	$C_{19}H_{18}O_8$	55084-08-7	5,6'-Dihydroxy-6,7,8,2'-tetramethoxyflavone [Skullcapflavone II]	SCU	373 $[M-H]^-$	MS^2 [373]: 343, 328, 300, 257 (Qiao et al., 2016)
						MS^n [373]: 358, 343, 328, 300, 285 (Wang et al., 2014b)
						MS^2 [373]: 358 (Wang et al., 2013a)
						MS^2 [373]: 358, 343 (Luo et al., 2012)
						MS^2 [373]: 358, 343 MS^3 [358]: 343 MS^4 [343]: 328, 300, 285, 169 MS^5 [328]: 300, 272, 228 (Han et al., 2007)
					375 $[M+H]^+$	MS^2 [375]: 375, 360, 345, 327, 314, 299, 227, 197, 175, 167, 148, 137 (Seo et al., 2013)

Appendix XIV List of compounds isolated from botanical drugs making up the hexa-herbal formula (HHCF).

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
						MS^2 [375]: 345, 327, 227, 167 MS^3 [345]: 167, 197 MS^3 [358]: 343, 169 (Wang et al., 2013a)
						MS^2 [375]: 360, 342, 345, 327 (Liu et al., 2009)
374.34	$C_{19}H_{18}O_8$	NA	5,7-Dihydroxy-8,2',3',6'-tetramethoxyflavone	SCU	375 $[M+H]^+$	NA (Long et al., 2015)
					397 $[M+Na]^+$	NA (Long et al., 2015)
374.38	$C_{20}H_{22}O_7$	155014-35-0	3,5,7,2',6'-Pentamethoxyflavanone	SCU	NA	NA (Zhang et al., 1994)
374.43	$C_{18}H_{30}O_8$	202278-92-0	Dictamnoside E	DIC	+	MS [392, 230] (Zhao et al., 1998b)
374.43	$C_{18}H_{30}O_8$	359845-47-9	Dictamnoside N	DIC	397 $[M+Na]^+$	NA (Chang et al., 2001)
					413 $[M+K]^+$	
376.31	$C_{18}H_{16}O_9$	1173194-48-3	Tetrahydroxy-trimethoxyflavone	SCU	375 $[M-H]^-$	MS^2 [375]: 360, 345, 330 (Qiao et al., 2016)
378.42	$C_{20}H_{26}O_7$	2316-18-9	1-(4-Hydroxy-3-methoxyphenyl)-2-[4-(3-hydroxy-propyl)-2-methoxyphenoxy]-propane-1,3-diol	PHE	NA	NA (Lian et al., 2013)
382.36	$C_{18}H_{22}O_9$	154418-15-2	Methyl 3-O-feruloylquinate	PA	NA	NA (Ida et al., 1993)
					381 $[M-H]^-$	MS^2 [381]: 381, 367, 337, 324, 191, 173 (Hu et al., 2010)
382.36	$C_{18}H_{22}O_9$	154461-64-0	Methyl 5-O-feruloylquinate	PA	NA	NA (Ida et al., 1993)
383.35	$C_{20}H_{17}NO_7$	71700-15-7	Chilenine	PHE	NA	NA (Liu et al., 2010b)
384.33	$C_{14}H_{24}O_{12}$	NA	Acetylmaltose	R	383 $[M-H]^-$	MS^2 [383]: 341, 323, 179 (Yang et al., 2015a)
384.44	$C_{22}H_{26}NO_5$	713148-32-4	N-Methylphoebine	PA	384 $[M]^+$	MS^2 [384]: 356, 328, 221, 149, 136 (Hu et al., 2010)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
386.39	$C_{18}H_{26}O_9$	666849-46-3	4-(4'-O-β-D-Glucosyl-3',5',-dimethoxyphenyl)-2-butanone	RHE	NA	NA (Gao et al., 2014a)
386.65	$C_{27}H_{46}O$	57-88-5	3β-Hydroxy-cholesta-5-ene	DIC	NA	NA (Bai et al., 2014b)
388.63	$C_{25}H_{44}N_2O$	7759-51-5	Dihydrocyclobuxine D	PA	389 $[M+H]^+$	MS^2 [389]: 345, 330 (Xian et al., 2014)
390.34	$C_{19}H_{18}O_9$	1347666-84-5	Trihydroxy-tetramethoxyflavone	SCU	389 $[M-H]^-$	MS^2 [389]: 374, 359, 344 (Qiao et al., 2016)
390.38	$C_{20}H_{22}O_8$	27208-80-6	Resveratrol-3-O-β-D-glucoside [Pieceid]	RP	389 $[M-H]^-$	MS^2 [389]: 227, 185, 143 (Liu et al., 2016)
390.38	$C_{20}H_{22}O_8$	38963-95-0	Resveratrol-4'-O-β-D-glucoside	R	389 $[M-H]^-$	MS^2 [389]: 227 (Yang et al., 2015a)
						NA (Lin et al., 2006)
				RO	NA	NA (Komatsu et al., 2006)
				RP		
					389 $[M-H]^-$	MS^2 [389]: 227, 185, 143 (Liu et al., 2016)
				RHE		MS^2 [389]: 227 (Jin et al., 2007)
					NA	NA (Jin et al., 2006b, Jin et al., 2006a)
				R	391 $[M+H]^+$	NA (Lin et al., 2006)
392.40	$C_{17}H_{28}O_{10}$	479026-41-0	Dasycarpuside B	DIC	415 $[M+Na]^+$	NA (Chang et al., 2002)
394.37	$C_{19}H_{22}O_9$	30861-27-9	Aloesin	R	393 $[M-H]^-$	MS^2 [393]: 231 (Yang et al., 2015a)
394.37	$C_{19}H_{22}O_9$	23566-96-3	6-Hydroxymusizin-8-O-β-D-glucoside	R	393 $[M-H]^-$	MS^2 [393]: 231 (Dong et al., 2011a)
				RHE		MS^2 [393]: 231 (Jin et al., 2007)
					NA	NA (Gao et al., 2012a)
396.39	$C_{19}H_{24}O_9$	676145-15-6	Ethyl 5-O-feruloylquinate	PHE	NA	NA (Qin and Wang, 2003)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
396.39	$C_{19}H_{24}O_9$	94356-36-2	2-(2'-Hydroxypropyl)-5-methyl-7-hydroxychromone 7-O-β-D-glucoside	RP	NA	NA (Kashiwada et al., 1984)
397.38	$C_{18}H_{23}NO_9$	1393580-72-7	3-[1β-hydroxy-2-(β-D-glucosyloxy)-ethyl)-4-methoxy-2(1H)-quinolinone	DIC	398 $[M+H]^+$	NA (Yoon et al., 2012)
400.68	$C_{28}H_{48}O$	474-62-4	Campesterol	SCU	NA	NA (Takido et al., 1975)
402.39	$C_{18}H_{26}O_{10}$	172428-49-8	Benzyl O-β-D-apiofuranosyl-(1 à 2)- β-D-glucoside	SCU	NA	NA (Miyaichi and Tomimori, 1995)
404.41	$C_{21}H_{24}O_8$	30197-14-9	Desoxyrhaponticin	RHE	NA	NA (Li et al., 2014)
408.40	$C_{20}H_{24}O_9$	64032-49-1	Torachrysone-8-O-β-D-glucoside	R	407 $[M-H]^-$	MS^2 [407]: 245, 230, 215, 187 (Yang et al., 2015a)
				RP		MS^2 [407]: 245, 230 MS^3 [245]: 230 MS^4 [230]: 215 MS^5 [215]: 187, 159 (Han et al., 2008)
				RHE		MS^2 [407]: 245, 230 (Jin et al., 2007)
					NA	NA (Gao et al., 2012a, Jin et al., 2006b)
408.49	$C_{25}H_{28}O_5$	99217-63-7	Kushenol A	SOP	409 $[M+H]^+$	MS^2[409]: 391, 285, 267, 289, 165 (Zhang et al., 2007a)
					NA	NA (Kim et al., 2010b)
410.42	$C_{20}H_{26}O_9$	1009320-59-5	9α-Hydroxyfraxinellone-9-O-β-D-glucoside	DIC	433 $[M+Na]^+$	NA (Yoon et al., 2008)
410.67	$C_{29}H_{46}O$	55722-32-2	β-Sitosta-4,22-diene-3-one	DIC	NA	NA (Wu et al., 1994)
412.69	$C_{29}H_{48}O$	1058-61-3	β-Sitost-4-en-3-one	DIC	NA	NA (Wu et al., 1994)
412.69	$C_{29}H_{48}O$	83-48-7	Stigmasterol	DIC	NA	NA (Wu et al., 1994)
				KOC	NA	NA (Zhang et al., 2013c)

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				PHE	NA	NA (Wang et al., 2009)
				SCU	NA	NA (Takido et al., 1975)
414.49	$C_{21}H_{34}O_8$	359845-45-7	Dictamnoside L	DIC	437 $[M+Na]^+$	NA (Chang et al., 2001)
414.71	$C_{29}H_{50}O$	83-46-5	β-Sitosterol	DIC	415 $[M+H]^+$	NA (Bai et al., 2014b)
					437 $[M+Na]^+$	
					+	MS [414, 398, 382, 255, 214, 146, 107] (Du et al., 2005)
					NA	NA (Chen et al., 2000, Zhao et al., 2008, Wu et al., 1994, Xiang et al., 2008)
				KOC	NA	NA (Xu et al., 2012, Lu et al., 2012)
				PHE	NA	NA (Wang et al., 2009)
				RHE	NA	NA (Jin et al., 2006a)
				SCU	NA	NA (Takido et al., 1975)
				SOP	NA	NA (Zhang et al., 2000, Zhang et al., 2010b, Li et al., 2004)
416.38	$C_{21}H_{20}O_9$	160880-89-7	Chrysin-8-C-β-D-glucoside	SCU	415 $[M-H]^-$	MS^2 [415]: 295, 267 (Qiao et al., 2016)
						MS^2 [415]: 295,267 (Seo et al., 2013)
						MS^2 [415]: 397, 295 (Zhang et al., 2007b)
416.38	$C_{21}H_{20}O_9$	4839-60-5	Chrysophanol	RO, RP, RHE	NA	NA (Ye et al., 2007)
416.38	$C_{21}H_{20}O_9$	29013-17-0	Chrysophanol-O-glucoside	R	415 $[M-H]^-$	MS^2 [415]: 253, 225 (Yang et al., 2015a)
				RP		MS^2 [415]: 253, 225 (Liu et al., 2016)
416.38	$C_{21}H_{20}O_9$	4839-60-5	Chrysophanol 1-O-β-D-glucoside	RO	415 $[M-H]^-$	NA (Ye et al., 2007)
				RP		
				RHE		
416.38	$C_{21}H_{20}O_9$	13241-28-6	Chrysophanol 8-O-β-D- glucoside	R	415 $[M-H]^-$	MS^2 [415]: 253 (Lin et al., 2006)
				RO		NA (Ye et al., 2007)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
				RP		MS^2 [415]: 253, 225 (Liu et al., 2016)
						NA (Ye et al., 2007)
					NA	NA (Zhang et al., 2010a)
				RHE	415 $[M-H]^-$	MS^2 [415]: 253, 225, 210, 182 (Jin et al., 2007)
						NA (Ye et al., 2007)
					NA	NA (Jin et al., 2006a, Jin et al., 2006b, Gao et al., 2014a)
416.38	$C_{21}H_{20}O_9$	28368-57-2	Chrysin 6-C-glucoside	SCU	415 $[M-H]^-$	MS^2 [415]: 325, 295, 267 (Qiao et al., 2016)
					NA	NA (Miyaichi and Tomimori, 1994)
416.51	$C_{21}H_{36}O_8$	359844-05-6	Dictamnoside H	DIC	439 $[M+Na]^+$	NA (Chang et al., 2001)
418.39	$C_{21}H_{22}O_9$	8015-61-0	Aloin	R	417 $[M-H]^-$	MS^2 [417]: 255, 225 (Yang et al., 2015a)
418.39	$C_{21}H_{22}O_9$	696663-58-8	2,5-Dimethyl-8-hydroxynaphthopyrone-10-O-β-D-glucoside	RHE	NA	NA (Gao et al., 2014a)
418.61	$C_{26}H_{42}O_4$	158306-36-6	*trans*-Hexadecyl ferulic acid	SOP	446 $[M]^+$	MS [446, 194, 177] (Jung et al., 2005a)
420.41	$C_{21}H_{24}O_9$	155-58-8	Rhaponticin	RP	419 $[M-H]^-$	MS^2 [419]: 255, 227, 185, 145 (Liu et al., 2016)
				RHE	NA	NA (Li et al., 2014)
420.45	$C_{22}H_{28}O_8$	116498-58-9/ 75679-28-6	5,5'-Dimethoxylariciresinol	PHE	NA	NA (Wang et al., 2009)
				PA	NA	NA (Ida et al., 1993)
				SCU	NA	NA (Miyaichi and Tomimori, 1994, Liu et al., 2009)
420.45	$C_{22}H_{28}O_8$	1768-94-2/ 14464-90-5	(±)-Lyoniresinol	PHE	NA	NA (Wang et al., 2009)
				PA	419 $[M-H]^-$	MS^2 [419]: 411, 391, 383, 209, 153 (Hu et al., 2010)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
422.38	$C_{20}H_{22}O_{10}$	288622-12-8	6-Methoxy-2-acetyl-3-methyl-1,4-naphthoquinone-8-O-β-D-glucoside	RHE	NA	NA (Gao et al., 2014a)
422.47	$C_{25}H_{26}O_6$	883859-83-4	8-Lavandulylkaempferol	SOP	NA	NA (Jung et al., 2005b)
422.51	$C_{26}H_{30}O_5$	254886-71-0	Kosamol R	SOP	423 $[M+H]^+$	MS^2[423]: 405, 299, 303, 179 (Zhang et al., 2007a)
422.51	$C_{26}H_{30}O_5$	254886-74-3	Kushenol U	SOP	NA	NA (Kim et al., 2010b)
424.49	$C_{25}H_{28}O_6$	1106920-70-0	Demethylkuraridin	SOP	423 $[M-H]^-$	MS^2 [423]: 423, 261, 161 MS^3 [161]: 161, 133 MS^3 [261]: 261, 206, 193(50), 192(34), 191(8), 138(16), 137, 124 (Zhang et al., 2008)
					425 $[M+H]^+$	MS^2 [425]: 407, 301, 289, 283 MS^3 [289]: 289, 221, 207, 197, 183, 165 MS^3 [301]: 283, 191 MS^4 [283]: 283, 255 (Zhang et al., 2008)
424.49	$C_{25}H_{28}O_6$	99119-72-9	Kushenol E	SOP	NA	NA (Ryu et al., 1997, Wu et al., 1985a)
424.49	$C_{25}H_{28}O_6$	958788-35-7	Kushenol F	SOP	423 $[M-H]^-$	MS^2 [423]: 405, 423, 261, 161 MS^3 [161] : 161, 133 MS^3 [261]: 261, 243, 219, 207, 193, 192, 191, 137, 125, 124 (Zhang et al., 2008)
					425 $[M+H]^+$	MS^2 [425]: 301, 289, 283 MS^3 [301]: 283 MS^4 [283]: 283, 255 (Zhang et al., 2008)
					NA	NA (Wu et al., 1985a)
424.49	$C_{25}H_{28}O_6$	97938-30-2	Sophoraflavanone G/ Norkurarinone	SOP	423 $[M-H]^-$	MS^2 [423]: 423, 405, 261, 161 MS^3 [261]: 261, 219, 193, 192, 137, 125, 124 MS^3 [161]: 161, 133 (Zhang et al., 2008)
						NA (Zhang et al., 2013a)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
					425 $[M+H]^+$	MS^2 [425]: 407, 383, 315, 301, 289, 283 MS^3 [407]: 407, 283 MS^3 [289]: 289, 233, 221, 207, 197, 183, 165 MS^4 [165]: 197, 183, 165, 137 MS^5 [183]: 197, 183, 165 (Zhang et al., 2008)
						MS^2 [425]: 407, 289, 179 (Zhang et al., 2007a)
						NA (Zhang et al., 2013a)
					447 $[M+Na]^+$	NA (Zhang et al., 2007a, Zhang et al., 2013a)
					463 $[M+K]^+$	NA (Zhang et al., 2013a)
					NA	NA (Kang et al., 2000b, Kim et al., 2010b, Quang et al., 2012)
426.50	$C_{25}H_{30}O_6$	254886-73-2	Kushenol T	SOP	NA	NA (Quang et al., 2012)
426.72	$C_{30}H_{50}O$	545-47-1	Lupeol	SOP	NA	NA (Zheng et al., 2014)
428.69	$C_{29}H_{48}O_2$	36450-02-9	(6β)-6-Hydroxystigmast-4-en-3-one	DIC	NA	NA (Wu et al., 1994)
430.36	$C_{21}H_{18}O_{10}$	35775-49-6	Chrysin 7-O-β-D-glucurondie	SCU	429 $[M-H]^-$	MS^2 [429]: 253 (Qiao et al., 2016)
						MS^2 [429]: 253, 175 (Wang et al., 2013a)
						MS^2 [426]: 253, 175 (Luo et al., 2012)
						MS^2 [429]: 253 (Liu et al., 2009)
						MS^2 [447]: 253, 175 (Zhang et al., 2007b)
					431 $[M+H]^+$	MS^2 [431]: 255 MS^3 [255]: 153 (Wang et al., 2013a)
430.71	$C_{29}H_{50}O_2$	34427-61-7	7α-Hydroxysitosterol	DIC	NA	NA (Zhao et al., 1998a)
432.38	$C_{21}H_{20}O_{10}$	266997-58-4	Aloe-emodin 1-O-β-D- glucoside	RHE	NA	NA (Gao et al., 2014a)
432.38	$C_{21}H_{20}O_{10}$	50488-89-6		R	431	MS^2 [431]: 269 (Lin et al., 2006)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
			Aloe-emodin-3-CH_2-O-β-D- glucoside	RP	$[M-H]^-$	MS^2 [431]: 269, 268 (Liu et al., 2016)
					NA	NA (Zhang et al., 2010a)
				R	433 $[M+H]^+$	NA (Lin et al., 2006)
432.38	$C_{21}H_{20}O_{10}$	33037-46-6	Aloe-emodin 8-O-β-D-glucoside	R	431 $[M-H]^-$	MS^2 [431]: 269, 240 (Yang et al., 2015a)
						MS^2 [431]: 269 (Lin et al., 2006)
				RP		MS^2 [431]: 269, 240 (Liu et al., 2016)
						MS^2 [431]: 431, 395, 311, 269 (Alolga et al., 2015)
					NA	NA (Zhang et al., 2010a)
				RHE	431 $[M-H]^-$	MS^2 [431]: 269, 239, 211 (Jin et al., 2007)
					NA	NA (Jin et al., 2006b, Jin et al., 2006a, Gao et al., 2014a)
432.38	$C_{21}H_{20}O_{10}$	57396-78-8	Baicalein 7-O-β-D-glucoside	SCU	431 $[M-H]^-$	MS^2 [431]: 269 (Qiao et al., 2016)
						MS^2 [431]: 269 MS^3 [269]: 251, 195, 169, 223 (Wang et al., 2013a)
						MS^2 [431]: 269 (Liu et al., 2009)
						MS^2 [431]: 269(100) MS^3 [269]: 251, 241, 197 (Han et al., 2007)
					433 $[M+H]^+$	MS^2 [433]: 271 MS^3 [271]: 123, 169, 225, 253 (Wang et al., 2013a)
432.38	$C_{21}H_{20}O_{10}$	1884395-09-8	Dihydroxyflavanone-O-glucuronide	SCU	431 $[M-H]^-$	MS^2 [431]: 255, 175, 113 (Qiao et al., 2016)
432.38	$C_{21}H_{20}O_{10}$	29090-10-6	Emodin-O-glucoside	R	431 $[M-H]^-$	MS^2 [431]: 269, 241, 225 (Yang et al., 2015a)
				RO		MS^2 [431]: 269 MS^3 [269]: 225 (Ye et al., 2007)
				RP		MS^2 [431]: 269, 225 (Wang et al., 2011a)
						MS^2 [431]: 269 MS^3 [269]: 225 (Han et al., 2008)
432.38	$C_{21}H_{20}O_{10}$	38840-23-2	Emodin 1-O-β-D-glucoside	R	431	MS^2 [431]: 269 (Lin et al., 2006)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
				RO	$[M-H]^-$	MS^2 [431]: 269(15), 268(100) MS^3 [268]: 224(1) (Ye et al., 2007)
				RP		MS^2 [431]: 269, 240, 225 (Liu et al., 2016)
						MS^2 [431]: 311, 269, 268 MS^3 [269]: 241, 225 (Han et al., 2008)
					NA	NA (Zhang et al., 2010a)
				R	455 $[M+Na]^+$	NA (Lin et al., 2006)
432.38	$C_{21}H_{20}O_{10}$	23313-21-5	Emodin 8-O-β-D-glucoside	R	431 $[M-H]^-$	MS^2 [431]: 269, 241, 255 (Yang et al., 2015a)
				RO		MS^2 [431]: 311, 269 MS^3 [269]: 241, 225(Ye et al., 2007)
				RP		MS^2 [431]: 269, 240, 225 (Liu et al., 2016)
						NA (Wang et al., 2014f)
						MS^2 [431]: 311, 293, 269, 268 MS^3 [431 à 269]: 269, 241, 225 MS^4 [431 à 269 à 225]: 210, 182 (Zhao et al., 2013a)
					NA	NA (Zhang et al., 2010a)
					431 $[M-H]^-$	MS^2 [431]: 311, 269 MS^3 [269]:241, 225 (Han et al., 2008)
						MS^2 [431]: 311, 269 MS^3 [269]: 241, 225(Ye et al., 2007)
				RHE		MS^2 [431]: 269(100), 241, 225, 210, 182 (Jin et al., 2007)
						MS^2 [431]: 311, 269 MS^3 [269]: 241, 225(Ye et al., 2007)
432.38	$C_{21}H_{20}O_{10}$	NA	Drihydroxyflavone O-glucoside	SCU	431 $[M-H]^-$	MS^2 [431]: 269 (Qiao et al., 2016)
432.42	$C_{19}H_{28}O_{11}$	149596-95-2	Darendoside A	SCU	NA	NA (Miyaichi and Tomimori, 1995)
432.42	$C_{19}H_{28}O_{11}$	149155-70-4		PHE	431 $[M-H]^-$	MS^2 [431]: 293, 259, 137, 113 (Hu et al., 2010)
				PA		MS^2 [431]: 293, 259, 137, 113 (Hu et al., 2010)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
			2-(p-Hydroxyphenyl)-ethanol 1-O-β-D-apiofuranosyl (1→6)-β-D-glucoside [Osmanthuside H]		NA	NA (Ida et al., 1993, Li et al., 2012b)
432.51	$C_{21}H_{36}O_9$	202278-88-4	Dictamnoside A	DIC	+	MS [450, 288, 162] (Zhao et al., 1998b)
					NA	NA (Chang et al., 2001)
432.51	$C_{21}H_{36}O_9$	202278-89-5	Dictamnoside B	DIC	+	MS [450, 288, 162] (Zhao et al., 1998b)
					NA	NA (Chang et al., 2001)
432.51	$C_{21}H_{36}O_9$	202278-90-8	Dictamnoside C	DIC	+	MS [450, 288, 162] (Zhao et al., 1998b)
434.52	$C_{21}H_{38}O_9$	359844-60-3	Dictamnoside I	DIC	NA	NA (Chang et al., 2001)
434.52	$C_{21}H_{38}O_9$	359845-48-0	Dictamnoside J	DIC	457 $[M+Na]^+$	NA (Chang et al., 2001)
436.41	$C_{21}H_{24}O_{10}$	60-81-1	Phlorizin	RHE	NA	NA (Gao et al., 2014a)
438.47	$C_{25}H_{26}O_7$	99119-73-0	Kushenol C	SOP	439 $[M+H]^+$	MS^2[439]: 421, 315, 289, 165 (Zhang et al., 2007a)
					NA	NA (Wu et al., 1985a)
438.51	$C_{26}H_{30}O_6$	1106920-66-4	Isokuraridin	SOP	437 $[M-H]^-$	MS^2 [437]: 437, 405, 313, 301, 287, 261 MS^3 [287] : 287, 243, 219, 218, 217, 201, 190, 189, 175, 164, 163, 151, 150 MS^3 [313]: 313, 243, 222, 190, 163 MS^4 [190]: 222, 190, 162, 134, 122 (Zhang et al., 2008)
					439 $[M+H]^+$	MS^2 [439]: 437, 315, 289 MS^3 [289]: 289, 221, 207, 197, 183, 167, 165 MS^3 [315]: 315, 283, 197, 191, 183, 177, 165, 153, 151, 137, 125 MS^4 [191]: 191, 163 (Zhang et al., 2008)
438.51	$C_{26}H_{30}O_6$	97938-31-3	Isokurarinone/	SOP	437 $[M-H]^-$	MS^2 [437]: 405, 319, 313, 301, 287, 261, 163, 149

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
			Leachianone A			MS^3 [287]: 287, 243, 219, 218, 217, 201, 190, 189, 176, 164, 163, 151 MS^3 [313]: 313, 243, 190, 163 (Zhang et al., 2008)
					439 $[M+H]^+$	MS^2 [439]: 439, 327, 315, 289, 177 MS^3 [327]: 285, 203, 195, 177 MS^4 [177]: 177, 162, 149, 134, 121 MS^3 [289]: 321, 289, 247, 233, 221, 207, 197, 183, 165, 153 (Zhang et al., 2008)
						MS^2 [439]: 315, 289, 165 (Zhang et al., 2007a)
					NA	NA (Kang et al., 2000b, Kim et al., 2010b)
438.51	$C_{26}H_{30}O_6$	34981-25-4	Kuraridin/ Kuraridine	SOP	437 $[M-H]^-$	MS^2 [437]: 437, 419, 275, 161 MS^3 [161] : 161, 133 MS^3 [275]: 275, 260, 191, 151, 139, 137 (Zhang et al., 2008)
					439 $[M+H]^+$	MS^2 [439]: 421, 315, 303, 297 MS^3 [303]: 303, 211, 197, 179 MS^3 [315]: 297, 273, 205 (Zhang et al., 2008)
						MS^2 [439]: 424, 303, 179 (Zhang et al., 2007a)
					461 $[M+Na]^+$	NA (Zhang et al., 2007a)
					NA	NA (Woo et al., 1998, Kim et al., 2010b, Quang et al., 2012)
438.51	$C_{26}H_{30}O_6$	34981-26-5	(-)-Kurarinone	SOP	437 $[M-H]^-$	MS^2 [437]: 437, 419, 275, 161 MS^3 [275]: 275, 260, 257, 217, 206, 191, 189, 177, 151, 139, 137, 136 MS^3 [161]:161, 133, 117 (Zhang et al., 2008)
						NA (Zhang et al., 2013a)
					439 $[M+H]^+$	MS^2 [439]: 439, 397, 323, 315, 303 MS^3 [303]: 303, 211, 197, 179 MS^4 [179]: 211, 197, 179 (Zhang et al., 2008)

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						MS^2 [439]: 421, 315, 303 297, 179 (Zhang et al., 2007a)
						NA (Zhang et al., 2013a)
					461 $[M+Na]^+$	NA (Zhang et al., 2013a)
					899 $[2M+Na]^+$	NA (Zhang et al., 2013a)
					NA	NA (Kang et al., 2000b, Kim et al., 2010b, Quang et al., 2012)
438.51	$C_{26}H_{30}O_6$	49599-04-4	Kuratinone	SOP	NA	NA (Zhang et al., 2010b)
440.44	$C_{21}H_{28}O_{10}$	1009320-60-8	Dictamnusine	DIC	441 $[M+H]^+$	NA (Yoon et al., 2008)
440.49	$C_{25}H_{28}O_7$	101236-50-4	Kushenol L	SOP	439 $[M-H]^-$	MS^2 [439]: 439, 421, 411, 395, 261, 217, 177, 149 MS^3 [261]: 261, 192, 124 MS^3 [411]: 411, 261, 149 MS^4 [261] : 261, 218 217, 206, 205, 192, 149, 137, 125, 124 (Zhang et al., 2008)
					441 $[M+H]^+$	MS^2 [441]: 423, 385, 367, 289, 233 MS^3 [385]: 367, 265, 233 MS^4 [367]: 311, 265, 251, 233 MS^5 [233]: 265, 251, 233, 209, 195, 177 MS^6 [195]: 209, 195, 177 (Zhang et al., 2008)
440.49	$C_{25}H_{28}O_7$	254886-77-6	Kushenol X	SOP	NA	NA (Yang et al., 2011b)
442.37	$C_{22}H_{18}O_{10}$	101840-48-6	(+)-Catechin gallate	RP	441 $[M-H]^-$	MS^2 [441]: 331, 289, 169 (Wang et al., 2011a)
442.37	$C_{22}H_{18}O_{10}$	1257-08-5	(-)-Epicatechin 3-O-gallate	R	441 $[M-H]^-$	MS^2 [441]: 289, 271, 169, 125 (Yang et al., 2015a)
				RO	NA	NA (Komatsu et al., 2006)
				RP	441	MS^2 [441]: 441 (Liu et al., 2016)

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					$[M-H]^-$	NA (Wang et al., 2014f)
					NA	NA (Komatsu et al., 2006)
				RHE	441 $[M-H]^-$	MS^2 [441]: 289, 109 (Jin et al., 2007)
					NA	NA (Komatsu et al., 2006, Jin et al., 2006a, Jin et al., 2006b)
442.50	$C_{25}H_{30}O_7$	952491-35-9	Kosamol Q	SOP	443 $[M+H]^+$	MS^2 [443]: 425, 407, 301, 283, 307, 289, 165 (Zhang et al., 2007a)
442.50	$C_{25}H_{30}O_7$	52483-01-9	Norkurarinol	SOP	443 $[M+H]^+$	MS^2 [443]: 425, 407, 301, 283, 307, 289, 165 (Zhang et al., 2007a)
					NA	NA (Quang et al., 2012)
446.36	$C_{21}H_{18}O_{11}$	29741-09-1	Apigenin 7-O-β-D-glucuronide	SCU	447 $[M+H]^+$	MS^2 [447]: 271, 169, 129 (Seo et al., 2013)
						MS^2 [447]: 269, 175 (Zhang et al., 2007b)
446.36	$C_{21}H_{18}O_{11}$	35990-03-5	Baicalein 6-O-β-D-glucuronide	SCU	445 $[M-H]^-$	MS^2 [445]: 269 (Qiao et al., 2016)
						MS^2 [445]: 269 MS^2 [269]: 251 (Wang et al., 2013a)
						MS^2 [445]: 269 (Liu et al., 2009)
					447 $[M+H]^+$	MS^2 [447]: 447, 337, 271 (Seo et al., 2013)
						MS^2 [447]: 271 MS^3 [271]: 253, 123, 169, 225 (Wang et al., 2013a)
						MS^2 [447]: 271 (Chen et al., 2010)
						MS [447, 271] MS^2 [271]: 253, 229, 225, 197, 169, 123 (Liu et al., 2009)
446.36	$C_{21}H_{18}O_{11}$	21967-41-9	Baicalein 7-O-β-D-glucuronide [Baicalin]	SCU	445 $[M-H]^-$	MS^2 [445]: 269 (Qiao et al., 2016)
						MS^n [445]: 269, 251 (Wang et al., 2014b)
						MS^2 [445]: 445, 269, 175, 113 (Seo et al., 2013)
						MS^2 [445]: 269 MS^3 [269]: 251, 195, 169, 223 (Wang et al., 2013a)
						MS^2 [445]: 269 (Luo et al., 2012)

Appendix XIV List of compounds isolated from botanical drugs making up the hexa-herbal formula (HHCF).

DIC= root bark of *Dictamnus dasycarpus* Turcz.; KOC= fruit *of Kochia scoparia* (L.) Schrad.; P= bark of *Phellodendron chinense* C.K. Schneid. or *Phellodendron amurense* Rupr. ;PA= bark of *Phellodendron amurense* Rupr.; PHE= bark of *Phellodendron chinense* C.K. Schneid.; R= rootstock of *Rheum* species; RHE= rootstock of *Rheum tanguticum* Maxim. ex Balf.; RO= rootstock of *Rheum officinale* Baill.; RP= rootstock of *Rheum palmatum* L.; SCU= rootstock of *Scutellaria baicalensis* Georgi; SOP= rootstock of *Sophora flavescens* Aiton

Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
						MS^2 [445]: 269 (Liu et al., 2009)
						MS^2 [445]: 269, 175 MS^3 [269]: 251, 241, 225, 223, 197 MS^4 [251]: 223 (Han et al., 2007)
						MS^2 [445]: 269, 175 (Zhang et al., 2007b)
					447 $[M+H]^+$	MS^2 [891]: 445, 269 MS^3 [445]: 241, 225, 197, 183 MS^4 [269]: 239 (Wang et al., 2013a)
						MS^2 [447]: 271 (Chen et al., 2010)
446.36	$C_{21}H_{18}O_{11}$	114005-89-9	Rhein 1-O-β-D-glucoside	RP	445 $[M-H]^-$	MS^2 [445]: 325, 283, 269
				RHE		MS^3 [283]: 257, 239 (Ye et al., 2007)
446.36	$C_{21}H_{18}O_{11}$	34298-86-7	Rhein 8-O-β-D-glucoside	R	445 $[M-H]^-$	MS^2 [445]: 283, 239 (Yang et al., 2015a)
				RO		MS^2 [445]: 235, 283, 269 MS^3 [283]: 257, 239 (Ye et al., 2007)
				RP		MS^2 [445]: 283, 239 (Liu et al., 2016, Alolga et al., 2015)
					NA	NA (Zhang et al., 2010a)
				RHE	445 $[M-H]^-$	MS^2 [445]: 283, 239, 211, 183 (Jin et al., 2007)
					NA	NA (Gao et al., 2014a)
446.36	$C_{21}H_{18}O_{11}$	119152-50-0	Norwogonin 7-O-β-D-glucuronide	SCU	445 $[M-H]^-$	MS^2 [445]: 269 (Qiao et al., 2016)
						MS^2 [445]: 269, 197, 225, 171, 113 (Seo et al., 2013)
						MS^2 [445]: 269 MS^3 [269]: 197, 169 (Wang et al., 2013a)
						MS^2 [445]: 269 (Liu et al., 2009)
					447 $[M+H]^+$	MS^2 [447]: 271 MS^3 [271]: 123, 169, 225, 253 (Wang et al., 2013a)
						MS [447, 271] MS^2 [271]: 253, 229, 225, 215, 201, 197, 187, 173, 169, 123 (Liu et al., 2009)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
446.36	$C_{21}H_{18}O_{11}$	118525-47-6	Norwogonin 8-O-β-D-glucuronide	SCU	445 $[M-H]^-$	MS^2 [445]: 269 (Qiao et al., 2016)
446.40	$C_{22}H_{22}O_{10}$	6807-83-6	(-)-Macckiain-3-O-glucoside [Trifolirhizin]	SOP	481 $[M+Cl]^-$	NA (Zhang et al., 2013a)
					447 $[M+H]^+$	MS^2[533]: 285 (Zhang et al., 2007a)
					469 $[M+Na]^+$	NA (Zhang et al., 2007a, Zhang et al., 2013a)
					485 $[M+K]^+$	NA (Zhang et al., 2013a)
					NA	NA (Woo et al., 1998)
446.40	$C_{22}H_{22}O_{10}$	36948-77-3	Oroxylin A-7-O-β-D-glucoside	SCU	445 $[M-H]^-$	MS^2 [445]: 430, 283, 268, 267 (Qiao et al., 2016)
						MS^2 [445]: 431, 283, 268, 240 (Wang et al., 2013a)
						MS^2 [445]: 431, 283, 268, 240 (Seo et al., 2013)
						MS [445, 283] MS^2 [445]: 283 (Liu et al., 2009)
					447 $[M+H]^+$	MS^2 [447]: 285 MS^3 [285]: 270 (Wang et al., 2013a)
446.40	$C_{22}H_{22}O_{10}$	NA	Physcion glucoside	RP	445 $[M-H]^-$	MS^2 [445]: 283, 269 MS^3 [269]: 225 (Han et al., 2008)
446.40	$C_{22}H_{22}O_{10}$	23451-01-6	Physcion 8-β-D-glucoside	R	445 $[M-H]^-$	MS^2 [445]: 283, 268, 240 MS^3 [283]: 268, 240 (Yang et al., 2014a)
						MS^2 [445]: 283, 269, 241, 210, 182 (Dong et al., 2011a)
						NA (Lin et al., 2006)
				RP		MS^2 [445]: 283, 240 (Liu et al., 2016)
					NA	NA (Zhang et al., 2010a)
				RHE	445 $[M-H]^-$	MS^2 [445]: 283, 253, 225, 210 (Jin et al., 2007)
				RP	469	NA (Lin et al., 2006)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
					$[M+Na]^+$	
446.40	$C_{22}H_{22}O_{10}$	80366-14-9	Wogonin 5-O-β-D-glucoside	SCU	445 $[M-H]^-$	MS^2 [445]: 430, 283, 267, 239 (Qiao et al., 2016)
						NA (Chen et al., 2010)
						MS^2 [445]: 430, 283, 268 MS^3 [430]: 267 (Han et al., 2007)
					447 $[M+H]^+$	MS^2 [447]: 271 (Chen et al., 2010)
446.40	$C_{22}H_{22}O_{10}$	866621-11-6	Wogonin 7-O-β-D-glucoside	SCU	445 $[M-H]^-$	MS^2 [445]: 283 MS^3 [283]:268 (Wang et al., 2013a)
						MS [445, 283] MS^2 [445]: 283 (Liu et al., 2009)
					447 $[M+H]^+$	MS^2 [447]: 285 MS^3 [285]:270 (Wang et al., 2013a)
446.66	$C_{28}H_{46}O_4$	133882-78-7	cis-Octadecyl ferulic acid	SOP	446 $[M]^+$	MS [446, 194, 177] (Jung et al., 2005a)
447.48	$C_{23}H_{29}NO_8$	154418-17-4	N-methylhigenamine O-β-D-glucoside	PA	446 $[M-H]^-$	MS^2 [446]: 430, 403, 315, 284 MS^2 [284]: 240, 267, 193, 175 (Hu et al., 2010)
					448 $[M+H]^+$	MS^2 [448]: 286, 255 (Xian et al., 2014)
					NA	NA (Ida et al., 1993)
447.52	$C_{30}H_{25}NO_3$	685135-05-1	8-[(Dibenzylamino)methyl]-7-hydroxy-3-phenyl-4H-chromen-4-one	PHE	446 $[M-H]^-$	MS^2 [446]: 431, 357, 271, 137, 134, 62 (Yan et al., 2015)
						MS^2 [446]: 284, 240, 267, 193, 175,
					448 $[M+H]^+$	MS^2 [448]: 357, 343, 147, 131, 130 (Yan et al., 2015)
448.38	$C_{21}H_{20}O_{11}$	185145-32-8	5,7,2',6'-Tetrahydroxyflavone 2'-O-β-D-glucoside	SCU	447 $[M-H]^-$	MS^2 [447]: 285 (Qiao et al., 2016)
448.38	$C_{21}H_{20}O_{11}$	5373-11-5	5,7,3',4'-Tetrahydroxyflavone 7-O-β-D-glucoside [Cynaroside]	SCU	447 $[M-H]^-$	MS^2 [447]: 285 (Zhang et al., 2007b)
448.38	$C_{21}H_{20}O_{11}$			SCU	447	MS^2 [447]: 271, 243 (Qiao et al., 2016)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
		56226-98-3/724448-74-2	5,6,7-Trihydroxyflavanone 7-O-glucuronide [Dihydrobaicalin]		$[M-H]^-$	MS^2 [447]: 271 MS^3 [271]: 243, 227 (Wang et al., 2013a)
						MS [447, 271] MS^2 [447]: 271 (Liu et al., 2009)
						MS^2 [447]: 271 MS^3 [71]: 253, 243, 227, 199, 167, 253(Han et al., 2007)
						MS^2 [447]: 271, 175 (Zhang et al., 2007b)
					449 $[M+H]^+$	MS^2 [449]: 273 MS^3 [273]: 169, 131 (Wang et al., 2013a)
						MS^2 [449]: 273 MS^3 [273]: 255, 187, 169, 131 (Liu et al., 2009)
448.42	$C_{22}H_{24}O_{10}$	172428-48-7	5,7-Dihydroxy-6-methoxyflavanone 7-O-β-D-glucoside	SCU	448 $[M]^+$	MS [448, 286, 182, 167] (Miyaichi and Tomimori, 1995)
448.64	$C_{27}H_{44}O_5$	286938-83-8	*trans*-Hexadecyl sinapic acid	SOP	448 $[M]^+$	MS [448, 224, 207, 180, 167] (Jung et al., 2005a)
					NA	NA (Zhang et al., 2000)
450.39	$C_{21}H_{22}O_{11}$	1884390-96-8	5,7,2',6'-Tetrahydroxyflavanone 2'-O-β-D-glucoside	SCU	449 $[M-H]^-$	MS^2 [449]: 287, 227, 161, 125 (Qiao et al., 2016)
450.44	$C_{22}H_{26}O_{10}$	1184734-25-5	Torachrysone-8-O-(6'-O-acetyl)-glucoside	R	449 $[M-H]^-$	MS^2 [449]: 245, 230, 215, 187 (Yang et al., 2015a)
				RP		MS^2 [449]: 245, 230 MS^3 [245]: 230 MS^4 [230]: 215 MS^5 [215]: 187 (Han et al., 2008)
450.52	$C_{21}H_{38}O_{10}$	202278-91-9	Dictamnoside D	DIC	468 $[M+NH_4]^+$	NA (Zhao et al., 1998b)
					NA	NA (Chang et al., 2001)
450.52	$C_{21}H_{38}O_{10}$	361432-29-3	Dictamnoside K	DIC	473 $[M+Na]^+$	NA (Chang et al., 2001)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
					489 $[M+K]^+$	
452.54	$C_{27}H_{32}O_6$	270249-38-2	2'-Methoxykurarinone	SOP	451 $[M-H]^-$	MS^2[451] : 451, 419, 319, 315, 301, 149 MS^3[149]: 149, 134 MS^3[301]: 333, 319, 301, 257, 242, 233, 232, 231, 227, 217, 201, 187, 173, 163 (Zhang et al., 2008)
					453 $[M+H]^+$	MS^2[453]: 453, 329, 303, 179, 177 MS^3[303]: 303, 211, 197, 179 MS^3[329]: 289, 211, 197, 179 (Zhang et al., 2008)
						MS^2[453]: 438, 410, 329, 303, 179 (Zhang et al., 2007a)
					475 $[M+Na]^+$	NA (Zhang et al., 2007a)
					NA	NA (Kang et al., 2000b, Quang et al., 2012)
452.41	$C_{21}H_{24}O_{11}$	1300727-08-5	Catechin glucoside	R	451 $[M-H]^-$	MS^2 [451]: 289, 245 (Yang et al., 2015a)
				RP		NA (Wang et al., 2014f)
						MS^2 [451]: 289, 205, 137 (Wang et al., 2011a)
452.54	$C_{27}H_{32}O_6$	99217-65-9	Kushenol D	SOP	451 $[M-H]^-$	MS^2[451]: 451, 419, 333, 315, 301 MS^3[301]: 301, 257, 242, 233, 231, 227, 217, 201, 187, 173, 163 (Zhang et al., 2008)
					453 $[M+H]^+$	MS^2[453]: 453, 329, 303, 179 MS^3[329]: 329, 287, 211, 197, 179, 151 MS^4[179]: 211, 197, 179, 151 (Zhang et al., 2008)
						MS^2[453]: 329, 303, 179 (Zhang et al., 2007a)
454.51	$C_{26}H_{30}O_7$	99119-69-4	Kushenol I	SOP	453 $[M-H]^-$	MS^2[453]: 453, 452, 435, 425, 421, 303, 275, 177, 149 MS^3[177]: 177, 149, 133, 123, 121 (Zhang et al., 2008)
					455 $[M+H]^+$	MS^2[455]: 437, 409, 331, 313, 303, 277, 179 MS^3[437]: 437, 409, 313, 303 MS^3[303]: 303, 211, 197, 179 (Zhang et al., 2008)
					477	NA (Zhang et al., 2007a)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
					$[M+Na]^+$	
					NA	NA (Wu et al., 1985a)
454.51	$C_{26}H_{30}O_7$	102490-65-3	Kushenol N	SOP	455 $[M+H]^+$	MS^2[445]: 437, 409, 331, 303, 288 , 179 (Zhang et al., 2007a)
					477 $[M+Na]^+$	NA (Zhang et al., 2007a)
454.51	$C_{26}H_{30}O_7$	751-03-1	Obacunone	DIC	455 $[M+H]^+$	MS^2 [455]: 437, 409, 161, 95 (Lv et al., 2015)
						NA (Bai et al., 2014b)
					477 $[M+Na]^+$	NA (Bai et al., 2014b)
					+	MS [454, 438, 331, 228] (Du et al., 2005)
				PHE	453 $[M-H]^-$	MS^2 [453]: 291, 171 (Yan et al., 2015)
					+	MS^2 [437, 409, 366] (Alolga et al., 2015)
					455 $[M+H]^+$	MS^2[455]: 439, 419, 395, 359, 333, 249, 163 (Yan et al., 2015)
					NA	NA (Qin and Wang, 2003)
				PA	455 $[M+H]^+$	MS^2[455]: 427, 410 (Xian et al., 2014)
						MS^2[455]: 455, 437, 411, 409, 359 (Wang et al., 2013c)
					469 $[M+CH_3-H]^-$	MS^2[469]: 515, 469, 411, 261, 233, 177, 175 (Hu et al., 2010)
456.48	$C_{25}H_{28}O_8$	1801987-68-7	4-(4'-Hydroxyphenyl)-2-butanone-4'-O-β-D-(6"-O-cinnamoyl)-glucoside	RP	455 $[M-H]^-$	MS^2 [455]: 163, 103 (Liu et al., 2016)
				RHE	NA	NA (Gao et al., 2012a)
456.48	$C_{25}H_{28}O_8$	99119-71-8	Kushenol G	SOP	NA	NA (Wu et al., 1985a)
456.53	$C_{26}H_{32}O_7$	13187-24-1	Dihydroobacunone	DIC	NA	NA (Chen et al., 2000)
456.53	$C_{26}H_{32}O_7$	52482-98-1	Kuraridinol	SOP	455 $[M-H]^-$	MS^2 [455]: 437, 293, 161 MS^3[293]: 293, 23

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
						MS^3[161]: 161, 133, 117 (Zhang et al., 2008)
					457 $[M+H]^+$	MS^2[457]: 439, 321, 315, 303, 297 MS^3[315]: 297, 273, 205 MS^3[321]: 321, 303, 211, 197, 179 MS^4[303]: 303, 211, 197, 179 (Zhang et al., 2008)
						MS^2[457]: 439, 315, 321, 303, 293, 179 (Zhang et al., 2007a)
					479 $[M+Na]^+$	NA (Zhang et al., 2007a)
456.53	$C_{26}H_{32}O_7$	855746-98-4	Kurarinol	SOP	455 $[M-H]^-$	MS^2[455]: 455, 454, 437, 293, 161 MS^3[293]: 293, 235 MS^3[161]: 161, 133, 123, 117 MS^4[235]: 235, 220, 193, 191, 177, 152, 151, 139, 137, 124 (Zhang et al., 2008)
					457 $[M+H]^+$	MS^2[457]: 439, 421, 321, 315, 303 MS^3[439]: 439, 438, 421, 397, 315, 303, 217 MS^3[321]: 303, 179 (Zhang et al., 2008)
					NA	NA (Woo et al., 1998)
456.53	$C_{26}H_{32}O_7$	254886-69-6	Kushenol P	SOP	NA	NA (Yang et al., 2011b)
456.70	$C_{30}H_{48}O_3$	508-02-1	Oleanolic acid	KOC	NA	NA (Wang et al., 2003, Lu et al., 2012, Zhang et al., 2013c)
458.46	$C_{21}H_{30}O_{11}$	690954-76-8	Dasycarpuside A	DIC	+	MS [978, 962, 956, 940, 497, 481] (Chang et al., 2002)
458.50	$C_{25}H_{30}O_8$	1357090-87-9	Kushenol Y	SOP	481 $[M+Na]^+$	NA (Yang et al., 2011b)
460.39	$C_{22}H_{20}O_{11}$	82475-03-4	Baicalin-methyl ester	SCU	459 $[M-H]^-$	MS^2 [459]: 269 (Qiao et al., 2016)
					NA	NA (Ishimaru et al., 1995)
460.39	$C_{22}H_{20}O_{11}$	NA	2-Carboxyl-chrysophanol-O-glucose	RP	459 $[M-H]^-$	MS^2 [459]: 415, 253 MS^3 [253]: 225 (Han et al., 2008)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
						MS^2 [459]: 415, 253 (Wang et al., 2011a)
460.39	$C_{22}H_{20}O_{11}$	1562421-28-6	1-methyl-8-hydroxyl-9,10-anthraquinone-3-O-β-D-glucoside	RO	NA	NA (Xia et al., 2012)
460.39	$C_{22}H_{20}O_{11}$	36948-76-2	Oroxylin A 7-O-β-D-glucuronide	SCU	459 $[M-H]^-$	MS^2 [459]: 283, 268 (Qiao et al., 2016)
						MS^n [459]: 283, 268 (Wang et al., 2014b)
						MS^2 [459]: 283 MS^3 [483]: 268 (Wang et al., 2013a)
						NA (Chen et al., 2010)
						MS [459, 283] MS^2 [459]: 283 (Liu et al., 2009)
						MS^2 [459]: 283, 268, 175 (Zhang et al., 2007b)
					919 $[2M-H]^-$	MS^2 [919]: 459, 283, 268 MS^3 [459]: 283, 175 MS^4 [283]: 268 (Han et al., 2007)
					461 $[M+H]^+$	MS^2 [461]: 285 MS^3 [285]: 270 (Wang et al., 2013a)
						MS^2 [461]: 285, 270 (Chen et al., 2010, Seo et al., 2013)
460.39	$C_{22}H_{20}O_{11}$	51059-44-0	Wogonin 7-O-β-D-glucuronide [Wogonoside]	SCU	459 $[M-H]^-$	MS^2 [459]: 283, 268 (Qiao et al., 2016, Alolga et al., 2015)
						MS^2 [459]: 283 MS^2 [283]: 268 (Wang et al., 2013a)
						MS^2 [459]: 283, 268, 175 (Luo et al., 2012)
						NA (Chen et al., 2010)
						MS [459, 283] MS^2 [459]: 283 (Liu et al., 2009)
					461 $[M+H]^+$	MS^n [461]: 283, 268 (Wang et al., 2014b)
						MS^2 [461]: 285, 270 (Chen et al., 2010, Seo et al., 2013)
						MS^2 [461]: 285, 270 MS^2 [285]: 270 (Wang et al., 2013a)
						MS^2 [459]: 283, 268, 175 (Zhang et al., 2007b)

Appendix XIV List of compounds isolated from botanical drugs making up the hexa-herbal formula (HHCF).

DIC= root bark of *Dictamnus dasycarpus* Turcz.; KOC= fruit *of Kochia scoparia* (L.) Schrad.; P= bark of *Phellodendron chinense* C.K. Schneid. or *Phellodendron amurense* Rupr. ;PA= bark of *Phellodendron amurense* Rupr.; PHE= bark of *Phellodendron chinense* C.K. Schneid.; R= rootstock of *Rheum* species; RHE= rootstock of *Rheum tanguticum* Maxim. ex Balf.; RO= rootstock of *Rheum officinale* Baill.; RP= rootstock of *Rheum palmatum* L.; SCU= rootstock of *Scutellaria baicalensis* Georgi; SOP= rootstock of *Sophora flavescens* Aiton

Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
					919 $[2M-H]^-$	MS^2 [919]: 459 MS^3 [459]: 283 MS^4 [283]: 268 (Han et al., 2007)
462.36	$C_{21}H_{18}O_{12}$	27740-01-8	Scutellarein 7-O-β-D-glucuronide [Scutellarin]	SCU	461 $[M-H]^-$	MS^2 [461]: 285 (Qiao et al., 2016, Alolga et al., 2015)
						MS [461, 285] MS^2 [461]: 285 (Liu et al., 2009)
462.40	$C_{22}H_{22}O_{11}$	NA	Cinnamoyl-glucogallin	R	461 $[M-H]^-$	MS^2 [461]: 313, 169, 161, 151, 147 (Yang et al., 2015a)
462.40	$C_{22}H_{22}O_{11}$	791836-69-6	1-O-Galloyl-2-O-cinnamoylglucose	R	461 $[M-H]^-$	MS^2 [461]: 313, 169 (Dong et al., 2011a)
				RO	NA	NA (Komatsu et al., 2006)
				RP	461 $[M-H]^-$	MS^2 [461]: 401, 313, 271, 169 MS^3 [271]: 211, 169 MS^4 [211]: 168, 124 (Han et al., 2008)
					NA	NA (Komatsu et al., 2006)
				RHE	461 $[M-H]^-$	MS^2 [461]: 291, 169, 125 (Jin et al., 2007)
					NA	NA (Komatsu et al., 2006)
462.40	$C_{22}H_{22}O_{11}$	1370002-08-6	5,7-Dihydroxy-6-methoxyflavanone 7-O-β-D-glucuronide	SCU	461 $[M-H]^-$	MS^2 [461]: 285, 270 (Qiao et al., 2016)
462.40	$C_{22}H_{22}O_{11}$	1169879-98-4	5,7-Dihydroxy-2'-methoxy flavanone-7-O-β-D-glucuronide	SCU	461 $[M-H]^-$	MS [461, 285] MS^2 [461]: 285 (Liu et al., 2009)
					463 $[M+H]^+$	MS [463, 287 MS^2 [287]: 153 (Liu et al., 2009)
462.40	$C_{22}H_{22}O_{11}$	NA	Trihydroxy-methoxyflavone O-glucoside	SCU	461 $[M-H]^-$	MS^2 [461]: 299, 284, 166/ MS^2 [461]: 299, 283, 173 (Qiao et al., 2016)
462.40	$C_{22}H_{22}O_{11}$	226879-03-4	5,7,2'-Trihydroxy-6-methoxyflavone 7-O-β-D-glucoside	SCU	461 $[M-H]^-$	MS^2 [461]: 299, 284, 166 (Qiao et al., 2016)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
462.45	$C_{20}H_{30}O_{12}$	478977-47-8	2-Methoxy-4-hydroxymethylphenol 1-O-α-rhamnosyl-(1" à 6')- β-glucoside	DIC	485 $[M+Na]^+$	NA (Chang et al., 2002)
464.37	$C_{18}H_{24}O_{14}$	NA	Galloyl-primeverose	RP	463 $[M-H]^-$	MS^2 [463]: 313, 271, 169 MS^3 [313]: 169, 151, 125 MS^4 [169]: 151, 125 (Han et al., 2008)
464.37	$C_{18}H_{24}O_{14}$	NA	Gallic acid-3-O-glucose-4-O-xylose	RP	463 $[M-H]^-$	MS^2 [463]: 445, 403, 313, 253, 211, 193, 169, 151 MS^3 [169]: 125 (Han et al., 2008)
464.38	$C_{21}H_{20}O_{12}$	482-36-0	Hyperoside	KOC	NA	NA (Xu et al., 2012)
464.38	$C_{21}H_{20}O_{12}$	172428-47-6	3,5,7,2',6'-Pentahydroxyflavone 2'-O- β-D-glucopyranoside [Viscidulin I-2-O-β-D-glucoside]	SCU	465 $[M+H]^+$	MS [302, 285] (Miyaichi and Tomimori, 1995)
					486 $[M+Na]^+$	NA (Miyaichi and Tomimori, 1995)
464.38	$C_{21}H_{20}O_{12}$	482-35-9	Quercetin 3-β-D-glucoside	DIC	NA	NA (Komissarenko et al., 1983)
464.38	$C_{21}H_{20}O_{12}$	NA	Tetrahyroxyflavanone O-glucuronide	SCU	463 $[M-H]^-$	MS^2 [463]: 287, 153 (Qiao et al., 2016)
464.38	$C_{21}H_{20}O_{12}$	119600-60-1	5,7,8,4'-Tetrahydroxyflavanone 7-O-glucuronide [Carthamidin 7-O-glucuronide]	SCU	463 $[M-H]^-$	MS^2 [463]: 287, 153 (Qiao et al., 2016)
464.38	$C_{21}H_{20}O_{12}$	119600-61-2	5,6,7,4'-Tetrahydroxyflavanone 7-O-glucuronide [Isocarthamidin 7-O-glucuronide]	SCU	463 $[M-H]^-$	MS^2 [463]: 287, 269, 243, 175, 167, 153, 131, 113 (Seo et al., 2013)
470.51	$C_{26}H_{30}O_8$	1180-71-8	Obaculatcone	DIC	471 $[M+H]^+$	MS^2 [471]: 453, 425, 161, 95 (Lv et al., 2015)
						NA (Bai et al., 2014b)
					NA	NA (Zhao et al., 1998a, Wu et al., 1994, Xiang et al., 2008, Yoon et al., 2008, Zhao et al., 2008, Jiang et al., 2006a, Bai et al., 2014a)
				PHE	469 $[M-H]^-$	MS^2[469]: 427, 411, 330, 283, 197, 62 (Yan et al., 2015)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
					+	MS^2 [453, 425, 367] (Alolga et al., 2015)
					471 $[M+H]^+$	MS^2[471]: 435, 425, 347, 205 (Yan et al., 2015)
						MS^2[471]: 453, 425, 409, 367 (Li et al., 2010)
				PA	471 $[M+H]^+$	MS^2[471]: 471, 453, 425, 367, 312 (Wang et al., 2013c)
						MS^2[471]: 425, 409 (Xian et al., 2014)
470.55	$C_{27}H_{34}O_7$	52483-00-8	Neokurarinol	SOP	NA	NA (Yang et al., 2011b)
472.48	$C_{25}H_{28}O_9$	950184-00-6/1609583-04-1	4-(4'-Hydroxyphenyl)-2-butanone-4'-O-β-D-(6''-O-p-coumaroyl)-glucoside	RP	471 $[M-H]^-$	MS^2 [471]: 307, 163, 119 (Liu et al., 2016)
				RHE		NA (Jin et al., 2007)
					NA	NA (Gao et al., 2014a)
472.49	$C_{22}H_{28}N_6O_6$	904523-83-7	Benzoic acid, 3,5-dimethoxy-,2-[4-(2,3,6,7-tetrahydro-1,3-dimethyl-2,6-dioxo-1H-purin-8-yl)-1-piperazinyl]ethyl ester	PHE	471 $[M-H]^-$	MS^2 [471]: 375, 323, 307, 265 (Yan et al., 2015)
472.53	$C_{26}H_{32}O_8$	99119-70-7	Kushenol H	SOP	471 $[M-H]^-$	MS^2[471]: 471, 453, 439, 293, 177, 149 MS^3[177] : 177, 149 MS^3[293]: 293, 235 (Zhang et al., 2008)
					473 $[M+H]^+$	MS^2[473]: 472, 455, 437, 409, 337, 331, 321, 313, 303, 179 MS^3[303]: 303, 211, 197, 179(, 167 MS^3[321]: 303, 197, 179 MS^3[331]: 330, 313, 299, 179 MS^3[455]: 454, 437, 436, 423, 409, 331, 329, 313, 303, 277, 179, 153 MS^4[437]: 437, 419, 409, 381, 369, 367, 315, 313, 303, 285, 179 MS^4[331]: 330, 313, 302, 301, 299, 298, 274, 270, 242, 211, 179 MS^5[313]: 313, 285, 283, 281, 259, 253, 227, 211, 179 (Zhang et al., 2008)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
					NA	NA (Wu et al., 1985a, Woo et al., 1998)
472.53	$C_{26}H_{32}O_8$	101236-49-1	Kushenol K	SOP	495 $[M+Na]^+$	NA (Yang et al., 2011b)
					NA	NA (Woo et al., 1998)
472.53	$C_{26}H_{32}O_8$	751-29-1	Obacunoic acid	PA	487 $[M+CH_3-H]^-$	MS^2 [487]: 470, 459, 417, 329, 287, 233 MS^2 [233]: 175, 164 (Hu et al., 2010)
474.41	$C_{23}H_{22}O_{11}$	928262-56-0	Aloe-emodin 8-O-(6'-O-acetyl)-glucoside	R	473 $[M-H]^-$	MS^2 [473]: 269, 268, 240, 224 (Yang et al., 2015a)
				RP		MS^2 [473]: 311, 269 (Ye et al., 2007)
474.41	$C_{23}H_{22}O_{11}$	440087-84-3	Emodin-8-O-(6'-O-acetyl)-glucoside	R	473 $[M-H]^-$	MS^2 [473]: 311, 269, 241 (Yang et al., 2015a)
				RP		MS^2 [473]: 269, 225 (Liu et al., 2016)
						MS^2 [473]: 311, 269 MS^3 [269]: 241, 225(Han et al., 2008)
474.41	$C_{23}H_{22}O_{11}$	82475-02-3	Oroxylin A 7-O-β-D-methylglucuronide	SCU	474 $[M]^+$	MS [474, 284, 269, 102] (Tomimori et al., 1982)
474.46	$C_{21}H_{30}O_{12}$	159681-01-3	2-Methoxy-4-acetylphenol 1-O-α-rhamnosyl-(1" à 6')-β-glycoside	DIC	497 $[M+Na]^+$	NA (Chang et al., 2002)
476.39	$C_{22}H_{20}O_{12}$	NA	Laccaic acid D-O-glucoside	RP	475 $[M-H]^-$	MS^2 [475]: 431, 269 MS^3 [431]: 269, 268, 213 MS^4 [268]: 240, 225 (Han et al., 2008)
476.39	$C_{22}H_{20}O_{12}$	NA	Trihydroxy-methoxyflavone O-glucuronide	SCU	475 $[M-H]^-$	MS^2 [475]: 299, 284 (Qiao et al., 2016)
476.39	$C_{22}H_{20}O_{12}$	164022-76-8	5,7,8-Trihydroxy-6-methoxyflavone 7-O-glucuronide	SCU	475 $[M-H]^-$	MS^2 [475]: 299 MS^3 [299]: 284 (Wang et al., 2013a)
						MS [475, 299] MS^2 [475]: 299 MS^3 [299]: 284 (Liu et al., 2009)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
					477 $[M+H]^+$	MS^2 [477]: 301 MS^3 [301]: 286 (Wang et al., 2013a)
476.39	$C_{22}H_{20}O_{12}$	1169879-99-5	5,6,7-Trihydroxy-8-methoxyflavone 7-O-glucuronide	SCU	475 $[M-H]^-$	MS^2 [475]: 299 MS^3 [299]: 284 (Wang et al., 2013a)
						MS [475, 299] MS^2 [475]: 299 MS^3 [299]: 284 (Liu et al., 2009)
					477 $[M+H]^+$	MS^2 [477]: 301 MS^3 [301]: 286 (Wang et al., 2013a)
476.39	$C_{22}H_{20}O_{12}$	160880-88-6	5,7,2'-Trihydroxy-6-methoxyflavone 7-O-β-D-glucuronide	SCU	475 $[M-H]^-$	MS^2 [475]: 299, 284 (Qiao et al., 2016)
						MS [475, 299] MS^2 [475]: 299 MS^3 [299]: 284 (Liu et al., 2009)
476.39	$C_{22}H_{20}O_{12}$	938447-93-9	5,7,2'-Trihydroxy-6'-methoxyflavone 7-O-β-D-glucuronide	SCU	951 $[2M-H]^-$	MS^2 [951]: 574, 497, 475, 299 (Luo et al., 2012)
						MS^2 [951]: 475, 299 MS^3 [475]: 299 MS^4 [299]: 284 (Han et al., 2007)
476.47	$C_{21}H_{32}O_{12}$	94410-28-3	Darendoside B	SCU	NA	NA (Miyaichi and Tomimori, 1995)
476.47	$C_{21}H_{32}O_{12}$	478977-48-9	2-Methoxy-4-(8-hydroxyethyl)-phenol 1-O-α-rhamnosyl-(1'' à 6')-β-glycoside	DIC	499 $[M+Na]^+$	NA (Chang et al., 2002)
478.40	$C_{22}H_{22}O_{12}$	NA	Coumaroyl-O-galloyl-glucose	RP	477 $[M-H]^-$	MS^2 [477]: 331, 313, 169, 163, 147 (Wang et al., 2011a)
478.40	$C_{22}H_{22}O_{12}$	6743-92-6	Isorhamnetin 3-O-β-D-galactoside	KOC	NA	NA (Xu et al., 2012)
478.40	$C_{22}H_{22}O_{12}$	5041-82-7	Isorhamnetin 3-O-β-D-glucoside	KOC	NA	NA (Lu et al., 2012)
478.40	$C_{22}H_{22}O_{12}$	NA	Trihydroxy-methoxyflavanone O-glucuronide	SCU	477 $[M-H]^-$	MS^2 [477]: 301, 286, 181, 167 / MS^2 [477]: 301, 273, 175, 167 (Qiao et al., 2016)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
478.40	$C_{22}H_{22}O_{12}$	NA	5,7,2'-Trihydroxy-6-methoxyflavanone 7-O-β-D-glucuronide	SCU	477 $[M-H]^-$	MS^2 [477]: 301, 286, 181, 167 (Qiao et al., 2016)
478.44	$C_{20}H_{30}O_{13}$	731016-26-5	2-[3,4-Dihydroxyphenyl]ethyl-3-O-β-D-glucosyl-β-D-glucoside	PHE	477 $[M-H]^-$	MS^2 [477]: 447, 415, 357, 311, 294, 205, 191, 137, 125, 85 (Yan et al., 2015)
478.44	$C_{20}H_{30}O_{13}$	87562-76-3	Kelampayoside A	PA	NA	NA (Li et al., 2012b)
478.45	$C_{23}H_{26}O_{11}$	59282-56-3	Lindleyin	R	477 $[M-H]^-$	MS^2 [477]: 313, 211, 169, 147 (Yang et al., 2015a)
						MS^2 [477]: 313, 169 MS^3 [313]: 169, 125 (Yang et al., 2014a)
				RO	NA	NA (Komatsu et al., 2006)
				RP	NA	NA (Komatsu et al., 2006)
				RHE	477 $[M-H]^-$	MS^2 [477]: 313, 169, 125 (Jin et al., 2007)
					NA	NA (Komatsu et al., 2006, Jin et al., 2006a, Jin et al., 2006b)
478.45	$C_{23}H_{26}O_{11}$	87075-18-1	Isolindleyin	R	477 $[M-H]^-$	MS^2 [477]: 313, 211, 169, 125 (Yang et al., 2015a)
				RO	NA	NA (Komatsu et al., 2006)
				RP	477 $[M-H]^-$	MS^2 [477]: 313 (Liu et al., 2016)
					NA	NA (Komatsu et al., 2006)
				RHE	477 $[M-H]^-$	MS^2 [477]: 313, 169, 125 (Jin et al., 2007)
					NA	NA (Komatsu et al., 2006, Jin et al., 2006a, Jin et al., 2006b)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
480.46	$C_{23}H_{28}O_{11}$	339079-19-5	(S)-4-(4'-hydroxyphenyl)-2-butanol 2-O-(6-O-galloyl)-β-D-glucoside	RP	479 M-H]$^-$	MS^2 [479]: 163, 315, 169, 125 (Liu et al., 2016)
484.36	$C_{20}H_{20}O_{14}$	950184-01-7	Gallic acid 3-O-β -D-(6'-O-galloyl)glucoside	RHE	483 [M-H]$^-$	MS^2 [483]: 331, 169, 125 (Jin et al., 2007)
484.36	$C_{20}H_{20}O_{14}$	87087-62-5	Gallic acid 4-O-β -D-(6'-O-galloyl)glucoside	RHE	483 [M-H]$^-$	MS^2 [483]: 331, 169, 125 (Jin et al., 2007)
484.36	$C_{20}H_{20}O_{14}$	23363-08-8	1,6-Di-O-galloyl-β-D-glucose	RO	NA	NA (Komatsu et al., 2006)
				RP		
				RHE		
484.36	$C_{20}H_{20}O_{14}$	71610-85-0	Di-galloyl-glucose	R	483 [M-H]$^-$	MS^2 [483]: 315, 299, 169, 125 (Yang et al., 2015a)
				RP		MS^2 [483]: 331, 169 (Wang et al., 2011a)
						MS^2 [483]: 439 331, 313, 271, 211, 169 MS^3 [169]: 125 (Han et al., 2008)
486.46	$C_{19}H_{34}O_{14}$	131401-06-4	Methyl-3,6-dideoxy-α-D-xylo-hexosyl-(1→3)-[α-D-galactosyl-(1→2)]-α-D-mannoside	PHE	485 [M-H]$^-$	MS^2 [485]: 453, 441, 397, 295, 265, 211 (Yan et al., 2015)
484.50	$C_{26}H_{28}O_9$	22318-10-1	Limonin diosphenol	DIC	NA	NA (Zhao et al., 1998a, Zhao et al., 2008, Xiang et al., 2008, Du et al., 2005)
486.51	$C_{26}H_{30}O_9$	74563-65-2	3,11-Bis(4-hydroxy-3-methoxyphenyl)-2,4,10,12-tetradispiro-hexadecan-7-one	PHE	485 [M-H]$^-$	MS^2 [485]: 407, 313, 211, 209, 167, 61 (Yan et al., 2015)
486.51	$C_{26}H_{30}O_9$	125276-62-2	Kihadanin A	DIC	NA	NA (Wang et al., 2014c)
486.51	$C_{26}H_{30}O_9$	73793-68-7	Kihadanin B	DIC	+	MS [487, 469, 443, 429, 165, 136, 107, 104, 91, 77, 55, 43] (Du et al., 2005)
					NA	NA (Wang et al., 2014c, Xiang et al., 2008)
486.51	$C_{26}H_{30}O_9$	33237-37-5		DIC	487	MS^2 [487]: 469, 441, 383, 161, 95 (Lv et al., 2015)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
			Rutaevin		$[M+H]^+$	
					NA	NA (Bai et al., 2014b, Du et al., 2005)
					+	MS [486, 469, 429, 143, 364, 363, 361, 348, 347, 345, 305, 135, 133, 119, 115, 109, 105, 95] (Wang et al., 1992)
				PA	485 $[M-H]^-$	MS^2 [485]: 485, 467, 423, 411 (Wang et al., 2013c)
						MS^2 [485]: 467, 457, 417, 398, 311, 233, 175 (Hu et al., 2010)
486.55	$C_{27}H_{34}O_8$	751-48-4	Methyl obacunoate	PA	487 $[M+H]^+$	MS^2 [487]: 233, 175, 164/ MS^2 [487]: 321, 268, 242, 101 (Hu et al., 2010)
488.40	$C_{23}H_{20}O_{12}$	440087-85-4	Rhein-1-O-(O-acetyl)-glucoside	R	487 $[M-H]^-$	MS^2 [487]: 283, 267, 239 (Yang et al., 2015a)
				RP		MS^2 [487]: 443, 325, 283, 269, 239 MS^3 [239]: 211 (Han et al., 2008)
						MS^2 [487]: 427, 283, 269, 267, 239 MS^3 [283]: 257, 239 (Ye et al., 2007)
				RP, RHE		MS^2 [487]: 325, 283, 269, 239 MS^3 [283]: 257, 239 (Ye et al., 2007)
488.44	$C_{24}H_{24}O_{11}$	60679-70-1	Trifolirhizin 6'-monoacetate	SOP	487 $[M-H]^-$	NA (Zhang et al., 2013a)
					523 $[M+Cl]^-$	
					511 $[M+Na]^+$	
					NA	NA (Li et al., 2004)
490.41	$C_{23}H_{22}O_{12}$	164022-74-6	5,7-Dihydroxy-6,8-dimethoxyflavone 7-O-β-D-glucuronide	SCU	489 $[M-H]^-$	MS [489, 313] MS^2 [489]: 313 (Liu et al., 2009)
						MS^2 [489]: 313 (Wang et al., 2013a)
					491 $[M+H]^+$	MS^2 [491]: 315 (Wang et al., 2013a) MS^2 [315]: 300, 285, 267 (Liu et al., 2009)

Appendix XIV List of compounds isolated from botanical drugs making up the hexa-herbal formula (HHCF).

DIC= root bark of *Dictamnus dasycarpus* Turcz.; KOC= fruit *of Kochia scoparia* (L.) Schrad.; P= bark of *Phellodendron chinense* C.K. Schneid. or *Phellodendron amurense* Rupr. ;PA= bark of *Phellodendron amurense* Rupr.; PHE= bark of *Phellodendron chinense* C.K. Schneid.; R= rootstock of *Rheum* species; RHE= rootstock of *Rheum tanguticum* Maxim. ex Balf.; RO= rootstock of *Rheum officinale* Baill.; RP= rootstock of *Rheum palmatum* L.; SCU= rootstock of *Scutellaria baicalensis* Georgi; SOP= rootstock of *Sophora flavescens* Aiton

Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
490.41	$C_{23}H_{22}O_{12}$	112408-70-5	5,7-Dihydroxy-8,2'-dimethoxyflavone 7-O-β-D-glucuronide	SCU	489 $[M-H]^-$	MS^2 [489]: 313, 298, 283 (Qiao et al., 2016)
492.43	$C_{23}H_{24}O_{12}$	168293-27-4	5,2',6'-Trihydroxy-6,7-dimethoxyflavone 2'-O-β-D-glucoside	SCU	491 $[M-H]^-$	MS^2 [491]: 329, 314, 299 (Qiao et al., 2016)
					NA	NA (Ishimaru et al., 1995)
492.43	$C_{23}H_{24}O_{12}$	172428-46-5	5,2',6'-Trihydroxy-7,8-dimethoxyflavone 2'-O-β-D-glucoside [Viscidulin II 2'-O-β-D-glucoside]	SCU	491 $[M-H]^-$	MS^2 [491]: 329, 314, 299 (Qiao et al., 2016)
					492 $[M]^+$	MS [492, 330, 315] (Miyaichi and Tomimori, 1995)
492.43	$C_{23}H_{24}O_{12}$	1146124-54-0	7,3',4'-Trihydroxy-5,6-dimethoxyflavone 7-O-β-D-glucoside	SCU	491 $[M-H]^-$	MS^2 [491]: 329 MS^3 [329]: 314, 299, 261 MS^4 [314]: 299 MS^5 [299]: 271, 165 (Han et al., 2007)
492.43	$C_{23}H_{24}O_{12}$	1884395-11-2	Dihydroxy-dimethoxyflavanone O-glucuronide	SCU	491 $[M-H]^-$	MS^2 [491]: 315, 300, 166, 113 (Qiao et al., 2016)
492.60	$C_{30}H_{36}O_6$	99217-64-8	Kushenol B	SOP	NA	NA (Ryu et al., 1997)
494.40	$C_{19}H_{26}O_{15}$	NA	Glucopyranosyl-galloyl-glucose	R	493 $[M-H]^-$	MS^2 [493]: 331, 313, 169 (Wang et al., 2011a)
				RP		MS^2 [493]: 313, 283, 169, 125 (Yang et al., 2015a)
498.56	$C_{28}H_{34}O_8$	85643-95-4	7α-Obacunyl acetate	DIC	NA	NA (Zhao et al., 1998a, Bai et al., 2014a)
502.51	$C_{26}H_{30}O_{10}$	99026-99-0	Shihulimonin A	PHE	NA	NA (Lian et al., 2013)
504.44	$C_{24}H_{24}O_{12}$	NA	Cinnamoyl-O-galloyl-(acetyl)-glucose	RP	503 $[M-H]^-$	MS^2 [503]: 355, 169 MS^3 [355]: 311, 295, 179, 169, 151, 125 MS^4 [169]: 125 (Han et al., 2008)
504.44	$C_{18}H_{32}O_{16}$	597-12-6	(+)-Melezitose	R	503 $[M-H]^-$	MS^2 [503]: 179, 161, 131, 113 (Yang et al., 2015a)
504.53	$C_{26}H_{32}O_{10}$	475482-29-2	Dodecahydrodibenzo-octaoxacyclotetracosine-2,17-dicarbaldehyde	PHE	503 $[M-H]^-$	MS^2 [503]: 387, 367, 327, 305, 281, 97 (Yan et al., 2015)
506.41	$C_{23}H_{22}O_{13}$	NA	Dihydroxy-dimethoxyflavone-2'-O-glucuronide	SCU	505 $[M-H]^-$	MS^2 [505]: 329, 314, 299, 183 (Qiao et al., 2016)

Appendix XIV List of compounds isolated from botanical drugs making up the hexa-herbal formula (HHCF).

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
506.41	$C_{23}H_{22}O_{13}$	NA	Viscidulin II 2'-O-β-D-glucuronide	SCU	505 $[M-H]^-$	MS^2 [505]: 329, 314, 299, 183 (Qiao et al., 2016)
506.54	$C_{26}H_{34}O_{10}$	22153-41-9	Limonoic acid	DIC	NA	NA (Yang et al., 2011a)
508.43	$C_{23}H_{24}O_{13}$	155014-34-9	Viscidulin III 2'-O-β-D-glucoside	SCU	507 $[M-H]^-$	MS^2 [507]: 345, 330, 315, 181 (Qiao et al., 2016)
						MS^2 [507]: 345, 330, 315 (Zhang et al., 2007b)
508.60	$C_{30}H_{36}O_7$	101236-51-5	Kushenol M	SOP	NA	NA (Ryu et al., 1997, Ryu et al., 1995)
518.42	$C_{24}H_{22}O_{13}$	928262-58-2	Emodin-8-O-(6'-O-malonyl)-glucoside	R	517 $[M-H]^-$	MS^2 [517]: 473, 269, 241, 225, 210, 182 (Dong et al., 2011a)
				RP		MS^2 [517]: 269, 225 (Liu et al., 2016)
				RO,RP, RHE		MS^2 [517]: 473 MS^3 [473]: 311, 269 MS^4 [269]: 225(Ye et al., 2007)
522.46	$C_{24}H_{26}O_{13}$	168293-26-3	5,2',6'-Trihydroxy-6,7,8-trimethoxyflavone-2'-O-β-D-glucoside	SCU	521 $[M-H]^-$	MS^2 [521]: 359, 344, 329 (Qiao et al., 2016)
					NA	NA (Ishimaru et al., 1995)
526.26	$C_{30}H_{38}O_8$	182556-80-5	Kosamol A	SOP	NA	NA (Ryu et al., 1995)
528.55	$C_{28}H_{32}O_{10}$	62306-81-4	Rutaevin acetate	DIC	NA	NA (Yang et al., 2011a)
530.48	$C_{26}H_{26}O_{12}$	96990-65-7	3-Feruoyl-4-caffeoylquinic acid	PA	529 $[M-H]^-$	MS^2[529]: 336, 321, 293 (Xian et al., 2014)
						MS^2[529]: 529, 485, 367, 353, 193, 191 (Hu et al., 2010)
530.48	$C_{23}H_{30}O_{14}$	231280-24-3	Pikuroside	PHE	529 $[M-H]^-$	MS^2[529]: 481,393, 359, 197, 151 (Yan et al., 2015)
532.45	$C_{25}H_{24}O_{13}$	135574-57-1	Trifolirhizin 6'-O-malonate	SOP	533 $[M+H]^+$	MS^2[533]: 515, 285 (Zhang et al., 2007a)
					555 $[M+Na]^+$	NA (Zhang et al., 2007a)
538.46	$C_{30}H_{18}O_{10}$	135309-02-3	8'-8"-Bibaicalein	SCU	537 $[M-H]^-$	MS^2 [537]: 391, 245 (Qiao et al., 2016)
					539	MS^2 [539]: 419, 393, 269 (Liu et al., 2009)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
					$[M+H]^+$	MS^2 [539]: 519, 501 (Zhang et al., 2007b)
542.49	$C_{27}H_{26}O_{12}$	105304-51-6	Resveratrol-4'-O-β-D-(2"-O-galloyl)-glucoside	R	541 $[M-H]^-$	MS^2 [541]: 313, 169, 227 (Dong et al., 2011a)
						MS^2 [541]: 227, 313, 169 (Lin et al., 2006)
				RP		MS^2 [541]: 227, 185, 143 (Liu et al., 2016)
				RHE		MS^2 [541]: 313, 169, 125, 227 (Jin et al., 2007)
					NA	NA (Jin et al., 2006a, Jin et al., 2006b)
				R	543 $[M+H]^+$	NA (Lin et al., 2006)
542.49	$C_{27}H_{26}O_{12}$	64898-03-9	Resveratrol-4'-O-β-D-(6"-O-galloyl)-glucoside	R	541 $[M-H]^-$	MS^2 [541]: 227, 313, 169 (Lin et al., 2006)
				RO	NA	NA (Komatsu et al., 2006)
				RP	541 $[M-H]^-$	MS^2 [541]: 227, 185, 143 (Liu et al., 2016)
					NA	NA (Komatsu et al., 2006)
				RHE	541 $[M-H]^-$	MS^2 [541]: 313, 169, 125, 227 (Jin et al., 2007)
					NA	NA (Jin et al., 2006a, Jin et al., 2006b)
546.43	$C_{25}H_{22}O_{14}$	1333328-11-2	Rhein-8-O-D-[6'-O-(3"-methoxylmalonyl)]glucoside	RP	545 $[M-H]^-$	NA (Zhang et al., 2010a)
					1091 $[2M-H]^-$	
					1110.2325 $[2M+NH_4]^+$	
548.49	$C_{26}H_{28}O_{13}$	1884390-97-9	Chrysin 6-C-α-L-arabinoside-8-C-β-D-glucoside	SCU	547 $[M-H]^-$	MS^2 [547]: 487, 457, 427, 367, 337 (Qiao et al., 2016)
						MS^n [547]: 529, 487, 457, 427, 367, 337, 309 (Wang et al., 2014b)
						MS^2 [547]: 529, 487, 457, 427, 367, 337 MS^3 [337]: 281, 309 (Wang et al., 2013a)

Appendix XIV List of compounds isolated from botanical drugs making up the hexa-herbal formula (HHCF).

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
						MS^2 [547]: 487, 457, 427, 409, 367, 337, 309, 281 (Seo et al., 2013)
						MS^2 [547]: 510, 487, 457, 427, 367, 337 (Luo et al., 2012)
						MS^2 [547]: 529, 487, 457, 427, 367, 337 (Liu et al., 2009)
						MS^2 [547]: 529, 487, 457, 427, 367, 337 MS^3 [457]: 337 MS^3 [427]: 367(10), 337 MS^4 [337]: 309(100), 281 MS^5 [309]: 281 (Han et al., 2007)
					549 $[M+H]^+$	MS^2 [549]: 531, 459, 429, 465, 411 MS^3 [411]: 393, 363, 333, 279 MS^3 [531]: 513 (Wang et al., 2013a)
548.49	$C_{26}H_{28}O_{13}$	185145-33-9	Chrysin 6-C-β-L-arabinoside-8-C-β-D-glucoside	SCU	547 $[M-H]^-$	MS^2 [547]: 457, 427, 367, 337 (Qiao et al., 2016)
548.49	$C_{26}H_{28}O_{13}$	185145-34-0	Chrysin 6-C-β-D glucoside-8-C- α-L-arabinoside	SCU	547 $[M-H]^-$	MS^2 [547]: 457, 427, 367, 337 (Qiao et al., 2016)
						MS^n [547]: 529, 487, 457, 427, 367, 337, 309 (Wang et al., 2014b)
						MS^2 [547]: 529 (Wang et al., 2013a)
						MS^2 [547]: 457, 427, 367, 337, 309, 281 (Seo et al., 2013)
						MS^2 [547]: 510, 487, 457, 427, 367, 337 (Luo et al., 2012)
						MS^2 [547]: 529, 487, 457, 427, 367, 337 MS^3 [457]: 367, 337 MS^3 [427]: 337, 367 MS^4 [337]: 309, 281 MS^5 [309]: 281 (Han et al., 2007)
						MS^2 [547]: 529, 487, 457, 427, 367, 337 (Liu et al., 2009, Zhang et al., 2007b)
					549 $[M+H]^+$	MS^2 [549]: 531, 495, 483, 477, 465, 453, 411, 435 MS^3 [531]: 513, 495, 483, 477, 465, 453, 441, 435, 399, 363 (Wang et al., 2013a)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
548.49	$C_{26}H_{28}O_{13}$	1884390-98-0	Chrysin 6-C-β-D-glucoside -8-C-β-L-arabinoside	SCU	547 $[M-H]^-$	MS^2 [547]: 457, 427, 367, 337 (Qiao et al., 2016)
548.49	$C_{26}H_{28}O_{13}$	1884395-07-6	Chrysin 6-C-hexoside-8-C-pentoside	SCU	547 $[M-H]^-$	MS^2 [547]: 457, 427, 367, 337 (Qiao et al., 2016)
548.49	$C_{26}H_{28}O_{13}$	1884395-06-5	Chrysin 6-C-pentoside-8-C-hexoside	SCU	547 $[M-H]^-$	MS^2 [547]: 529, 487, 457, 427, 367, 337 (Qiao et al., 2016)
550.59	$C_{28}H_{38}O_{11}$	1632410-41-3	Kihadanin C	DIC	573 $[M+Na]^+$	NA (Wang et al., 2014c)
556.51	$C_{28}H_{28}O_{12}$	94356-29-3	Desoxyrhaponticin-6''-O-gallate	RP	555 $[M-H]^-$	MS^2 [555]: 255, 227 (Liu et al., 2016)
558.62	$C_{30}H_{38}O_{10}$	66879-86-5	7-Acetyldihydronomilin	DIC	NA	NA (Zhao et al., 1998a)
562.52	$C_{27}H_{30}O_{13}$	149158-08-7	Apigenin 7,4'-di-O-rhamnoside	SCU	561 $[M-H]^-$	MS^2 [561]: 543, 517, 415, 269, 251, 241, 225, 151 (Seo et al., 2013)
562.52	$C_{27}H_{30}O_{13}$	125310-04-5	4'-methoxyisoflavone-7-O- β-D-apiofuranosyl-(1 à 6)- β-D-glucoside	SOP	561 $[M-H]^-$	NA (Zhang et al., 2013a)
					1123 $[2M-H]^-$	
					563 $[M+H]^+$	
					585 $[M+Na]^+$	
					1147 $[2M+Na]^+$	
562.52	$C_{27}H_{30}O_{13}$	102390-91-0	Kushenol O	SOP	561 $[M-H]^-$	NA (Zhang et al., 2013a)
					1123 $[2M-H]^-$	NA (Zhang et al., 2013a)
					563	MS^2[563]: 269 (Zhang et al., 2007a)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
					$[M+H]^+$	
					585 $[M+Na]^+$	NA (Zhang et al., 2007a, Zhang et al., 2013a)
					1147 $[2M+Na]^+$	NA (Zhang et al., 2013a)
564.49	$C_{26}H_{28}O_{14}$	52012-29-0	Apigenin 6-C-α-L-arabinoside 8-C-β-D-glucoside [Isoschaftoside]	SCU	563 $[M-H]^-$	MS^2 [563]: 503, 473, 443, 383, 353 (Qiao et al., 2016)
					565 $[M+H]^+$	MS^2 [565]: 547, 529, 511, 499, 445, 427, 419, 403, 271, 121 (Seo et al., 2013)
564.49	$C_{26}H_{28}O_{14}$	51938-32-0	Apigenin 8-C-α-L-arabinoside 6-C-β-D-glucoside [Schaftoside]	SCU	563 $[M-H]^-$	MS^2 [563]: 473, 443, 383, 353 (Qiao et al., 2016)
						MS^2 [563]: 473, 443, 395, 383, 353 (Seo et al., 2013)
						MS^2 [563]: 545, 503, 473, 443, 383, 353 MS^3 [443]: 353, 383 MS^4 [353]: 325 MS^5 [325]: 297 (Han et al., 2007)
564.49	$C_{26}H_{28}O_{14}$	51938-32-0	Schaftoside isomer	SCU	563 $[M-H]^-$	MS^2 [563]: 473, 443, 383, 353 (Qiao et al., 2016)
564.49	$C_{26}H_{28}O_{14}$	224957-09-9	6''-β-D-Xylopyranosylgenistin	SOP	599 $[M+Cl]^-$	NA (Zhang et al., 2013a)
					565 $[M+H]^+$	
568.48	$C_{28}H_{24}O_{13}$	266997-57-3	Chrysophanol-8-O-(6'-O-galloyl)glucoside	RP	567 $[M-H]^-$	MS^2 [567]: 253 (Liu et al., 2016)
				RO,RP, RHE		MS^2 [567]: 313, 271, 253, 211, 169 MS^3 [313]: 253, 241, 211, 193, 169, 125 MS^4 [169]: 125 (Ye et al., 2007)
568.57	$C_{27}H_{36}O_{13}$	105279-10-5	Citrusin B	PA	NA	NA (Li et al., 2012b)
576.85	$C_{35}H_{60}O_6$	474-58-8	β-Sitosterol 3-O-β-D-glucoside [Daucosterol]	DIC	575 $[M-H]^-$	NA (Bai et al., 2014b)
					NA	NA (Xiang et al., 2008)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
				KOC	NA	NA (Lu et al., 2012, Zhang et al., 2013c, Xu et al., 2012, Wang et al., 2003)
				PHE	NA	NA (Qin and Wang, 2003)
578.52	$C_{27}H_{30}O_{14}$	850621-76-0	Chrysin 6,8-di-C-glucoside	SCU	577 $[M-H]^-$	MS^2 [577]: 559, 517, 487, 457, 367, 337 MS^3 [457]: 367, 337 MS^4 [337]: 309, 281 MS^5 [309]: 281 (Han et al., 2007)
578.52	$C_{27}H_{30}O_{14}$	938447-90-6	Chrysin-7-O-glucosyl-8-C-glucoside	SCU	577 $[M-H]^-$	MS^2 [577]: 487, 457, 415, 295 MS^3 [457]: 295, 337 MS^4 [295]: 267 (Han et al., 2007)
578.52	$C_{27}H_{30}O_{14}$	NA	Chrysophanol-8-O-(6'-O-glucosyl)glucoside	RHE	577 $[M-H]^-$	MS^2 [577]: 253 (Jin et al., 2007)
578.52	$C_{30}H_{26}O_{12}$	15514-06-4	Procyanidin B	R	577 $[M-H]^-$	MS^2 [577]: 407, 289, 245, 12, 109 (Yang et al., 2015a)
				RHE		NA (Jin et al., 2007)
580.53	$C_{27}H_{32}O_{14}$	101236-48-0	Kushenol J	SOP	NA	NA (Wu et al., 1985b)
580.58	$C_{28}H_{36}O_{13}$	7374-79-0	(+)-Syringaresinol O-β-D-glucoside	SCU	NA	NA (Miyaichi and Tomimori, 1994)
582.55	$C_{27}H_{34}O_{14}$	1051926-06-7	2',4',6'-Trihyroxydihydrochalcone 3'-C-β-D-glucoside-6'-O-β-D-glucoside	SCU	581 $[M-H]^-$	MS^2 [581]: 461, 329, 299, 167 (Qiao et al., 2016)
582.55	$C_{27}H_{34}O_{14}$	1051926-06-7	2',4',6'-Trihyroxydihydrochalcone 3'-C-β-D-glucoside-6'-O-β-D-glucoside isomer	SCU	581 $[M-H]^-$	MS^2 [581]: 491, 461, 329, 299 (Qiao et al., 2016)
582.59	$C_{28}H_{38}O_{13}$	154418-16-3	5,5'-Dimethoxylariciresinol 4'-O-β-D-glucoside	PHE	581 $[M-H]^-$	MS^2 [581]: 552, 439, 411, 353, 391, 355, 339, 193, 191 MS^2 [353]: 191, 179 (Hu et al., 2010)
				PA		MS^2 [581]: 552, 439, 411, 353, 391, 355, 339, 193, 191 MS^2 [353]: 191, 179 (Hu et al., 2010)
					NA	NA (Ida et al., 1993)
584.48	$C_{28}H_{24}O_{14}$	1374014-36-4	Aloe-emodin-8-O-β-D-(6'-galloyl)glucoside	RHE	583	MS^1 [583]: 269, 239 (Jin et al., 2007)

Appendix XIV List of compounds isolated from botanical drugs making up the hexa-herbal formula (HHCF).

DIC= root bark of *Dictamnus dasycarpus* Turcz.; KOC= fruit *of Kochia scoparia* (L.) Schrad.; P= bark of *Phellodendron chinense* C.K. Schneid. or *Phellodendron amurense* Rupr. ;PA= bark of *Phellodendron amurense* Rupr.; PHE= bark of *Phellodendron chinense* C.K. Schneid.; R= rootstock of *Rheum* species; RHE= rootstock of *Rheum tanguticum* Maxim. ex Balf.; RO= rootstock of *Rheum officinale* Baill.; RP= rootstock of *Rheum palmatum* L.; SCU= rootstock of *Scutellaria baicalensis* Georgi; SOP= rootstock of *Sophora flavescens* Aiton

Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
					$[M-H]^-$	
588.81	$C_{35}H_{56}O_7$	1644086-02-1	Dictabretol A	DIC	587 $[M-H]^-$	NA (Kim et al., 2015)
					NA	NA (Choi et al., 2016)
590.53	$C_{31}H_{26}O_{12}$	1454302-46-5	1-Methyl-8-hydroxyl-9,10-anthraquinone-3-O-B-D-(6'-O-cinnamoyl)glucoside	RO, RP	589 $[M-H]^-$	NA (Zhang et al., 2010a, Xia et al., 2012)
					608.1760 $[M+NH_4]^+$	
590.53	$C_{28}H_{30}O_{14}$	NA	Wogonin O-acetyl-diarabinoside	SCU	589 $[M-H]^-$	MS^2 [589]: 283. 268 (Seo et al., 2013)
590.83	$C_{35}H_{58}O_7$	1644086-03-2	Dictabretol B	DIC	589 $[M-H]^-$	NA (Kim et al., 2015)
594.52	$C_{27}H_{30}O_{15}$	111545-29-0	Rheinoside C	R	NA	NA (Yamagishi et al., 1987)
594.52	$C_{27}H_{30}O_{15}$	111614-11-0	Rheinoside D	R	NA	NA (Yamagishi et al., 1987)
594.65	$C_{27}H_{46}O_{14}$	256528-97-9	Dictamnoside G	DIC	+	MS [612, 450] (Zhao et al., 1999)
					NA	NA (Chang et al., 2001)
596.66	$C_{27}H_{48}O_{14}$	359845-46-8	Dictamnoside M	DIC	619 $[M+Na]^+$	NA (Chang et al., 2001)
					635 $[M+K]^+$	
598.47	$C_{28}H_{22}O_{15}$	1374014-37-5	Rhein-8-O- β-D-(6'-galloyl)-glucoside	RP	597 $[M-H]^-$	MS^2 [597]: 283, 239 (Liu et al., 2016)
606.52	$C_{31}H_{26}O_{13}$	NA	Laccaic acid D-8-O-(6'-cinnamoyl)-glucoside	RP	605 $[M-H]^-$	MS^2 [605]: 561, 413, 268 MS^3 [561]: 413, 323, 293, 269, 268, 240

Appendix XIV List of compounds isolated from botanical drugs making up the hexa-herbal formula (HHCF).

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
						MS^4 [268]: 241, 240, 225 (Han et al., 2008)
608.54	$C_{28}H_{32}O_{15}$	84268-38-2	Physcion-8-O-β-D-gentiobioside	R	NA	NA (Holzschuh et al., 1982)
608.55	$C_{31}H_{28}O_{13}$	NA	Coumaroyl-O-cinnamoyl-galloyl-glucose	RP	607 $[M-H]^-$	MS^2 [607]: 433, 295 MS^3 [443]: 299, 295, 169, 151 MS^4 [169]: 125 (Han et al., 2008)
608.59	$C_{32}H_{32}O_{12}$	356517-93-6	4-(4'-hydroxyphenyl)-2-butanone-4'-O-β-D-(2"-O-galloyl-6"-O-cinnamoyl)- glucoside	R	607 $[M-H]^-$	MS^2 [607]: 477, 459, 443, 295, 169, 147 (Yang et al., 2015a)
				RP		MS^2 [607]: 443, 163, 147, 103, 169, 125 (Liu et al., 2016)
				RHE		MS^2 [607]: 443, 295, 169, 125 (Jin et al., 2007)
					NA	NA (Jin et al., 2006a, Jin et al., 2006b, Gao et al., 2012a)
608.59	$C_{32}H_{32}O_{12}$	356517-94-7	4-(4'-hydroxyphenyl)-2-butanone-4'-O-β-D-(6"-O-galloyl-2"-O-cinnamoyl)- glucoside	RHE	NA	NA (Jin et al., 2006b)
610.52	$C_{27}H_{30}O_{16}$	111545-28-9	Rheinoside A	R	NA	NA (Yamagishi et al., 1987)
610.52	$C_{27}H_{30}O_{16}$	111614-10-9	Rheinoside B	R	NA	NA (Yamagishi et al., 1987)
610.52	$C_{27}H_{30}O_{16}$	153-18-4	Rutin	DIC	611 $[M+H]^+$	NA (Bai et al., 2014b)
					633 $[M+Na]^+$	
					NA	NA (Komissarenko et al., 1983)
				KOC	NA	NA (Lu et al., 2012)
				SCU	609 $[M-H]^-$	MS^2 [609]:609, 301 (Alolga et al., 2015)
612.66	$C_{27}H_{48}O_{15}$	256528-96-8	Dictamnoside F	DIC	NA	NA (Zhao et al., 1999)
614.51	$C_{29}H_{26}O_{15}$	NA	Cinnamoyl digalloyl-glucose	R	613 $[M-H]^-$	MS^2 [613]: 444, 169, 147 (Yang et al., 2015a)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
614.51	$C_{29}H_{26}O_{15}$	115746-70-8	1,2-Di-O-galloyl-6-O-cinnamoyl-β-D-glucose	RO,RP, RHE	NA	NA (Komatsu et al., 2006)
614.51	$C_{29}H_{26}O_{15}$	791836-72-1/94356-17-9	1,3-Di-O-galloyl-2-O-cinnamoyl-β-D-glucose	RO	NA	NA (Komatsu et al., 2006)
				RP		
				RHE	613 $[M-H]^-$	MS^2 [613]: 443, 69, 125 (Jin et al., 2007)
					NA	NA (Komatsu et al., 2006)
616.52	$C_{29}H_{28}O_{15}$	NA	Benzenepropanoyl-di-O-galloyl-glucose	RP	615 $[M-H]^-$	MS^2 [615]: 465, 313, 271 MS^3 [465]: 313, 295, 169 MS^4 [313]: 169, 125 (Han et al., 2008)
618.84	$C_{36}H_{58}O_8$	14162-53-9	28-O-β-D-Glucosyl oleanolic acid	KOC	NA	NA (Wang et al., 2003)
620.86	$C_{36}H_{60}O_8$	1807741-89-4	Dictamnin A	DIC	643 $[M+Na]^+$	NA (Bai et al., 2014a)
620.86	$C_{36}H_{60}O_8$	1807741-90-7	Dictamnin B	DIC	643 $[M+Na]^+$	NA (Bai et al., 2014a)
622.42	$C_{31}H_{27}O_{14}$	NA	Emodin-(2'-O-benzoyl-6'-O-malonyl)-glucoside	RP	621 $[M-H]^-$	MS^2 [621]: 577, 311, 269 MS^3 [577]: 311, 269 MS^4 [269]: 241 (Han et al., 2008)
622.53	$C_{28}H_{30}O_{16}$	NA	Wogonin-O-glucosyl-glucuronide	SCU	621 $[M-H]^-$	MS^2 [621]: 445, 430, 283, 268 (Qiao et al., 2016)
						MS^2 [621]: 445 (Han et al., 2007)
624.54	$C_{28}H_{32}O_{16}$	64723-32-6	Isorhamnetin-7-O-rhamnosyl-glucoside	SCU	623 $[M-H]^-$	MS^2 [623]: 461 (Luo et al., 2012)
						MS^2 [623]: 461 MS^2 [461]: 315, 135, 161 (Han et al., 2007)
624.59	$C_{29}H_{36}O_{15}$	61276-17-3	Acteoside	SCU	623 $[M-H]^-$	MS^2 [623]: 461, 179, 161 (Qiao et al., 2016)
						MS^2 [623]: 461, 315 MS^3 [461]: 315 (Wang et al., 2013a)
						MS^2 [623]: 461, 179, 161, 135, 133, 113 (Seo et al., 2013)
624.59	$C_{29}H_{36}O_{15}$	NA	Acteoside isomer	SCU	623	MS^2 [623]: 461, 315, 179, 161 (Qiao et al., 2016)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
					$[M-H]^-$	
624.59	$C_{32}H_{32}O_{13}$	949488-79-3	4-(4'-hydroxyphenyl)-2-butanone-4'-O-β-D-(2''-O-galloyl-6''-O-p-coumaroyl)-glucoside	R	623 $[M-H]^-$	MS^2 [623]: 459, 295, 169, 125 (Dong et al., 2011a)
				RP		MS^2 [623]: 459, 163, 119, 169, 125 (Liu et al., 2016)
				RHE		MS^2 [623]: 459, 295, 169, 125 (Jin et al., 2007)
					NA	NA (Jin et al., 2006a, Jin et al., 2006b)
					642 $[M+NH_4]^+$	NA (Jin et al., 2006a)
					647 $[M+Na]^+$	
630.51	$C_{29}H_{26}O_{16}$	NA	*p*-Coumaroyl-di-O-galloyl-glucose	RP	629 $[M-H]^-$	MS^2 [629]: 465, 459, 313, 271 MS^3 [465]: 409, 313, 295, 169 MS^4 [313]: 253, 169, 125 MS^5 [169]: 125 (Han et al., 2008)
630.55	$C_{30}H_{30}O_{15}$	105274-14-4	4-(4'-Hydroxyphenyl)-2-butanone-4'-O- β -D-(2''-O-galloyl-6''-O-galloyl)-glucoside	RHE	629 $[M-H]^-$	MS^2 [629]: 465, 313, 169 (Jin et al., 2007)
632.82	$C_{36}H_{56}O_9$	26020-14-4	Momordin Ib/Oleanolic acid 3-O-β-D-glucuronide	KOC	NA	NA (Lu et al., 2012, Yoshikawa et al., 1997a, Choi et al., 2002)
636.47	$C_{30}H_{30}O_{15}$	79886-49-0	1,2,6-Tri-O-galloyl-glucose	RO,RP, RHE	NA	NA (Komatsu et al., 2006)
				RHE	635 $[M-H]^-$	MS^2 [635]: 465, 313, 169 (Jin et al., 2007)
638.53	$C_{28}H_{30}O_{17}$	1884395-05-4	Trihydroxy-methoxxyflavone-O-glucosyl-O-glucuronide	SCU	637 $[M-H]^-$	MS^2 [637]: 475, 461, 299, 284, 175 (Qiao et al., 2016)
638.61	$C_{30}H_{38}O_{15}$	94492-22-5	Cistanoside C	SCU	637 $[M-H]^-$	MS^2 [637]: 179, 161, 133, 113 (Qiao et al., 2016)
638.61	$C_{30}H_{38}O_{15}$	83529-62-8		SCU	637	MS^2 [637]: 461, 193, 175 (Qiao et al., 2016)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
			Leucosceptoside A		$[M-H]^-$	
					NA	NA (Miyaichi and Tomimori, 1994)
638.61	$C_{30}H_{38}O_{15}$	83529-62-8D	Leucosceptoside A isomer	SCU	637 $[M-H]^-$	MS^2 [637]: 461, 193, 175,160 (Qiao et al., 2016)
640.63	$C_{36}H_{32}O_{11}$	NA	Sennoside	RP	639 $[M-H]^-$	MS^2 [639]: 621, 477, 238 MS^3 [477]: 449, 238 (Han et al., 2008)
646.85	$C_{37}H_{58}O_9$	51724-38-0	Oleanolic acid 3-O-β-D-glucoside-6-O-methyl ester	KOC	NA	NA (Wang et al., 2003)
648.82	$C_{36}H_{56}O_{10}$	193894-08-5	Kochianoside I	KOC	647 $[M-H]^-$	NA (Yoshikawa et al., 1997a)
					671 $[M+Na]^+$	
652.64	$C_{31}H_{40}O_{15}$	94492-21-4	Cistansoide D	SCU	651 $[M-H]^-$	MS^2 [651]: 475, 193, 175, 160 (Qiao et al., 2016)
652.64	$C_{31}H_{40}O_{15}$	94492-21-4D	Cistansoide D isomer	SCU	651 $[M-H]^-$	MS^2 [651]: 475, 329, 193, 175 (Qiao et al., 2016)
652.64	$C_{31}H_{40}O_{15}$	80377-39-5	2-(3-hydroxy-4-methoxyphenyl)ethyl 1-O-α-L-rhamnosyl-(1 à 3)-β-D-(4-feruloyl)glucoside	SCU	NA	NA (Takagi et al., 1981b)
652.64	$C_{31}H_{40}O_{15}$	94410-22-7	Isomartynoside	SCU	NA	NA (Miyaichi and Tomimori, 1994)
658.95	$C_{40}H_{66}O_7$	1644086-04-3	Dictabretol C	DIC	657 $[M-H]^-$	NA (Kim et al., 2015)
670.66	$C_{37}H_{34}O_{12}$	NA	Sennoside	RP	669 $[M-H]^-$	MS^2 [669]: 507, 268 MS^3 [507]: 492 (Han et al., 2008)
672.97	$C_{41}H_{68}O_7$	1644086-05-4	Dictabretol D	DIC	671 $[M-H]^-$	NA (Kim et al., 2015)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
730.62	$C_{37}H_{30}O_{16}$	79907-45-2	Procyanidin B_1 3-O-gallate	R	729 $[M-H]^-$	MS^2 [729]: 577, 559, 407, 289, 269, 169, 125 (Yang et al., 2015a)
730.62	$C_{37}H_{30}O_{16}$	73086-04-1	Procyanidin B 2 3'-O-gallate	RO,RP, RHE	NA	NA (Komatsu et al., 2006)
742.72	$C_{34}H_{46}O_{18}$	66791-77-3	Syringaresinol di-O-β-D-glucoside	PHE	742 $[M-H]^-$	MS^2 [742]: 488, 724, 579 MS^2 [724]: 487, 417, 339 (Hu et al., 2010)
				PA		MS^2 [742]: 488, 724, 579 MS^2 [724]: 487, 417, 339 (Hu et al., 2010)
					NA	NA (Ida et al., 1993)
744.73	$C_{34}H_{48}O_{18}$	143522-30-9	Salvadoraside	PA	NA	NA (Li et al., 2012b)
746.75	$C_{37}H_{46}O_{16}$	209864-39-1	Hedyotol C- 4"-O-β-D-glucoside	SCU	769 $[M+Na]^+$	NA (Miyaichi and Tomimori, 1998)
746.75	$C_{37}H_{46}O_{16}$	209864-40-4	Hedyotol D- 4"-O-β-D-glucoside	SCU	769 $[M+Na]^+$	NA (Miyaichi and Tomimori, 1998)
764.94	$C_{41}H_{64}O_{13}$	193894-16-5	Kochianoside IV	KOC	763 $[M-H]^-$	NA (Yoshikawa et al., 1997a)
					787 $[M+Na]^+$	
764.94	$C_{41}H_{64}O_{13}$	95851-40-4	Momordin I	KOC	NA	NA (Yoshikawa et al., 1997a)
764.94	$C_{41}H_{64}O_{13}$	96990-18-0	Momordin Ic	KOC	+	MS [787, 655, 439] (Wen et al., 1995)
					NA	NA (Yoshikawa et al., 1997a, Yoshikawa et al., 1997b, Wang et al., 2003, Xu et al., 2012, Lu et al., 2012)
764.94	$C_{41}H_{64}O_{13}$	195971-47-2	Scoparianoside B	KOC	763 $[M-H]^-$	NA (Yoshikawa et al., 1997b)
					787 $[M+NA]^+$	
764.94	$C_{41}H_{64}O_{13}$	195971-48-3	Scoparianoside C	KOC	763 $[M-H]^-$	NA (Yoshikawa et al., 1997b)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
					787 $[M+NA]^+$	
776.78	$C_{38}H_{48}O_{17}$	209864-41-5	Eythro-guaiacylglycerol-β-syringaresinol ether 4"-O-β-D-glucoside	SCU	799 $[M+Na]^+$	NA (Miyaichi and Tomimori, 1998)
778.97	$C_{42}H_{66}O_{13}$	126223-65-2	Momordin Ic 6'-methyl ester	KOC	+	MS [817, 801,669, 439] (Wen et al., 1995)
					NA	NA (Wang et al., 2003, Yoshikawa et al., 1997a, Lu et al., 2012)
780.94	$C_{41}H_{64}O_{14}$	193894-14-3	Kochianoside III	KOC	779 $[M-H]^-$	MS [647, 471] (Yoshikawa et al., 1997a)
					803 $[M+Na]^+$	NA (Yoshikawa et al., 1997a)
780.94	$C_{41}H_{64}O_{14}$	195971-46-1	Scoparianoside A	KOC	779 $[M-H]^-$	MS [647, 471] (Yoshikawa et al., 1997b)
					803 $[M+Na]^+$	NA (Yoshikawa et al., 1997b)
794.97	$C_{42}H_{66}O_{14}$	51415-02-2	3-O-β-D-Glucosyl-oleanolic acid 28-O-β-D-glucoside	KOC	NA	NA (Lu et al., 2012)
832.75	$C_{42}H_{40}O_{18}$	NA	Sennoside	RP	831 $[M-H]^-$	MS^2 [831]: 669, 625, 507, 386 MS^3 [669]: 625, 507, 461, 386 MS^4 [507]: 463/ MS^2 [831]: 787, 669, 651, 507, 386 MS^3 [669]: 625, 507, 463, 386 MS^4 [507]: 463 MS^4 [386]: 224/ MS^2 [831]: 787, 669, 507, 463, 386 MS^3 [669]: 625, 507, 463, 386, 224 MS^4 [507]: 463 (Han et al., 2008)
848.76	$C_{42}H_{40}O_{19}$	37271-16-2	Sennoside C	R	847	MS^2 [847]: 685, 386, 253 (Yang et al., 2015a)

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Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
				RHE	$[M-H]^-$	MS^2 [847]: 685 (Jin et al., 2007)
848.76	$C_{42}H_{40}O_{19}$	37271-17-3	Sennoside D	RHE	847 $[M-H]^-$	MS^2 [847]: 685 (Jin et al., 2007)
862.74	$C_{42}H_{38}O_{20}$	81-27-6	Sennoside A	R	861 $[M-H]^-$	MS^2 [861]: 699, 655, 557, 386(Yang et al., 2015a)
						MS^2 [861]: 699, 537, 268, 224 (Dong et al., 2011a)
						MS^2 [861]: 817, 699, 655,537 (Lin et al., 2006)
				RP		MS^2 [861]: 386, 224 (Liu et al., 2016)
						MS^2 [861]: 817, 699, 655, 537, 386 MS^3 [699]: 655, 537, 493, 386, 224 MS^4 [537]: 519, 493, 448, 268 MS^5 [493]: 449 (Han et al., 2008)
						MS^2 [861]: 817, 699, 655, 537 (Lin et al., 2006)
				RHE		MS^2 [861]: 699 (Jin et al., 2007)
					NA	NA (Jin et al., 2006a, Jin et al., 2006b)
					885 $[M+Na]^+$	NA (Jin et al., 2007)
862.74	$C_{42}H_{38}O_{20}$	128-57-4	Sennoside B	RP	861 $[M-H]^-$	MS^2 [861]: 386, 224 (Liu et al., 2016)
						MS^2 [861]: 817, 699, 698, 655, 537 MS^3 [861 à 699]: 655, 654, 537, 535, 493 MS^4 [861 à 699 à 537]: 519, 493, 449, 224 (Zhao et al., 2013a)
						MS^2 [861]: 817, 699, 655, 537 (Lin et al., 2006)
				RHE		MS^2 [861]: 699 (Jin et al., 2007)
					NA	NA (Jin et al., 2006a, Jin et al., 2006b)
					885 $[M+Na]^+$	NA (Jin et al., 2007)
866.77	$C_{45}H_{38}O_{18}$	201304-46-3	Catechin trimer	RP	865 $[M-H]^-$	MS^2 [865]: 577, 289, 245, 205, 203, 137 (Wang et al., 2011a)

Appendix XIV List of compounds isolated from botanical drugs making up the hexa-herbal formula (HHCF).

DIC= root bark of *Dictamnus dasycarpus* Turcz.; KOC= fruit *of Kochia scoparia* (L.) Schrad.; P= bark of *Phellodendron chinense* C.K. Schneid. or *Phellodendron amurense* Rupr. ;PA= bark of *Phellodendron amurense* Rupr.; PHE= bark of *Phellodendron chinense* C.K. Schneid.; R= rootstock of *Rheum* species; RHE= rootstock of *Rheum tanguticum* Maxim. ex Balf.; RO= rootstock of *Rheum officinale* Baill.; RP= rootstock of *Rheum palmatum* L.; SCU= rootstock of *Scutellaria baicalensis* Georgi; SOP= rootstock of *Sophora flavescens* Aiton

Molecular weight	Molecular formula	CAS no.	Name of compound	Source	Adduct ion(s)	MS, MS/MS or MS^n fragment ions
882.73	$C_{44}H_{34}O_{20}$	79907-44-1	Procyanidin B2 3,3'-di-O-gallate	RO,RP, RHE	NA	NA (Komatsu et al., 2006)
927.08	$C_{47}H_{74}O_{18}$	152203-45-7	2'-O-β-D-Glucosyl momordin Ic	KOC	+	MS [972, 949, 840, 817, 787, 439] (Wen et al., 1995)
						NA (Yoshikawa et al., 1997a, Yoshikawa et al., 1997b, Wang et al., 2003, Xu et al., 2012)
927.08	$C_{47}H_{74}O_{18}$	193894-13-2	Kochianoside II	KOC	925 $[M-H]^-$	NA (Yoshikawa et al., 1997a)
					949 $[M+Na]^+$	
927.08	$C_{47}H_{74}O_{18}$	96990-19-1	Momordin IIc	KOC	+	MS [949, 787, 439] (Wen et al., 1995)
					NA	NA (Yoshikawa et al., 1997a, Yoshikawa et al., 1997b, Wang et al., 2003, Xu et al., 2012, Lu et al., 2012)
941.11	$C_{48}H_{76}O_{18}$	193826-28-7	Momordin IIc 6'-methyl ester	KOC	NA	NA (Yoshikawa et al., 1997a)
943.12	$C_{48}H_{78}O_{18}$	51330-27-9	Soyasaponin I	SOP	NA	NA (Yoshikawa et al., 1985)
1089.22	$C_{53}H_{84}O_{23}$	152203-46-8	2'-O-β-D-Glucosylmomordin IIc	KOC	+	MS [949, 817, 439] (Wen et al., 1995)
1237.37	$C_{59}H_{96}O_{27}$	100201-60-3	Sophoraflavoside I	SOP	NA	NA (Yoshikawa et al., 1985)

Appendix XV: Output from the EXCEL template for ions in positive ionization mode.

Step 1: The *m/z* value of ions in the HHCF LC-MS profile with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value, start time and end time of ions in the single botanical drug (SBD) [i.e. DIC, RHE, SOP, SCU, PHE, KOC] LC-MS profile. Criteria set in the match function are explained in section 2.3.3 and illustrated in Table 2.2.
Step 2: The *m/z* value of ions in the HHCF with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value of potential adduct ions of compounds in database Appendix XIV.

Step 1										**Step 2**					
HHCF			**Abundance in SBD (3 x average)**						**Source**	**Potential adduct ions of compounds in database (CAS no.)**					
m/z	**RT**	**Abundant**	**DIC**	**RHE**	**SOP**	**SCU**	**PHE**	**KOC**							
249	5.722	6215790	35467	9857	6464903	5709		19991	SOP	M+H (641-39-4)	M+H (17801-36-4)	M+H (550-90-3)	M+H (519-02-8)	M+H (6882-68-4)	M+2Na-H (6220-47-9)
265	8.021	5663374	2089	1305	7580852	1562		3679	SOP	M+H (3411-37-8)	M+H (88509-92-6)	M+H (183074-18-2)	M+H (18688-40-9)	M+H (16837-52-8)	M+H (1217501-78-4)
336	52.873	5230353	2661		4480	4759	9841235	1274	PHE	M+ (2086-83-1)	M+ (2086-83-1DP)	M+ (6873-09-2)	M+Na (524-20-9)	M+2K-H (83-95-4)	M+2K-H (878424-66-9)
										M+2K-H (27495-37-0)	M+2K-H (318465-89-3)				
249	6.466	4521969	30057	11414	5409397			31374	SOP	M+H (641-39-4)	M+H (17801-36-4)	M+H (550-90-3)	M+H (519-02-8)	M+H (6882-68-4)	M+2Na-H (6220-47-9)
342	20.078	3873040		769			7954454	1446	PHE	M+ (303126-79-6)	M+ (531-29-3)	M+ (1168-42-9)	M+ (2141-09-5)	M+ (2141-09-5DP)	M+ (6873-13-8)
										M+H (255845-85-3)	M+H (27313-86-6)	M+Na (472965-96-1)	M+K (1437691-40-1)	M+K (518-17-2)	
180	4.399	3569033		2916		2334	6292219	10172	PHE	M+ (6656-13-9)	M+2Na-H (2592-95-2)				
247	6.466	3140248	14463	4687	1695997	2548		11529	SOP	M+H (46862-63-9)	M+H (68398-59-4)	M+H (6483-15-4)	M+K (1257392-35-0)		
265	11.478	2979294	4360	1723	7476543				SOP	M+H (3411-37-8)	M+H (88509-92-6)	M+H (183074-18-2)	M+H (18688-40-9)	M+H (16837-52-8)	M+H (1217501-78-4)
342	22.906	2611923	841				3997984	1695	PHE	M+ (303126-79-6)	M+ (531-29-3)	M+ (1168-42-9)	M+ (2141-09-5)	M+ (2141-09-5DP)	M+ (6873-13-8)

Appendix XV: Output from the EXCEL template for ions in positive ionization mode.

Step 1: The *m/z* value of ions in the HHCF LC-MS profile with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value, start time and end time of ions in the single botanical drug (SBD) [i.e. DIC, RHE, SOP, SCU, PHE, KOC] LC-MS profile. Criteria set in the match function are explained in section 2.3.3 and illustrated in Table 2.2.
Step 2: The *m/z* value of ions in the HHCF with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value of potential adduct ions of compounds in database Appendix XIV.

Step 1										**Step 2**					
HHCF			**Abundance in SBD (3 x average)**						**Source**	**Potential adduct ions of compounds in database (CAS no.)**					
m/z	**RT**	**Abundant**	**DIC**	**RHE**	**SOP**	**SCU**	**PHE**	**KOC**							
										M+H (255845-85-3)	M+H (27313-86-6)	M+Na (472965-96-1)	M+K (1437691-40-1)	M+K (518-17-2)	
263	8.021	2295527	4231	1285	1415747			34515	SOP	M+H (1257392-34-9)	M+H (907607-58-3)	M+H (147731-96-2)	M+H (60394-92-5)	M+H (26904-64-3)	
314	26.842	2134064					4980423		PHE	M+ (6871-67-6)	M+ (6801-40-7)	M+ (152230-57-4)	M+H (524-20-9)		
150	2.911	1178597	265375			12429	3508011		PHE						
265	4.151	1025398	3017		1757698				SOP	M+H (3411-37-8)	M+H (88509-92-6)	M+H (183074-18-2)	M+H (18688-40-9)	M+H (16837-52-8)	M+H (1217501-78-4)
266	8.021	1017214			1448726			10906	SOP	M+NH4 (641-39-4)	M+NH4 (17801-36-4)	M+NH4 (550-90-3)	M+NH4 (519-02-8)	M+NH4 (6882-68-4)	
250	6.466	695020	6000	3853	937965	1318		10532	SOP	M+NH4 (56293-29-9)					
121	3.754	691266	189958	606998		6501	2064608	370200	PHE						
263	5.524	691122	1310		344087			4812	SOP	M+H (1257392-34-9)	M+H (907607-58-3)	M+H (147731-96-2)	M+H (60394-92-5)	M+H (26904-64-3)	
130	2.762	639329	84237	751777	880557	480749		85964	MULTI						
349	21.119	594710	1015	1273589				1176	RHE	M+Na (14364-05-7)	M+Na (38963-94-9)	M+K (40004-96-4)			
164	3.936	560097						4358377	KOC						
205	3.357	503298			2726496	6335			SOP	M+H (6220-47-9)					

Appendix XV: Output from the EXCEL template for ions in positive ionization mode.

Step 1: The *m/z* value of ions in the HHCF LC-MS profile with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value, start time and end time of ions in the single botanical drug (SBD) [i.e. DIC, RHE, SOP, SCU, PHE, KOC] LC-MS profile. Criteria set in the match function are explained in section 2.3.3 and illustrated in Table 2.2.
Step 2: The *m/z* value of ions in the HHCF with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value of potential adduct ions of compounds in database Appendix XIV.

Step 1										**Step 2**					
HHCF			**Abundance in SBD (3 x average)**						**Source**	**Potential adduct ions of compounds in database (CAS no.)**					
m/z	**RT**	**Abundant**	**DIC**	**RHE**	**SOP**	**SCU**	**PHE**	**KOC**							
265	4.746	499090	3537		1908655			19034	SOP	M+H (3411-37-8)	M+H (88509-92-6)	M+H (183074-18-2)	M+H (18688-40-9)	M+H (16837-52-8)	M+H (1217501-78-4)
118	2.58	471525	26487	73543	42400	18994		1486319	KOC						
529	8.021	459172			1094774				SOP	2M+H (3411-37-8)	2M+H (88509-92-6)	2M+H (183074-18-2)	2M+H (18688-40-9)	2M+H (16837-52-8)	2M+H (1217501-78-4)
137	3.357	447107				11921	53579	88799	MULTI						
519	5.722	409674			556049				SOP	2M+Na (641-39-4)	2M+Na (17801-36-4)	2M+Na (550-90-3)	2M+Na (519-02-8)	2M+Na (6882-68-4)	
121	4.399	392825	296419	1809			712899	6001	PHE						
196	3.357	305832					923237		PHE	M+ (4707-47-5)	M+NH4 (305-01-1)				
166	2.762	298518						296497	KOC	No putative compound matched in database					
314	16.77	296876		2571			2145710	1269	PHE	M+ (6871-67-6)	M+ (6801-40-7)	M+ (152230-57-4)	M+H (524-20-9)		
118	2.762	251559	26487	104926	62846	23782		1486319	KOC						
497	5.722	248170			338935				SOP	2M+H (641-39-4)	2M+H (17801-36-4)	2M+H (550-90-3)	2M+H (519-02-8)	2M+H (6882-68-4)	
136	2.762	234313	28132	159319	238122	85855		426837	KOC						
525	8.021	234141			330895				SOP	2M+H (1257392-34-9)	2M+H (907607-58-3)	2M+H (147731-96-2)	2M+H (60394-92-5)	2M+H (26904-64-3)	
265	3.754	219100	3438		735527			7736	SOP	M+H (3411-37-8)	M+H (88509-92-6)	M+H (183074-18-2)	M+H (18688-40-9)	M+H (16837-52-8)	M+H (1217501-78-4)

Appendix XV: Output from the EXCEL template for ions in positive ionization mode.

Step 1: The *m/z* value of ions in the HHCF LC-MS profile with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value, start time and end time of ions in the single botanical drug (SBD) [i.e. DIC, RHE, SOP, SCU, PHE, KOC] LC-MS profile. Criteria set in the match function are explained in section 2.3.3 and illustrated in Table 2.2.
Step 2: The *m/z* value of ions in the HHCF with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value of potential adduct ions of compounds in database Appendix XIV.

Step 1										**Step 2**					
HHCF			**Abundance in SBD (3 x average)**						**Source**	**Potential adduct ions of compounds in database (CAS no.)**					
m/z	**RT**	**Abundant**	**DIC**	**RHE**	**SOP**	**SCU**	**PHE**	**KOC**							
178	4.995	216767						2591629	KOC						
132	4.151	215221	191075	86442	126630	32644		739952	KOC						
261	3.357	202043		12038	74798	17664			SOP	M+H (732-50-3)	M+H (259860-46-3)	M+H (85769-34-2)			
192	5.722	188788					3086869	4323	PHE	M+H (21796-14-5)	M+H (3382-18-1)	M+NH4 (138-59-0)			
136	2.58	186508	28132	389089	559456	32246		426837	MULTI						
154	3.357	172140		15363		7055		27865	MULTI						
344	21.119	170765		369991			14216		RHE	M+NH4 (14364-05-7)	M+NH4 (38963-94-9)	M+2Na-H (112-61-8)			
118	2.911	169777	26487			23782		1486319	KOC						
110	2.001	164735	79413	188280		172557		228365	MULTI						
132	3.754	155736	57902	90354	231007	22685	122996	314124	MULTI						
356	31.324	154530	2563				5322653		PHE	M+ (7224-60-4)	M+ (25342-82-9)	M+ (747366-57-0)	M+ (6872-88-4)	M+H (313476-83-4)	M+H (2934-97-6)
										M+NH4 (3621-36-1)	M+NH4 (3621-38-3)	M+2Na-H (85753-43-1)			
592	24.328	150431					323262		PHE	M+Na (105279-10-5)	2M+NH4 (84-26-4)				
519	6.466	146214			367339				SOP	2M+Na (641-39-4)	2M+Na (17801-36-4)	2M+Na (550-90-3)	2M+Na (519-02-8)	2M+Na (6882-68-4)	
243	11.875	145683	153718	47048	6815			39187	DIC	M+ (105988-99-6)	M+H (1419709-60-6)				

Appendix XV: Output from the EXCEL template for ions in positive ionization mode.

Step 1: The *m/z* value of ions in the HHCF LC-MS profile with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value, start time and end time of ions in the single botanical drug (SBD) [i.e. DIC, RHE, SOP, SCU, PHE, KOC] LC-MS profile. Criteria set in the match function are explained in section 2.3.3 and illustrated in Table 2.2.
Step 2: The *m/z* value of ions in the HHCF with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value of potential adduct ions of compounds in database Appendix XIV.

Step 1										**Step 2**					
HHCF			**Abundance in SBD (3 x average)**						**Source**	**Potential adduct ions of compounds in database (CAS no.)**					
m/z	**RT**	**Abundant**	**DIC**	**RHE**	**SOP**	**SCU**	**PHE**	**KOC**							
245	4.746	143811	3373	1231	678539	1227			SOP	M+H (486-89-5)	M+H (6882-66-2)				
268	3.754	139079	169467		10435	215550	232258	571892	KOC						
344	22.079	138110					135276	1520	PHE	M+ (NA)	M+ (18446-73-6)	M+H (857437-12-8)	M+2K-H (82992-78-7)		
130	2.58	137030	84237	271150	157266	292628		85964	MULTI						
144	2.58	135846	7143	6985	38326	444975		126470	SCU	No putative compound matched in database					
247	4.995	134996	13822	4375	962021	2620			SOP	M+H (46862-63-9)	M+H (68398-59-4)	M+H (6483-15-4)	M+K (1257392-35-0)		
215	3.357	122185		891894	168180	119659	59569	33507	RHE	M+Na (77-92-9)	M+Na (2373-79-7)	M+2Na-H (149-91-7)	M+2K-H (29656-58-4)		
160	2.762	114248	2984		444769				SOP						
263	11.478	111133			447927				SOP	M+H (1257392-34-9)	M+H (907607-58-3)	M+H (147731-96-2)	M+H (60394-92-5)	M+H (26904-64-3)	
759	26.263	110246					145099		PHE	2M+Na (1899-29-2)	2M+Na (40242-06-6)	2M+Na (1105047-98-0)	2M+Na (76144-80-4)	2M+Na (NA)	
151	2.911	109704	23435				281517		PHE						
116	2.58	108961	48921	44238	154686	230897		15703	SCU						
271	5.722	108171	2414	918	135776	1197			SOP	M+Na (641-39-4)	M+Na (17801-36-4)	M+Na (550-90-3)	M+Na (519-02-8)	M+Na (6882-68-4)	M+K (56293-29-9)
146	2.58	107179	30223	458696	36671	149812		53336	RHE						

Appendix XV: Output from the EXCEL template for ions in positive ionization mode.

Step 1: The *m/z* value of ions in the HHCF LC-MS profile with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value, start time and end time of ions in the single botanical drug (SBD) [i.e. DIC, RHE, SOP, SCU, PHE, KOC] LC-MS profile. Criteria set in the match function are explained in section 2.3.3 and illustrated in Table 2.2.
Step 2: The *m/z* value of ions in the HHCF with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value of potential adduct ions of compounds in database Appendix XIV.

Step 1										**Step 2**					
HHCF			**Abundance in SBD (3 x average)**						**Source**	**Potential adduct ions of compounds in database (CAS no.)**					
m/z	**RT**	**Abundant**	**DIC**	**RHE**	**SOP**	**SCU**	**PHE**	**KOC**							
263	11.296	104206			447927			5168	SOP	M+H (1257392-34-9)	M+H (907607-58-3)	M+H (147731-96-2)	M+H (60394-92-5)	M+H (26904-64-3)	
236	26.842	102089	1407	11573				328290	KOC						
157	2.58	101576			478526				SOP						
391	26.263	100678		958			78805		PHE	M+Na (1899-29-2)	M+Na (40242-06-6)	M+Na (1105047-98-0)	M+Na (76144-80-4)	M+Na (NA)	M+K (3486-67-7)
										M+K (NA)	M+2K-H (6871-67-6)	M+2K-H (6801-40-7)	M+2K-H (152230-57-4)		
188	11.296	100628	132061	120267		32103		159399	MULTI						
247	10.419	100117	12124	3505	1419943	2041		8586	SOP	M+H (46862-63-9)	M+H (68398-59-4)	M+H (6483-15-4)	M+K (1257392-35-0)		
191	3.357	97816			348758				SOP	M+H (485-35-8)					
132	3.936	96658	26017	90354	126630	22685		287323	KOC						

Appendix XVI: Output from the EXCEL template for ions in negative ionization mode.

Step 1: The *m/z* value of ions in the HHCF LC-MS profile with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value, start time and end time of ions in the single botanical drug (SBD) [i.e. DIC, RHE, SOP, SCU, PHE, KOC] LC-MS profile. Criteria set in the match function are explained in section 2.3.3 and illustrated in Table 2.2.
Step 2: The *m/z* value of ions in the HHCF with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value of potential adduct ions of compounds in database Appendix XIV.

Step 1										**Step 2**					
HHCF			**Abundance in SBD (3 x average)**						**Source**	**Potential adduct ions of compounds in database (CAS no.)**					
m/z	**RT**	**Abundance**	**DIC**	**RHE**	**SOP**	**SCU**	**PHE**	**KOC**							
255	8.707	1423375	465	362	1495362	318	376		SOP	M-H (35388-57-9)					
477	36.558	192644		105783	328	412			RHE	M-H (NA)	M-H (59282-56-3)	M-H (87075-18-1)	M+Cl (101840-48-6)	M+Cl (1257-08-5)	M+Na-2H (1801987-68-7)
										M+FA-H (266997-58-4)	M+FA-H (50488-89-6)	M+FA-H (33037-46-6)	M+FA-H (29090-10-6)	M+FA-H (38840-23-2)	M+FA-H (23313-21-5)
										2M+Na-2H (501-36-0)					
367	26.255	180349			183		132861		PHE	M-H (1899-29-2)	M-H (40242-06-6)	M-H (1105047-98-0)	M-H (76144-80-4)	M-H (NA)	M+Br (84-26-4)
										M+K-2H (163860-24-0)					
169	5.35	163454		359353					RHE	M-H (149-91-7)	M+Na-2H (140-10-3)	M+K-2H (104-55-2)			
735	26.255	161011					191245		PHE	2M-H (1899-29-2)	2M-H (40242-06-6)	2M-H (1105047-98-0)	2M-H (76144-80-4)	2M-H (NA)	
289	16.48	152137		148740	204	308		2202	RHE	M-H (154-23-4)	M-H (490-46-0)	M+Cl (481-74-3)	M+FA-H (NA)	M+FA-H (87087-60-3)	
511	8.707	138847			137270				SOP	2M-H (35388-57-9)					
541	39.204	105978		104136					RHE	M-H (105304-51-6)	M-H (64898-03-9)	M+K-2H (NA)	M+K-2H (597-12-6)		
371	21.095	93707		111074			2371		RHE	M+FA-H (14364-05-7)	M+FA-H (38963-94-9)	M-H2O-H (27208-80-6)	M-H2O-H (38963-95-0)		

Appendix XVI: Output from the EXCEL template for ions in negative ionization mode.

Step 1: The *m/z* value of ions in the HHCF LC-MS profile with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value, start time and end time of ions in the single botanical drug (SBD) [i.e. DIC, RHE, SOP, SCU, PHE, KOC] LC-MS profile. Criteria set in the match function are explained in section 2.3.3 and illustrated in Table 2.2.
Step 2: The *m/z* value of ions in the HHCF with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value of potential adduct ions of compounds in database Appendix XIV.

Step 1										**Step 2**					
HHCF			**Abundance in SBD (3 x average)**						**Source**	**Potential adduct ions of compounds in database (CAS no.)**					
m/z	**RT**	**Abundance**	**DIC**	**RHE**	**SOP**	**SCU**	**PHE**	**KOC**							
477	34.573	92717		84975					RHE	M-H (NA)	M-H (59282-56-3)	M-H (87075-18-1)	M+Cl (101840-48-6)	M+Cl (1257-08-5)	M+Na-2H (1801987-68-7)
										M+FA-H (266997-58-4)	M+FA-H (50488-89-6)	M+FA-H (33037-46-6)	M+FA-H (29090-10-6)	M+FA-H (38840-23-2)	M+FA-H (23313-21-5)
										2M+Na-2H (501-36-0)					
303	24.717	79858				350347			SCU	M-H (NA)	M-H (1402054-86-7)	M-H (NA)			
331	4.077	76311		172497		430			RHE	M-H (NA)	M-H (91984-84-8)	M-H (84274-52-2)	M-H (261510-23-0)	M-H (13405-60-2)	M-H (34781-46-9)
										2M-H (552-41-0)	M+Na-2H (40004-96-4)	M+FA-H (481-73-2)	M+FA-H (520-18-3)	M+FA-H (314255-80-6)	
269	71.024	73643		269	261	72017			SCU	M-H (28013-27-6)	M-H (491-67-8)	M-H (929064)	M-H (73046-40-9)	M-H2O-H (NA)	M-H2O-H (479-54-9)
										M-H2O-H (80604-16-6)	M-H2O-H (116301-03-2)				
243	88.34	71786		944		1342	1395		MULTI						
115	2.77	69721		58948	61463	102725	91447		MULTI						
579	16.48	69374		82286					RHE	2M-H (154-23-4)	2M-H (490-46-0)	M+K-2H (105304-51-6)	M+K-2H (64898-03-9)	M-H2O-H (1374014-37-5)	
301	32.06	65848				90051		1453	SCU	M-H (NA)	M-H (92519-95-4)	M-H (92519-97-6)	M-H (NA)	M-H (92519-96-5)	M+FA-H (NA)

Appendix XVI: Output from the EXCEL template for ions in negative ionization mode.

Step 1: The *m/z* value of ions in the HHCF LC-MS profile with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value, start time and end time of ions in the single botanical drug (SBD) [i.e. DIC, RHE, SOP, SCU, PHE, KOC] LC-MS profile. Criteria set in the match function are explained in section 2.3.3 and illustrated in Table 2.2.
Step 2: The *m/z* value of ions in the HHCF with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value of potential adduct ions of compounds in database Appendix XIV.

Step 1										**Step 2**					
HHCF			**Abundance in SBD (3 x average)**						**Source**	**Potential adduct ions of compounds in database (CAS no.)**					
m/z	**RT**	**Abundance**	**DIC**	**RHE**	**SOP**	**SCU**	**PHE**	**KOC**							
										M+FA-H (480-39-7)					
191	2.456	63734		13758	7644	11462	220323		PHE						
367	18.151	58854					139589		PHE	M-H (1899-29-2)	M-H (40242-06-6)	M-H (1105047-98-0)	M-H (76144-80-4)	M-H (NA)	M+Br (84-26-4)
										M+K-2H (163860-24-0)					
191	3.498	53495		19233	16170	9127	62298		PHE						
111	3.25	50162		41679	53626	72292	31649		MULTI						
128	3.498	49057		79443	24498	61036	24820		MULTI						
435	26.652	45957		41113	158		4491		RHE	M-H (60-81-1)	2M-H (94356-33-9)	M+FA-H (27208-80-6)	M+FA-H (38963-95-0)		
229	28.157	44934					1052		PHE	M+Cl (1135-24-6)	M+Na-2H (102-37-4)				
385	30.422	44226		371	393	318	66055		PHE						
331	4.606	44019		156291			431	5158	RHE	M-H (NA)	M-H (91984-84-8)	M-H (84274-52-2)	M-H (261510-23-0)	M-H (13405-60-2)	M-H (34781-46-9)
										2M-H (552-41-0)	M+Na-2H (40004-96-4)	M+FA-H (481-73-2)	M+FA-H (520-18-3)	M+FA-H (314255-80-6)	
195	2.34	41954		44085	17726	6379	22659		MULTI						

Appendix XVI: Output from the EXCEL template for ions in negative ionization mode.

Step 1: The *m/z* value of ions in the HHCF LC-MS profile with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value, start time and end time of ions in the single botanical drug (SBD) [i.e. DIC, RHE, SOP, SCU, PHE, KOC] LC-MS profile. Criteria set in the match function are explained in section 2.3.3 and illustrated in Table 2.2.
Step 2: The *m/z* value of ions in the HHCF with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value of potential adduct ions of compounds in database Appendix XIV.

Step 1										**Step 2**					
HHCF			**Abundance in SBD (3 x average)**						**Source**	**Potential adduct ions of compounds in database (CAS no.)**					
m/z	**RT**	**Abundance**	**DIC**	**RHE**	**SOP**	**SCU**	**PHE**	**KOC**							
353	16.48	40567				264	46294		PHE	M-H (327-97-9)	M-H (906-33-2)	M-H (26297-11-0)	M+Br (153789-69-6)	M+K-2H (74950-96-2)	M-H2O-H (118-34-3)
541	38.427	39129		46117					RHE	M-H (105304-51-6)	M-H (64898-03-9)	M+K-2H (NA)	M+K-2H (597-12-6)		
301	45.075	37816				71601			SCU	M-H (NA)	M-H (92519-95-4)	M-H (92519-97-6)	M-H (NA)	M-H (92519-96-5)	M+FA-H (NA)
										M+FA-H (480-39-7)					
239	18.151	36526			87702				SOP	M+Cl (6220-47-9)					
955	36.558	36210		46560					RHE	2M-H (NA)	2M-H (59282-56-3)	2M-H (87075-18-1)			
193	2.34	36130		1183	616	89734	2978		SCU	M-H (1135-24-6)					
431	58.935	34275		68157		989		518	RHE	M-H (266997-58-4)	M-H (50488-89-6)	M-H (33037-46-6)	M-H (29090-10-6)	M-H (38840-23-2)	M-H (23313-21-5)
										M+Cl (94356-36-2)	M+K-2H (30861-27-9)	M+K-2H (23566-96-3)	M+FA-H (666849-46-3)	M-H2O-H (1184734-25-5)	
533	8.707	34067			25176		377		SOP	M+Br (270249-38-2)	M+Br (99217-65-9)	M+FA-H (60679-70-1)	2M+FA-H (486-89-5)	2M+FA-H (6882-66-2)	2M+Na-2H (35388-57-9)
331	3.498	33119		104927	986	1289	647		RHE	M-H (NA)	M-H (91984-84-8)	M-H (84274-52-2)	M-H (261510-23-0)	M-H (13405-60-2)	M-H (34781-46-9)
										2M-H (552-41-0)	M+Na-2H (40004-96-4)	M+FA-H (481-73-2)	M+FA-H (520-18-3)	M+FA-H (314255-80-6)	

Appendix XVI: Output from the EXCEL template for ions in negative ionization mode.

Step 1: The *m/z* value of ions in the HHCF LC-MS profile with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value, start time and end time of ions in the single botanical drug (SBD) [i.e. DIC, RHE, SOP, SCU, PHE, KOC] LC-MS profile. Criteria set in the match function are explained in section 2.3.3 and illustrated in Table 2.2.
Step 2: The *m/z* value of ions in the HHCF with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value of potential adduct ions of compounds in database Appendix XIV.

Step 1										**Step 2**					
HHCF			**Abundance in SBD (3 x average)**						**Source**	**Potential adduct ions of compounds in database (CAS no.)**					
m/z	**RT**	**Abundance**	**DIC**	**RHE**	**SOP**	**SCU**	**PHE**	**KOC**							
113	16.48	32899		28033	11899	11235	15595		MULTI						
113	26.652	32190		24822	11186	9923	5179		MULTI						
431	46.911	31595		30540					RHE	M-H (266997-58-4)	M-H (50488-89-6)	M-H (33037-46-6)	M-H (29090-10-6)	M-H (38840-23-2)	M-H (23313-21-5)
										M+Cl (94356-36-2)	M+K-2H (30861-27-9)	M+K-2H (23566-96-3)	M+FA-H (666849-46-3)	M-H2O-H (1184734-25-5)	
331	5.35	29081		92487	327	640	431	3679	RHE	M-H (NA)	M-H (91984-84-8)	M-H (84274-52-2)	M-H (261510-23-0)	M-H (13405-60-2)	M-H (34781-46-9)
										2M-H (552-41-0)	M+Na-2H (40004-96-4)	M+FA-H (481-73-2)	M+FA-H (520-18-3)	M+FA-H (314255-80-6)	
547	37.253	29059				64881			SCU	M-H (1884390-97-9)	M-H (185145-33-9)	M-H (185145-34-0)	M-H (1884390-98-0)	M-H (1884395-07-6)	M-H (1884395-06-5)
491	55.478	28968		179	95651				SOP	2M-H (46862-63-9)	2M-H (68398-59-4)	2M-H (6483-15-4)	M+Cl (99119-71-8)	M+FA-H (6807-83-6)	
113	88.257	28426		11246		14143	15307		MULTI						
176	89.365	28382					352		PHE						
233	63.946	27285		68849		156			RHE	M-H (NA)	M-H (94356-34-0)	M-H (94356-35-1)			
439	21.095	25268		22382			465		RHE	M+Cl (30197-14-9)	M+Na-2H (8015-61-0)	M+Na-2H (696663-58-8)	M+FA-H (30861-27-9)	M+FA-H (23566-96-3)	

Appendix XVI: Output from the EXCEL template for ions in negative ionization mode.

Step 1: The *m/z* value of ions in the HHCF LC-MS profile with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value, start time and end time of ions in the single botanical drug (SBD) [i.e. DIC, RHE, SOP, SCU, PHE, KOC] LC-MS profile. Criteria set in the match function are explained in section 2.3.3 and illustrated in Table 2.2.
Step 2: The *m/z* value of ions in the HHCF with abundance > 1.5% of the ion that was present at the highest abundance was matched against the *m/z* value of potential adduct ions of compounds in database Appendix XIV.

Step 1										**Step 2**					
HHCF			**Abundance in SBD (3 x average)**						**Source**	**Potential adduct ions of compounds in database (CAS no.)**					
m/z	**RT**	**Abundance**	**DIC**	**RHE**	**SOP**	**SCU**	**PHE**	**KOC**							
113	52.997	25251		7533	13415	10841	10098		MULTI						
113	17.01	24921		28033	11899	11235	15595		MULTI						
289	22.765	24703		58878	135	281		2226	RHE	M-H (154-23-4)	M-H (490-46-0)	M+Cl (481-74-3)	M+FA-H (NA)	M+FA-H (87087-60-3)	
223	2.456	24323		10280	36958	10687	9856	17964	SOP	M-H2O-H (6882-66-2)					
547	34.573	24147			222	55016			SCU	M-H (1884390-97-9)	M-H (185145-33-9)	M-H (185145-34-0)	M-H (1884390-98-0)	M-H (1884395-07-6)	M-H (1884395-06-5)
337	22.765	23838					70985		PHE	M-H (3621-36-1)	M-H (3621-38-3)	M+Na-2H (74950-96-2)	M+K-2H (10338-51-9)	M-H2O-H (7224-60-4)	M-H2O-H (25342-82-9)
										M-H2O-H (747366-57-0)	M-H2O-H (6872-88-4)				
580	16.48	22800		27468					RHE						
113	19.457	21577		29056		11498	9159		MULTI						
125	5.35	4698276		34431		262			RHE	M+Cl (144-62-7)	M+Cl (50-21-5)				
577	13.88	666824		56527	129	199			RHE	M+Cl (105304-51-6)	M+Cl (64898-03-9)				
441	34.573	3305249		58725			407		RHE	M-H (101840-48-6)	M-H (1257-08-5)	M+Na-2H (155-58-8)	M+K-2H (30197-14-9)	M+FA-H (94356-36-2)	M-H2O-H (NA)
										M-H2O-H (1562421-28-6)					

Appendix XVII Ions present in the HHCF and more than one composing botanical drugs.

(Only ions with abundance > 1.5% of the ion which was present in the greatest amount were listed.)

R_t (min)	Ionization mode	Measured (m/z)	Source	Putative identity	Reference
2.00	Positive	110	DIC, RHE, SCU, KOC	NA	NA
2.34	Negative	195	RHE, SOP, SCU, PHE	Gluconic acid/Galactonic acid	(Institute of Food Research, n.d.)
2.58	Positive	136	DIC, RHE, SOP, SCU, KOC	Adenine	
2.58	Positive	130	DIC, RHE, SOP, SCU, KOC	Pyroglutamic acid	
2.76	Positive	130	DIC, RHE, SOP, SCU, KOC	NA	NA
2.77	Negative	133	RHE, SOP, SCU, PHE	Malic acid	(Institute of Food Research, n.d.)
2.77	Negative	115	RHE, SOP, SCU, PHE	Fumaric acid	
3.25	Negative	191	RHE, SOP, SCU, PHE	Citric acid/Isocitric acid	
3.25	Negative	111	RHE, SOP, SCU, PHE	Fragment from citric acid/isocitric acid	
3.36	Positive	137	SCU, PHE, KOC	Hypoxanthine/4-Hydroxyacetophenone	
3.36	Positive	154	RHE, SCU, KOC	Dopamine	
3.50	Negative	128	RHE, SOP, SCU, PHE	NA	NA
3.75	Positive	132	DIC, RHE, SOP, SCU, PHE, KOC	Hydroxyproline/Isoleucine/Leucine/Norleucine	(Institute of Food Research, n.d.)
11.30	Positive	188	DIC, RHE, SCU, KOC	NA	NA
16.48	Negative	113	RHE, SOP, SCU, PHE	NA	NA
17.01	Negative	113	RHE, SOP, SCU, PHE	NA	NA
19.46	Negative	113	RHE, SCU, PHE	NA	NA
26.65	Negative	113	RHE, SOP, SCU, PHE	NA	NA
52.60	Negative	113	RHE, SOP, SCU, PHE	NA	NA
88.26	Negative	113	RHE, SCU, PHE	NA	NA
88.26	Negative	103	SCU, PHE	NA	NA
88.34	Negative	243	RHE, SCU, PHE	NA	NA

Appendix XVIII Reported and percentage of fragment ions of compounds putatively identified in the HHCF by LC-MS/MS in positive ionization mode.

R_t (min)	No.	*m/z*	Adduct ion(s)	MS/MS fragment ions (*m/z*)	Source	Identity	Reported MS or MS/MS fragments (CE=collision energy)
2.58	**NA**	116	NA	NA	PHE	NA	NA
	NA	118	NA	NA	KOC	NA	NA
	NA	144	NA	NA	SCU	NA	NA
	NA	146	NA	NA	RHE	NA	NA
	NA	157	NA	NA	SOP	NA	NA
2.76	**NA**	118	NA	NA	KOC	NA	NA
	NA	136	NA	NA	KOC	NA	NA
	NA	160	NA	NA	SOP	NA	NA
	NA	166	NA	NA	KOC	NA	NA
2.91	**NA**	118	NA	NA	KOC	NA	NA
	NA	150	NA	NA	PHE	NA	NA
	NA	151	NA	NA	PHE	NA	NA
3.36	**P1**	191	$[M+H]^+$	191 (100%), 148 (25.73%), 162 (0.26%)	SOP	Cytisine	$MS^{n=2-4}$ [191] (CE: 50%) *m/z*(%): 148(100) (Liu et al., 2011)
	P2	196	$[M]^+$	196 (100%), 119 (67.72%), 137 (57.19%), 109 (2.33%), 151 (2.14%), 178 (0.83%), 114 (0.63%), 153 (0.41%), 107 (0.3%), 110 (0.29%)	PHE	Atraric aid	MS (CE: NA) *m/z*(%): 196(40), 164(60), 136(100) (Quintal-Novelo et al., 2013) MS (CE: NA) *m/z* (%): 196(14), 178(20), 150(100), 122(14), 83(25) (Choudhary et al., 2011)
	P3	205	$[M+H]^+$	205 (100%), 108 (1.79%), 110 (1.6%), 146 (1.57%), 162 (0.82%), 157 (0.67%), 990 (0.63%), 164 (0.48%), 160 (0.42%), 147 (0.28%), 204 (0.26%), 134 (0.25%), 144 (0.21%), 133 (0.18%), 161 (0.15%), 122 (0.13%), 148 (0.13%), 176 (0.13%)	SOP	N-Methylcytisine	MS^2 [205](CE: 10-30eV)) *m/z*: 205, 162, 146, 108, 58 (Wang et al., 2010a) $MS^{n=2-4}$ [205](CE: 50%) *m/z*(%): 146(91), 108(100) (Liu et al., 2011)
	P4	215	$[M]^+$	215 (100%), 169 (54.49%), 142 (11.88%), 141 (9.18%), 125 (8.06%), 171 (7.82%), 107 (5.42%), 112 (4.97%), 214 (3.64%), 136 (2.96%), 130 (2.47%)	RHE	Mecoprop	MS (CE:NA) *m/z*: 216, 214, 144, 142, 169, 107, 89, 77 (Brzezinka and Bertram, 2002)

Appendix XVIII Reported and percentage of fragment ions of compounds putatively identified in the HHCF by LC-MS/MS in positive ionization mode.

R_t (min)	No.	*m/z*	Adduct ion(s)	MS/MS fragment ions (*m/z*)	Source	Identity	Reported MS or MS/MS fragments (CE=collision energy)
	P5	261	$[M+H]^+$	261 (100%), 114 (29.86%), 243 (3.4%), 164 (1.57%), 146 (0.6%), 166 (0.41%), 110 (0.31%), 134 (0.31%), 148 (0.29%), 215 (0.25%), 122 (0.23%), 113 (0.22%), 162 (0.2%), 108 (0.19%), 150 (0.17%), 152 (0.16%), 241 (0.15%), 156 (0.14%), 132 (0.13%), 131 (0.12%), 120 (0.12%), 171 (0.11%), 260 (0.1%), 160 (0.09%), 172 (0.09%), 200 (0.08%), 129 (0.07%), 138 (0.07%), 136 (0.05%), 109 (0.04%), 168 (0.04%), 135 (0.04%), 133 (0.04%), 104 (0.03%), 225 (0.03%)	SOP	Baptifoline	$MS^{n=2-4}$[261](CE: 50%) *m/z*(%): 243(44), 164(24), 114(100) (Liu et al., 2011)
3.75	**NA**	121	NA	NA	PHE	NA	NA
	P6	265	$[M+H]^+$	265 (100%), 247 (2.98%), 263 (2.5%), 112 (2.49%), 164 (2.17%), 264 (2.1%), 245 (1.92%), 166 (1.78%), 176 (1.59%), 236 (1.44%), 262 (1.44%), 148 (1.32%), 175 (1.18%), 120 (0.93%), 163 (0.92%), 121 (0.79%), 131 (0.78%), 154 (0.75%), 124 (0.73%), 123 (0.7%), 150 (0.65%), 136 (0.59%), 162 (0.54%), 219 (0.52%), 190 (0.36%), 109 (0.33%), 122 (0.3%), 138 (0.26%)	SOP	5α-Hydroxymatrine OR 9α-Hydroxymatrine	5α-Hydroxymatrine: MS (CE: NA) *m/z*(%): 264(87), 263(29), 247(100), 246(24), 222(6), 221(26), 208(4), 193(10), 166(15), 112(3), 120(35), 98(4), 96(36) (2013) MS (CE: NA) *m/z*(%): 264(59), 248(12), 247(100), 245(45), 235(6), 222(12), 221(29), 208(5), 193(12), 178(3), 166(16), 153(6), 152(10), 148(12), 125(6), 112(30), 96(36), 55(20), 41(18) (Chen and Ding, 2005) 9α-Hydroxymatrine: $MS^{n=2-4}$ [265] (CE: 50%) *m/z*(%): 247(52), 150(63), 148(100), 112(20) (Liu et al., 2011) MS (CE: NA) *m/z*(%): 264(100), 263(67), 247(16), 246(5), 235(9), 222(10), 221(13), 219(21), 208(15), 205(84), 193(19), 178(8), 166(35), 164(22), 153(10), 152(10), 114(11), 112(18), 98(9), 96(43), 55(28), 41(24) (Chen and Ding, 2005)
	NA	268	NA	NA	KOC	NA	NA
3.94	**NA**	132	NA	NA	KOC	NA	NA
		164	NA	NA	KOC	NA	NA
4.15	**P7**	265	$[M+H]^+$	265 (100%), 247 (7.28%), 150 (5.59%), 148 (5.25%), 112 (2.24%), 176 (1.29%), 122 (1.15%), 188 (0.54%), 110 (0.49%), 120 (0.39%), 245 (0.36%), 136 (0.35%), 242 (0.3%), 152 (0.29%), 162 (0.26%), 230 (0.25%), 202 (0.24%), 134 (0.23%), 217	SOP	14β-Hydroxymatrine	MS (CE: NA) *m/z*: 247, 246, 192, 177, 150, 137, 136, 96 (Lourenço et al., 2002)

Appendix XVIII Reported and percentage of fragment ions of compounds putatively identified in the HHCF by LC-MS/MS in positive ionization mode.

R_t (min)	No.	*m/z*	Adduct ion(s)	MS/MS fragment ions (*m/z*)	Source	Identity	Reported MS or MS/MS fragments (CE=collision energy)
				(0.22%), 201 (0.22%), 133 (0.22%), 263 (0.22%), 190 (0.2%), 127 (0.2%), 229 (0.19%), 146 (0.18%), 219 (0.18%), 173 (0.16%), 131 (0.15%), 193 (0.15%), 145 (0.15%), 161 (0.14%), 124 (0.14%), 138 (0.13%), 218 (0.13%), 121 (0.13%), 174 (0.12%), 164 (0.12%), 168 (0.12%), 264 (0.12%), 204 (0.11%), 160 (0.1%), 179 (0.06%), 132 (0.05%), 163 (0.05%), 153 (0.05%), 246 (0.05%), 108 (0.04%), 111 (0.03%), 206 (0.03%), 200 (0.03%)			MS (CE: NA) *m/z*(%): 265(19), 264(100), 263(72), 247(3), 246(4), 235(13), 222(48), 221(55), *218*(30), 193(57), 192(26), 178(20), 177(19), 162(10), 150(29), 149(15), 148(17), 137(14), 136(21), 122(12), 109(8), 98(12), 96(33), 80(8), 55(9), 41(11) (Chen and Ding, 2005)
	NA	132	NA	NA	KOC	NA	NA
4.40	**P8**	180	$[M]^+$	121 (100%), 180 (16.62%), 103 (2.44%), 120 (0.11%), 151 (0.08%), 119 (0.05%)	PHE	Candicine	MS^2[180] (CE:NA) *m/z*: 150, 133, 122, 119, 70 (Yan et al., 2015) MS^2[180] (CE:NA) *m/z*: 121, 60; MS^3(180 à 121) (CE:NA) *m/z*: 121, 103, 95, 93, 91, 77 (Servillo et al., 2014)
	NA	121	NA	NA	PHE	NA	NA
4.75	**P9**	245	$[M+H]^+$	245 (100%), 150 (4.52%), 199 (3.76%), 162 (3.75%), 148 (3%), 158 (2.26%), 110 (2.14%), 122 (2%), 124 (1.6%), 145 (1.54%), 175 (1.54%), 228 (1.33%), 105 (1.26%), 174 (1.23%), 191 (1.2%), 136 (1.03%), 177 (0.94%), 125 (0.94%), 118 (0.93%), 217 (0.89%), 160 (0.63%), 202 (0.52%), 227 (0.38%)	SOP	Anagyrine	$MS^{n=2-4}$ [245] (CE: 50%) *m/z*: 148(100), 98(23) (Liu et al., 2011)
	P10	265	$[M+H]^+$	265 (100%), 168 (28.79%), 247 (8.6%), 150 (8.32%), 112 (3.93%), 148 (3.42%), 122 (0.87%), 188 (0.81%), 176 (0.57%), 136 (0.53%), 230 (0.53%), 206 (0.29%), 131 (0.25%), 160 (0.22%), 220 (0.21%), 134 (0.2%), 216 (0.2%), 124 (0.19%), 105 (0.19%), 167 (0.18%), 263 (0.18%), 190 (0.17%), 140 (0.16%), 107 (0.16%), 135 (0.16%), 204 (0.16%), 120 (0.15%), 195 (0.15%), 143 (0.13%), 248 (0.13%), 162 (0.13%), 184 (0.13%), 166 (0.13%), 165 (0.12%), 138 (0.12%), 110 (0.12%), 164 (0.12%), 229 (0.11%), 178 (0.11%), 132 (0.11%), 266 (0.1%), 100 (0.08%), 264 (0.08%), 183 (0.06%), 159 (0.06%), 192 (0.05%), 175 (0.04%)	SOP	5α-Hydroxymatrine OR 9α-Hydroxymatrine	5α-Hydroxymatrine: MS (CE: NA) *m/z*(%): 264(87), 263(29), 247(100), 246(24), 222(6), 221(26), 208(4), 193(10), 166(15), 112(3), 120(35), 98(4), 96(36) (2013) MS (CE: NA) *m/z*(%): 264(59), 248(12), 247(100), 245(45), 235(6), 222(12), 221(29), 208(5), 193(12), 178(3), 166(16), 153(6), 152(10), 148(12), 125(6), 112(30), 96(36), 55(20), 41(18) (Chen and Ding, 2005) 9α-Hydroxymatrine: $MS^{n=2-4}$ [265] (CE: 50%) *m/z*(%): 247(52), 150(63), 148(100), 112(20) (Liu et al., 2011) MS (CE: NA) *m/z*(%): 264(100), 263(67), 247(16), 246(5), 235(9), 222(10), 221(13),

Appendix XVIII Reported and percentage of fragment ions of compounds putatively identified in the HHCF by LC-MS/MS in positive ionization mode.

R_t (min)	No.	*m/z*	Adduct ion(s)	MS/MS fragment ions (*m/z*)	Source	Identity	Reported MS or MS/MS fragments (CE=collision energy)
							219(21), 208(15), 205(84), 193(19), 178(8), 166(35), 164(22), 153(10), 152(10), 114(11), 112(18), 98(9), 96(43), 55(28), 41(24) (Chen and Ding, 2005)
5.00	**P11**	247	$[M+H]^+$	247 (100%), 150 (33.66%), 148 (10.26%), 188 (2.07%), 122 (1.78%), 158 (0.75%), 105 (0.72%), 121 (0.7%), 134 (0.66%), 112 (0.61%), 149 (0.59%), 246 (0.58%), 110 (0.44%), 176 (0.42%), 147 (0.32%), 160 (0.31%), 136 (0.26%), 245 (0.22%), 129 (0.17%), 111 (0.15%)	SOP	Isosophocarpine	$MS^{n=2-4}$ [247] (CE: 50%) *m/z*(%): 179(100), 150(90), 148(51), 136(72) (Liu et al., 2011)
	NA	178	NA	NA	KOC	NA	NA
5.52	**P12**	263	$[M+H]^+$	150 (100%), 263 (41.59%), 148 (4.71%), 245 (3.13%), 128 (2.6%), 166 (2.52%), 125 (1.94%), 175 (1.93%), 153 (1.61%), 122 (1.47%), 191 (1.39%), 164 (1.33%), 110 (1.25%), 227 (1.22%), 119 (1.01%), 107 (0.97%), 235 (0.85%), 165 (0.84%), 146 (0.84%), 171 (0.46%), 103 (0.4%), 130 (0.36%), 188 (0.36%), 121 (0.34%), 186 (0.33%), 147 (0.32%)	SOP	(-)-9α-hydroxy-7, 11-dehydromatrine	NA
5.72	**P13**	192	$[M+H]^+$	192 (100%), 177 (42.56%), 149 (2.94%), 148 (2.54%), 176 (0.91%), 151 (0.48%), 147 (0.43%), 163 (0.35%), 161 (0.33%), 174 (0.32%), 133 (0.19%), 159 (0.19%), 119 (0.18%), 160 (0.16%), 132 (0.13%)	PHE	Noroxyhydrastinine	MS^2 [192] (CE:NA): 163, 160, 151, 60 (Yan et al., 2015)
	P14	249	$[M+H]^+$	249 (100%), 247 (1.8%), 148 (1.8%), 150 (0.81%), 112 (0.39%), 176 (0.33%), 110 (0.26%), 136 (0.25%), 138 (0.2%), 152 (0.2%), 218 (0.15%), 231 (0.14%), 190 (0.13%), 122 (0.12%), 166 (0.11%), 114 (0.11%), 204 (0.1%), 162 (0.09%), 232 (0.05%), 199 (0.02%), 120 (0.02%), 134 (0.02%), 158 (0.01%), 149 (0.01%), 133 (0.01%), 250 (0.01%), 147 (0%), 220 (0%)	SOP	Allomatrine OR Isomatrine OR Matrine OR Sophoridine	Allomatrine: MS(CE: NA) *m/z*(%): 249(8), 248(51), 247(100), 219(2), 205(4), 192(1), 177(37), 162(3), 150(28), 149(10), 148(9), 137(5), 136(15), 122(5), 109(2), 98(3), 96(7), 55(5), 41(4) (Chen and Ding, 2005) Matrine: $MS^{n=2-4}$ [249] (CE: 50%) *m/z*(%): 176(100), 150(10), 148(5) (Liu et al., 2011) Isomatrine: $MS^{n=2-4}$ [249] (CE: 50%) *m/z*(%): 176(100), 150(15), 148(10) (Liu et al., 2011) Sophoridine: $MS^{n=2-4}$ [249] (CE: 50%) *m/z*(%): 176(100), 150(15), 148(10) (Liu et al., 2011)
		519	$[2M+Na]^+$	271 (100%), 519 (1.67%), 314 (0.27%), 272 (0.15%)			
		497	$[2M+H]^+$	249 (100%), 351 (0.77%), 247 (0.44%), 150 (0.29%), 121 (0.11%)			
		271	$[M+Na]^+$	No fragment ion			

Appendix XVIII Reported and percentage of fragment ions of compounds putatively identified in the HHCF by LC-MS/MS in positive ionization mode.

R_t (min)	No.	*m/z*	Adduct ion(s)	MS/MS fragment ions (*m/z*)	Source	Identity	Reported MS or MS/MS fragments (CE=collision energy)
6.47	**P15**	247	$[M+H]^+$	247 (100%), 179 (6.18%), 245 (5.01%), 136 (3.66%), 150 (2.64%), 148 (0.75%), 229 (0.62%), 138 (0.56%), 110 (0.37%), 152 (0.3%), 122 (0.27%), 108 (0.26%), 230 (0.25%), 174 (0.23%), 149 (0.21%), 176 (0.2%), 134 (0.19%), 112 (0.17%), 162 (0.15%), 164 (0.14%), 188 (0.13%), 146 (0.13%), 216 (0.1%), 228 (0.1%), 226 (0.1%), 204 (0.09%), 218 (0.04%), 144 (0.04%), 178 (0.04%), 227 (0.04%), 131 (0.03%), 105 (0.02%), 201 (0.01%)	SOP	Sophocarpine	$MS^{n=2-4}$ [247] (CE: 50%) *m/z*(%): 227(19), 179(100), 150(93), 148(40), 136(63) (Liu et al., 2011) MS^2[247] (CE:30eV) *m/z*: 247, 228, 179, 160, 150, 136, 122, 108, 96 (Wu et al., 2013b)
	P16	249	$[M+H]^+$	249 (100%), 150 (0.59%), 152 (0.55%), 247 (0.5%), 112 (0.36%), 148 (0.32%), 180 (0.22%), 136 (0.18%), 178 (0.18%), 176 (0.16%), 110 (0.15%), 190 (0.13%), 122 (0.11%), 218 (0.1%), 138 (0.09%), 220 (0.08%), 135 (0.08%), 231 (0.07%), 120 (0.06%), 162 (0.06%), 114 (0.06%), 124 (0.03%), 106 (0.03%), 166 (0.03%), 195 (0.02%), 149 (0.01%), 174 (0.01%), 131 (0.01%), 186 (0.01%), 177 (0.01%)	SOP	Allomatrine OR Isomatrine OR Matrine OR Sophoridine	Allomatrine: MS(CE: NA) *m/z*(%): 249(8), 248(51), 247(100), 219(2), 205(4), 192(1), 177(37), 162(3), 150(28), 149(10), 148(9), 137(5), 136(15), 122(5), 109(2), 98(3), 96(7), 55(5), 41(4) (Chen and Ding, 2005) Matrine: $MS^{n=2-4}$ [249] (CE: 50%) *m/z*(%): 176(100), 150(10), 148(5) (Liu et al., 2011) Isomatrine: $MS^{n=2-4}$ [249] (CE: 50%) *m/z*(%): 176(100), 150(15), 148(10) (Liu et al., 2011) Sophoridine: $MS^{n=2-4}$ [249] (CE: 50%) *m/z*(%): 176(100), 150(15), 148(10) (Liu et al., 2011)
		250	$[M+2H]^+$	250 (100%), 249 (0.83%), 151 (0.72%), 248 (0.61%), 112 (0.51%), 153 (0.45%), 149 (0.4%), 150 (0.38%), 113 (0.34%), 190 (0.26%), 152 (0.25%), 179 (0.24%), 165 (0.23%), 204 (0.23%), 181 (0.23%), 178 (0.19%), 134 (0.19%), 122 (0.19%), 135 (0.17%), 136 (0.16%), 163 (0.16%), 148 (0.16%), 177 (0.15%), 219 (0.13%), 191 (0.13%), 110 (0.12%), 160 (0.12%), 189 (0.11%), 120 (0.1%), 180 (0.09%), 137 (0.09%), 147 (0.08%), 232 (0.07%), 123 (0.07%), 108 (0.06%), 111 (0.05%), 129 (0.05%), 176 (0.05%), 251 (0.04%)			
		519	$[2M+Na]^+$	271 (100%), 272 (1.89%), 519 (1.3%), 273 (1.09%), 270 (0.51%), 269 (0.25%)			
		497	$[2M+H]^+$	249 (100%), 250 (3.68%), 251 (2.71%), 248 (0.82%), 247 (0.6%), 232 (0.59%), 120 (0.42%), 283 (0.24%)			
8.02	**P17**	263	$[M+H]^+$	263 (100%), 245 (16.22%), 150 (4.09%), 136 (3.05%), 138 (2.57%), 246 (2.44%), 203 (2.43%), 177 (1.41%), 110 (1.33%), 137 (1.14%), 148 (0.88%), 159 (0.79%), 149 (0.72%), 122 (0.58%), 134 (0.55%), 162 (0.49%), 217 (0.48%), 231 (0.48%), 227 (0.47%), 195 (0.44%), 228 (0.39%), 160 (0.38%), 161 (0.36%), 174 (0.35%), 218 (0.34%), 109 (0.32%), 146 (0.31%), 124 (0.3%), 186 (0.3%), 135 (0.29%), 191 (0.27%), 151 (0.27%), 178 (0.26%), 163 (0.19%), 202 (0.19%), 189 (0.19%), 147 (0.19%), 187 (0.18%), 108 (0.18%), 112 (0.18%), 131 (0.15%), 166 (0.15%), 188 (0.15%), 176 (0.15%), 190 (0.15%), 132 (0.15%), 123 (0.15%), 175 (0.14%), 164 (0.13%), 200 (0.12%), 111 (0.11%), 216 (0.11%), 205 (0.1%), 204 (0.1%), 229 (0.1%), 243 (0.1%), 120 (0.1%), 168 (0.09%), 130 (0.08%), 172 (0.08%), 125 (0.08%), 133 (0.07%), 265 (0.05%), 121 (0.04%), 139 (0.03%), 201 (0.02%), 165	SOP	Oxysophocarpine	$MS^{n=2-4}$ [263] (CE: 50%): 245(100), 150(53), 138(39) (Liu et al., 2011)

Appendix XVIII Reported and percentage of fragment ions of compounds putatively identified in the HHCF by LC-MS/MS in positive ionization mode.

R_t (min)	No.	*m/z*	Adduct ion(s)	MS/MS fragment ions (*m/z*)	Source	Identity	Reported MS or MS/MS fragments (CE=collision energy)
				(0.02%), 262 (0.01%), 261 (0.01%), 157 (0.01%), 106 (0.01%), 158 (0.01%), 142 (0.01%), 235 (0.01%)			
		525	$[2M+H]^+$	263 (100%), 525 (1.69%), 245 (0.44%), 465 (0.24%), 246 (0.14%), 265 (0.14%), 150 (0.12%), 393 (0.09%), 136 (0.07%), 149 (0.06%), 203 (0.05%), 331 (0.04%), 138 (0.04%)			
	P18	265	$[M+H]^+$	265 (100%), 247 (6.37%), 205 (4.4%), 148 (3.69%), 136 (2.5%), 248 (2.21%), 137 (1.65%), 150 (1.57%), 162 (0.97%), 206 (0.92%), 220 (0.91%), 176 (0.86%), 177 (0.74%), 219 (0.61%), 112 (0.59%), 161 (0.41%), 120 (0.4%), 192 (0.36%), 149 (0.33%), 133 (0.33%), 124 (0.29%), 122 (0.23%), 190 (0.23%), 110 (0.2%), 134 (0.18%), 138 (0.18%), 178 (0.17%), 233 (0.16%), 188 (0.15%), 108 (0.14%), 151 (0.14%), 164 (0.14%), 189 (0.13%), 135 (0.13%), 204 (0.12%), 109 (0.12%), 163 (0.11%), 235 (0.11%), 174 (0.1%), 160 (0.1%), 191 (0.1%), 230 (0.09%), 202 (0.08%), 146 (0.04%), 152 (0.03%), 139 (0.03%), 245 (0.02%), 111 (0.02%), 264 (0.02%), 179 (0.01%), 217 (0.01%), 123 (0.01%), 107 (0.01%), 105 (0.01%), 229 (0.01%), 207 (0.01%), 175 (0.01%), 203 (0.01%)	SOP	Oxymatrine OR Oxysophoridine	Oxymatrine: $MS^{n=2-4}$ [265] (CE: 50%): 265(100), 247(26), 205(35), 148(53) (Liu et al., 2011)
		529	$[2M+H]^+$	265 (100%), 529 (1.03%), 247 (0.34%), 248 (0.26%), 176 (0.2%), 264 (0.2%), 205 (0.17%), 266 (0.17%), 263 (0.15%), 206 (0.15%), 220 (0.11%), 148 (0.1%), 136 (0.07%), 137 (0.07%), 267 (0.04%)			
	P19	266	$[M+NH_4]^+$	266 (100%), 248 (6.66%), 206 (4.05%), 249 (2.99%), 137 (2.95%), 149 (2.86%), 148 (1.78%), 151 (1.43%), 205 (1.37%), 138 (1.31%), 177 (1.24%), 136 (1.21%), 150 (1.1%), 221 (1.05%), 207 (0.96%), 220 (0.85%), 178 (0.8%), 162 (0.69%), 265 (0.63%), 163 (0.59%), 112 (0.5%), 110 (0.45%), 121 (0.41%), 193 (0.38%), 134 (0.36%), 120 (0.32%), 189 (0.3%), 123 (0.29%), 176 (0.28%), 113 (0.28%), 133 (0.25%), 124 (0.24%), 234 (0.23%), 161 (0.23%), 122 (0.2%), 135 (0.2%), 192 (0.19%), 165 (0.19%), 247 (0.19%), 139 (0.19%), 106 (0.19%), 164 (0.18%), 219 (0.17%), 179 (0.17%), 236 (0.17%), 204 (0.16%), 231 (0.15%), 152 (0.15%), 111 (0.14%), 107 (0.14%), 190 (0.13%), 108 (0.13%), 175 (0.13%), 171 (0.11%), 125 (0.11%), 109 (0.11%), 147 (0.11%), 167 (0.1%), 232 (0.1%), 230 (0.1%), 132 (0.09%), 153 (0.08%)	SOP	Lupanine	EI-MS(CE:45eV) *m/z*(%): 248(45), 150(38), 149(58), 136(100), 98(28) (Asres et al., 1997) MS (CE: NA) *m/z*(%): 247(25), 219(5), 205(3), 191(2), 150(35), 149(51), 148(18), 136(100), 122(12), 110(23), 98(29), 92(24), 84(17), 67(10), 55(30) (El-Shazly et al., 1996) $MS^{n=2-4}$ [249] (CE: 50%) *m/z*(%): 206(22), 166(33), 136(100) (Liu et al., 2011)
10.42	**P20**	247	$[M+H]^+$	247 (100%), 148 (76.77%), 176 (14.81%), 150 (7.33%), 110 (2.34%), 179 (2.13%), 229 (2.11%), 218 (1.57%), 190 (1.49%), 120 (1.48%), 230 (1.46%), 206 (1.42%), 188 (1.38%), 121 (1.35%), 146 (1.06%), 109 (1.04%), 219 (1.01%), 122 (1.01%), 112 (1.01%), 134 (0.91%), 165 (0.86%), 212 (0.84%), 157 (0.81%), 133 (0.72%), 204 (0.69%), 160 (0.61%), 132 (0.59%), 174 (0.57%), 186 (0.54%), 164 (0.52%), 216 (0.51%), 202 (0.49%), 105 (0.48%), 127 (0.47%), 111 (0.41%), 123 (0.4%), 124 (0.39%), 136 (0.37%), 162 (0.36%), 131 (0.35%), 245 (0.33%), 130 (0.32%), 113 (0.3%), 138 (0.28%), 161 (0.27%), 147 (0.26%), 159 (0.22%), 203 (0.2%), 119	SOP	(+)-7,11-Dehydromatrine	$MS^{n=2-4}$ [247] (CE: 50%) *m/z*(%): 176(100), 148(13) (Liu et al., 2011) MS (CE: NA) *m/z*(%): 245(100), 218(56), 204(22), 190(35), 176(15), 175(14) (Murakoshi et al., 1982) MS (CE: NA) *m/z*: 246, 218, 204, 190, 176 (Wink and Witte, 1991)

Appendix XVIII Reported and percentage of fragment ions of compounds putatively identified in the HHCF by LC-MS/MS in positive ionization mode.

R_t (min)	No.	*m/z*	Adduct ion(s)	MS/MS fragment ions (*m/z*)	Source	Identity	Reported MS or MS/MS fragments (CE=collision energy)
				(0.19%), 135 (0.19%), 173 (0.19%), 189 (0.18%), 137 (0.16%), 108 (0.15%), 106 (0.15%)			
11.30	**P21**	263	$[M+H]^+$	263 (100%), 245 (20.1%), 112 (9.14%), 235 (5.4%), 246 (5.34%), 195 (2.93%), 204 (2.77%), 149 (2.76%), 136 (2.1%), 218 (1.98%), 148 (1.64%), 162 (1.58%), 120 (1.4%), 138 (1.36%), 135 (1.19%), 122 (1.17%), 110 (1.02%), 180 (1%), 134 (1%), 191 (0.99%), 166 (0.91%), 202 (0.79%), 111 (0.74%), 200 (0.7%), 176 (0.68%), 146 (0.64%), 173 (0.59%), 159 (0.59%), 106 (0.57%), 124 (0.57%), 217 (0.57%), 177 (0.55%), 188 (0.54%), 150 (0.5%)	SOP	9α-Hydroxysophocarpine	$MS^{n=2-4}$ [263] (CE: 50%) *m/z*(%): 245(33), 164 (100) (Liu et al., 2011) MS(CE: NA) *m/z*(%): 262(77), 261(100), 245(12), 233(5), 219(6), 217(10), 203(25), 193(19), 166(30), 154(19), 153(6), 152(11),, 136(15), 122(9), 144(6), 112(14), 110(18), 109(8), 98(3), 96(37), 92(2), 68(23), 41(24) (2013)
11.48	**P22**	263	$[M+H]^+$	263 (100%), 164 (20.48%), 245 (19.12%), 246 (12.69%), 218 (6.89%), 204 (6.55%), 150 (4.09%), 176 (3.22%), 148 (3.14%), 166 (2.31%), 175 (2.03%), 190 (1.7%), 134 (1.39%), 146 (1.18%), 202 (1.07%), 152 (0.87%), 186 (0.85%), 136 (0.83%), 217 (0.77%), 188 (0.75%), 162 (0.73%), 203 (0.66%), 165 (0.64%), 147 (0.59%), 112 (0.57%), 180 (0.57%), 174 (0.55%), 108 (0.54%), 155 (0.52%), 160 (0.45%), 133 (0.43%), 189 (0.42%), 264 (0.42%), 122 (0.4%), 231 (0.39%), 138 (0.37%), 178 (0.26%), 179 (0.24%), 243 (0.2%), 200 (0.17%), 130 (0.16%), 161 (0.15%), 124 (0.15%), 132 (0.15%), 135 (0.14%), 220 (0.13%)	SOP	Leontalbinine N-oxide	$MS^{n=2-4}$ [263] (CE: 50%) *m/z*(%): 195(82), 166(100) (Liu et al., 2011) MS (CE: NA) *m/z*: 246, 245, 244, 218, 190 (Sekine et al., 1993)
	P23	265	$[M+H]^+$	265 (100%), 247 (17.02%), 205 (6.84%), 248 (5.94%), 150 (3.38%), 177 (2.27%), 137 (2.04%), 206 (1.61%), 220 (1.57%), 136 (1.53%), 148 (1.48%), 151 (1.35%), 149 (0.82%), 162 (0.74%), 219 (0.73%), 152 (0.71%), 138 (0.46%), 192 (0.4%), 176 (0.38%), 124 (0.38%), 161 (0.35%), 112 (0.32%), 122 (0.29%), 120 (0.28%), 165 (0.23%), 133 (0.23%), 175 (0.22%), 160 (0.19%), 166 (0.18%), 164 (0.18%), 204 (0.18%), 191 (0.18%), 111 (0.16%), 109 (0.16%), 194 (0.16%), 135 (0.14%), 110 (0.13%), 218 (0.12%), 134 (0.11%), 189 (0.1%), 168 (0.1%)	SOP	Oxymatrine OR Oxysophoridine	Oxymatrine: $MS^{n=2-4}$ [265] (CE: 50%): 265(100), 247(26), 205(35), 148(53) (Liu et al., 2011)
		529	$[2M+H]^+$	No fragment ions			
11.88	**P24**	243	$[M+H]^+$ OR $[M]^+$	No fragment ions	DIC	Dasycarpusenester A	NA
						O-Ethylnor-γ-fagarine	NA
16.77	**P25**	314	$[M]^+$	No fragment ions	PHE	(-)-Oblongine	MS^2 [314] (CE:NA) *m/z*: 298, 283, 269, 192 (Hu et al., 2010) MS^2 [314] (CE:NA) m/z: 270, 269, 191 (Xian et al., 2014)

Appendix XVIII Reported and percentage of fragment ions of compounds putatively identified in the HHCF by LC-MS/MS in positive ionization mode.

R_t (min)	No.	*m/z*	Adduct ion(s)	MS/MS fragment ions (*m/z*)	Source	Identity	Reported MS or MS/MS fragments (CE=collision energy)
20.08	**P26**	342	$[M+H]^+$	192 (100%), 342 (19.81%), 177 (6.11%)	PHE	Phellodendrine	MS^2 [342] (CE:NA) m/z: 342, 192 (Alolga et al., 2015) MS^2 [342] (CE:10/20/40 V) *m/z*: 192, 177, 149 (Wang et al., 2014a) MS^2 [342] (CE:10-40 V) m/z: 192 (Li et al., 2010)
21.12	**NA**	344	NA	107 (100%), 165 (15.81%), 145 (7.02%), 403 (6.68%), 192 (5.09%), 344 (4.14%), 193 (3.43%), 180 (2.66%), 127 (1.91%)	RHE	NA	NA
	NA	349	NA	349 (100%), 185 (1.85%), 187 (1.53%), 291 (0.65%), 257 (0.35%), 259 (0.29%), 247 (0.22%), 127 (0.21%), 189 (0.2%), 350 (0.08%), 159 (0.07%)	RHE	NA	NA
22.08	**P27**	344	$[M+H]^+$	344 (100%), 175 (16.68%), 299 (15.38%), 137 (14.51%), 301 (7.39%), 151 (6.26%), 143 (5.14%), 267 (2.52%), 269 (1.98%), 192 (1.42%), 312 (1.38%), 177 (1.24%), 107 (1.2%), 207 (1.1%), 193 (1.08%), 241 (1.05%), 239 (1.04%), 115 (0.66%), 235 (0.65%), 194 (0.6%), 145 (0.46%), 206 (0.44%), 237 (0.43%), 160 (0.43%), 163 (0.41%), 179 (0.41%), 119 (0.35%), 117 (0.35%), 329 (0.31%), 284 (0.31%), 209 (0.3%), 213 (0.29%), 294 (0.29%), 162 (0.28%), 205 (0.28%), 149 (0.26%), 272 (0.26%), 123 (0.24%), 131 (0.24%), 251 (0.23%), 180 (0.2%), 176 (0.2%), 118 (0.19%), 271 (0.19%), 109 (0.19%), 153 (0.18%), 122 (0.18%), 182 (0.17%), 187 (0.16%), 178 (0.15%), 161 (0.15%), 268 (0.15%), 125 (0.15%), 252 (0.14%), 223 (0.14%), 255 (0.14%), 188 (0.14%), 174 (0.13%), 165 (0.13%), 253 (0.13%), 181 (0.13%), 142 (0.12%), 225 (0.12%)	PHE	Tembetarine	MS^2 [344] (CE:NA) *m/z*: 344, 299, 207, 175, 137 (Alolga et al., 2015) MS^2 [344] (CE:NA) *m/z*: 298, 267, 192, 177 (Xian et al., 2014) MS^2 [344] (CE: NA) *m/z*: 299. 235, 207, 175, 137 (Wang et al., 2013c)
22.91	**P28**	342	$[M+H]^+$	342 (100%), 192 (65.27%), 130 (44.39%), 265 (38.79%), 297 (30.11%), 116 (23.34%), 203 (18.44%), 298 (16.58%), 300 (15.05%), 237 (7.11%), 282 (6.16%), 107 (5.29%), 299 (4.9%), 177 (4.72%), 132 (3.32%), 167 (2.84%), 279 (2.44%), 129 (2.43%)	PHE	Magnoflorine	MS^2[342] (CE:40%) *m/z*: 297, 282, 265, 237, 222, 219, 209, 191 (Sim et al., 2013) MS^2[342] (CE:23eV) *m/z*:342, 297, 282, 265, 237 (Tian et al., 2014) MS^2[342] (CE:NA) m/z: 342, 297, 265, 192 (Wang et al., 2013c)
24.33	**NA**	592	NA	592 (100%), 163 (13.44%), 286 (5.69%), 382 (3.82%)	PHE	NA	NA
26.26	**NA**	759	NA	391 (100%), 197 (0.34%), 392 (0.33%), 373 (0.33%), 215 (0.26%), 199 (0.26%), 214 (0.23%), 177 (0.23%), 759 (0.14%), 198 (0.12%)	PHE	NA	NA
		391	NA	391 (100%), 215 (17.25%), 199 (11.23%), 197 (10%), 373 (7.67%), 177 (7.08%), 179 (5.61%), 345 (4.14%), 196 (4.09%), 145 (2.08%), 217 (1.29%), 176 (1.26%), 390 (0.98%), 214 (0.8%), 169 (0.65%), 151 (0.56%), 135 (0.51%), 178 (0.46%), 308 (0.44%), 285 (0.38%)	PHE	NA	NA

Appendix XVIII Reported and percentage of fragment ions of compounds putatively identified in the HHCF by LC-MS/MS in positive ionization mode.

R_t (min)	No.	*m/z*	Adduct ion(s)	MS/MS fragment ions (*m/z*)	Source	Identity	Reported MS or MS/MS fragments (CE=collision energy)
26.84	**P29**	314	$[M+H]^+$	314 (100%), 107 (19.31%), 269 (12.39%), 143 (5.91%), 137 (3.47%), 121 (3.07%), 115 (2.42%), 175 (1.83%), 271 (1.6%), 145 (1.46%), 237 (1.46%), 147 (1.35%), 191 (1.33%), 251 (0.99%), 194 (0.96%), 163 (0.96%), 146 (0.82%), 177 (0.75%), 193 (0.73%), 178 (0.56%), 209 (0.56%)	PHE	Evoeuropine	MS^2[314] (CE:NA) *m/z*: 281, 189, 161, 150, 146, 121, 107 (Yan et al., 2015)
	NA	236	NA	NA	KOC	NA	NA
31.32	**P30**	356	$[M+H]^+$	356 (100%), 247 (47.81%), 311 (24.45%)	PHE	Menisperine	MS^2 [344] (CE:NA) *m/z*: 356, 311, 279 (Alolga et al., 2015) MS^2 [342] (CE:10-40 V) *m/z*: 311, 279, 248 (Li et al., 2010)
52.87	**P31**	336	$[M]^+$	336 (100%), 321 (26.43%), 320 (14%), 292 (13.06%), 306 (2.64%), 335 (1.54%), 304 (1.41%), 278 (1.37%), 275 (1.11%), 318 (0.51%)	PHE	Berberine	MS^2 [336] (CE:NA) *m/z*: 321, 306, 278 (Zhang et al., 2015b) MS^2 [336] (CE:35V) *m/z*: 320, 292 (Wang et al., 2015)

Appendix XIX Reported and percentage of fragment ions of compounds putatively identified in the HHCF by LC-MS/MS in negative ionization mode.

Rt (min)	No.	*m/z*	Adduct ion(s)	MS/MS fragment ions (*m/z*)	Source	Identity	Reported MS/MS fragments (CE=collision energy)
2.34	**N1**	193	$[M-H]^-$	113 (100%), 103 (39.1%), 101 (15.01%)	SCU	Glucuronic acid	NA (Institute of Food Research, n.d.)
2.46	**N2**	191	$[M-H]^-$	191 (100%), 127 (7.66%), 111 (4.1%), 173 (3.01%), 109 (2.98%), 145 (2.25%), 190 (2.16%), 171 (1.96%), 103 (1.05%), 129 (0.97%), 143 (0.79%)	PHE	Quinic acid	MS^2 [191] (CE:NA) *m/z*: 173, 127, 111, 93, 85 (Ng et al., 2004)
	N3	223	$[M-H]^-$	129 (100%), 111 (79.45%), 205 (47.14%), 101 (46.72%), 125 (37.99%), 223 (26.17%)	SOP	Sinapic acid	NA (Institute of Food Research, n.d.)
3.50	**N4**	191	$[M-H]^-$	111 (100%), 131 (7.5%), 129 (2.94%), 191 (2.19%), 190 (1.49%), 155 (1.41%)	PHE	Citric acid	MS^2 [191] (CE:NA): 173, 111 (Ng et al., 2004)
	N5	331	$[M-H]^-$	169 (100%), 211 (76.8%), 331 (43.3%), 125 (29.19%), 124 (21.17%), 123 (11.69%), 151 (9.12%), 167 (8.78%), 193 (8.31%), 168 (8.19%), 271 (8.09%), 112 (7.95%), 113 (7.03%), 119 (5.65%), 128 (4.98%), 183 (4.9%), 241 (4.72%), 101 (4.19%), 286 (2.89%), 107 (2.07%), 210 (1.41%), 270 (1.41%), 137 (1.13%)	RHE	Galloylglucose (i.e. 1-*O*-Galloyl-β-D-glucose or 6-*O*-Galloyl-β-D-glucose) OR Glucopyranosyloxyl gallic acid (i.e. Gallic acid-3-O-β-D-glucoside or Gallic acid-4-O-β-D-glucoside)	Glucopyranosyloxyl gallic acid: MS^2 [331] (CE:30-50V) *m/z*: 271, 211, 169, 125 (Yang et al., 2015a) 1-O-Galloylglucose: MS^2 [331] (CE:50%) *m/z*(%):169(100) (Jin et al., 2007) Galloylglucose: MS^2 [331] (CE:NA) *m/z*: 271, 241, 169, 125 (Han et al., 2008)
4.08	**N6**	331	$[M-H]^-$	169 (100%), 123 (38.65%), 331 (38.36%), 151 (34.32%), 125 (27.77%), 211 (26.08%), 271 (20.32%), 113 (8.98%), 183 (8.02%), 124 (5.04%), 241 (4.82%), 168 (4.77%), 101 (4.67%), 119 (3.85%), 107 (3.65%), 210 (3.33%), 153 (3.14%), 197 (2.41%), 167 (2.12%), 193 (2.06%), 162 (1.17%), 152 (0.76%), 165 (0.57%)	RHE		
4.61	**N7**	331	$[M-H]^-$	211 (100%), 271 (96.85%), 169 (84.6%), 125 (24.42%), 168 (19.07%), 124 (16.25%), 107 (9.53%), 331 (7.91%), 241 (4.09%), 165 (4.05%), 123 (3.53%), 151 (3.14%), 197 (1.89%), 139 (1.59%), 167 (1.58%), 270 (1.56%), 183 (1.31%), 101 (1.03%), 113 (0.88%)	RHE		
5.35	**N8**	125	$[M-H]^-$	125 (100%), 124 (13.85%)	RHE	Pyrogallol	NA
	N9	169	$[M-H]^-$	125 (100%), 169 (8.42%), 107 (3.58%), 124 (3.27%)	RHE	Gallic acid	MS^2 [169] (CE:30-50V) *m/z*: 125, 107 (Yang et al., 2015a)
	N10	331	$[M-H]^-$	211 (100%), 169 (66.81%), 271 (62.68%), 125 (21.96%), 331 (15.26%), 193 (12.23%), 124 (11.97%), 151 (10.94%), 241 (10.24%), 123 (7.63%), 103 (6.98%), 168 (4.58%), 183 (4.56%), 167 (3.64%), 113 (2.85%), 107 (1.27%)	RHE	Galloylglucose (i.e. 1-*O*-Galloyl-β-D-glucose or 6-*O*-Galloyl-β-D-glucose) OR Glucopyranosyloxyl gallic acid (i.e. Gallic acid-3-O-β-D-glucoside or Gallic acid-4-O-β-D-glucoside)	Glucopyranosyloxyl gallic acid: MS^2 [331] (CE:30-50V) *m/z*: 271, 211, 169, 125 (Yang et al., 2015a) 1-O-Galloylglucose: MS^2 [331] (CE:50%) *m/z*(%):169(100) (Jin et al., 2007) Galloylglucose: MS^2 [331] (CE:NA) *m/z*: 271, 241, 169, 125 (Han et al., 2008)
8.71	**N11**	255	$[M-H]^-$	165 (100%), 107 (38.58%), 179 (32.86%), 133 (22.4%), 193 (17.87%), 149 (16.97%), 147 (16.65%), 255 (13.5%), 131 (10.06%), 135 (8.43%), 119 (7.46%), 105 (3.15%), 175 (2.9%), 163 (2.02%), 211 (1.85%), 121 (1.8%), 137 (1.56%),	SOP	Piscidic acid	MS^2 [276] (CE:NA) *m/z*(%): 211(33), 193(96), 179(90), 165(87), 149(57) (Chahdoura et al., 2014)

Appendix XIX Reported and percentage of fragment ions of compounds putatively identified in the HHCF by LC-MS/MS in negative ionization mode.

Rt (min)	No.	*m/z*	Adduct ion(s)	MS/MS fragment ions (*m/z*)	Source	Identity	Reported MS/MS fragments (CE=collision energy)
				132 (1.55%), 181 (1.4%), 103 (1.23%), 151 (1.06%), 130 (1.05%), 134 (0.98%), 106 (0.98%), 162 (0.62%), 150 (0.6%), 109 (0.31%)			
		511	$[2M-H]^-$	255 (100%),165 (16.76%),193 (6.33%),179 (5.53%),149 (1.71%),107 (1.58%),211 (0.68%),175 (0.51%),133 (0.44%),146 (0.38%),119 (0.29%),135 (0.25%),131 (0.24%),166 (0.22%),256 (0.21%),181 (0.18%),209 (0.15%),147 (0.14%),237 (0.14%)			
		533	$[2M+Na-2H]^-$	255 (100%), 179 (18.08%), 165 (17.57%), 533 (13.39%), 192 (7.12%), 277 (4.37%), 193 (2.45%), 532 (2.45%), 149 (1.97%), 107 (1.81%)			
13.88	**N12**	577	$[M-H]^-$	289 (100%), 407 (65.72%), 125 (38.87%), 425 (22.46%), 577 (19.45%), 245 (14.76%), 451 (13.65%), 305 (9.9%), 161 (9.42%), 287 (7.36%), 273 (7.08%), 381 (5.51%), 137 (5.37%), 205 (4.92%), 299 (4.55%), 559 (4.07%), 151 (3.55%), 175 (3.43%), 243 (3.16%), 255 (2.83%), 203 (2.77%), 450 (2.51%), 256 (2.43%), 163 (2.25%), 328 (2.19%), 329 (2.1%), 229 (2.05%), 109 (2%), 339 (1.99%), 179 (1.92%), 269 (1.85%), 283 (1.74%)	RHE	Procyanidin B (Catechin dimers)	MS^2 [577] (CE:30-50V) *m/z*: 407, 289, 245, 125, 109 (Yang et al., 2015a)
16.48	**N13**	289	$[M-H]^-$	109 (100%), 123 (91.31%), 203 (82.01%), 151 (66.21%), 245 (56.6%), 125 (55.02%), 137 (47.19%), 205 (40.11%), 289 (35.92%), 149 (31.13%), 121 (30.99%), 221 (30.71%), 179 (29.9%), 188 (29.79%), 161 (25.5%), 165 (22.74%), 175 (22.34%), 187 (21.66%), 164 (20.04%), 202 (17.32%), 227 (16.9%), 247 (16.8%), 135 (12.93%), 199 (12.77%), 162 (11.73%), 167 (11.33%), 139 (11.08%), 159 (11.03%), 231 (10.45%), 173 (10.2%), 217 (9.78%), 145 (9.56%), 122 (8.76%), 157 (8.68%), 244 (8.36%), 163 (8.17%), 147 (7.96%), 158 (7.31%), 160 (7.14%), 212 (7.09%), 220 (7.09%), 201 (7%), 230 (6.97%), 117 (6.91%), 204 (6.8%), 138 (5.62%), 150 (5.44%), 177 (5.21%), 178 (5.17%), 185 (5.15%), 174 (4.93%), 107 (4.67%), 131 (4.61%), 271 (4.54%), 184 (4.46%), 166 (4.43%), 186 (3.81%), 183 (3.56%), 108 (2.94%), 226 (2.18%), 146 (2.03%), 211 (2.02%), 209 (1.94%), 229 (1.75%), 176 (1.54%), 113 (1.51%), 133 (1.26%), 111 (1.21%)	RHE	Catechin	MS^2 [298] (CE:30-50V) *m/z*: 271, 245, 125, 109 (Yang et al., 2015a) MS^2 [289] (CE:NA) *m/z*: 245, 205, 179, 165 MS^3 [245] (CE:NA) *m/z*: 227, 203, 187, 161 (Yang et al., 2014a) MS^2 [298] (CE:50%) m/z(%): 109(100), 152(40), 123(60) (Jin et al., 2007)
		579	$[2M-H]^-$	289 (100%), 245 (13.19%), 125 (3.06%), 179 (2.62%), 203 (2.41%), 205 (2.13%), 137 (1.79%), 109 (1.52%), 271 (1.19%), 187 (1.04%), 135 (1.01%), 217 (0.98%), 123 (0.96%), 175 (0.9%), 165 (0.85%), 151 (0.75%), 221 (0.74%), 247 (0.6%), 149 (0.51%), 227 (0.44%), 188 (0.44%), 161 (0.43%), 204 (0.41%), 160 (0.37%), 200 (0.3%), 121 (0.25%), 167 (0.19%), 164 (0.19%)			
	NA	580	NA	NA	RHE	NA	NA
	N14	353	$[M-H]^-$	191 (100%), 205 (2.98%), 127 (1.69%), 109 (0.83%), 265 (0.79%), 135 (0.63%), 161 (0.62%), 173 (0.49%), 179 (0.29%), 111 (0.24%)	PHE	Chlorogenic acid	MS^2 [353] (CE:20eV) *m/z*: 191, 173, 135, 127, 111 (Zou et al., 2014) MS^2[353] (CE:NA) m/z: 191, 179, 135 (Hu et al., 2010)
		707	$[2M-H]^-$	NA			

Appendix XIX Reported and percentage of fragment ions of compounds putatively identified in the HHCF by LC-MS/MS in negative ionization mode.

Rt (min)	No.	*m/z*	Adduct ion(s)	MS/MS fragment ions (*m/z*)	Source	Identity	Reported MS/MS fragments (CE=collision energy)
18.15	**N15**	367	$[M-H]^-$	193 (100%), 134 (52.75%), 149 (8.46%), 117 (6.01%), 191 (3.98%), 173 (3.75%), 155 (3.02%), 367 (2.41%), 109 (1.95%), 116 (1.9%), 111 (1.28%), 154 (0.87%), 190 (0.62%), 148 (0.43%)	PHE	3-*O*-Feruloylquinic acid	MS^2 [367] (CE:NA) *m/z*(%): 193(100), 191(1.8), 173(3.3), 134(4.5) (Parveen et al., 2011) MS^2 [367] (CE:NA) *m/z*: 191, 173, 194, 149, 134, 117, 111 (Wang et al., 2013c)
	NA	239	NA	NA	SOP	NA	NA
21.10	**N16**	325	$[M-H]^-$	NA	RHE	4-(4'-Hydroxylphenyl)-2-butanone 4'-O-β-D-glucoside	MS^2 [325] (CE:50%) *m/z*(%): 163(100), 57(45) (Jin et al., 2007) MS^2 [325] (CE:15-35V) *m/z*: 161 (Liu et al., 2016)
		371	$[M+FA-H]^-$	163 (100%), 121 (39.46%), 162 (12.41%), 113 (8.94%), 101 (7.9%), 161 (4.17%)			
		651	$[2M-H]^-$	NA			
	N17	415	$[M+Na-2H]^-$	NA	RHE	6-Hydroxymusizin-8-O- β-D-glucoside	MS^2 [439] (CE:50%) *m/z*(%): 231(100) (Jin et al., 2007)
		439	$[M+FA-H]^-$	231 (100%), 113 (77.31%), 393 (11.6%)			
22.77	**N18**	289	$[M-H]^-$	123 (100%), 109 (99.46%), 125 (63.81%), 203 (60.91%), 245 (45.97%), 205 (42.45%), 151 (36.41%), 289 (32.34%), 137 (31.47%), 221 (31.24%), 188 (24.48%), 159 (23.6%), 161 (23.03%), 175 (21.4%), 121 (19.64%), 163 (17.76%), 146 (17.55%), 122 (17.39%), 149 (14.55%), 187 (14%), 185 (13.59%), 145 (12.8%), 164 (11.92%), 139 (11.92%), 165 (10.61%), 217 (10.16%), 162 (9.71%), 227 (8.78%), 230 (8.05%), 138 (8.01%), 135 (7.29%), 179 (7.27%), 202 (6.52%), 174 (6.35%), 167 (6.1%), 199 (5.73%), 229 (5.42%), 143 (4.53%), 186 (4.17%), 244 (4.17%), 201 (4.02%)	RHE	Epicatechin	MS^2 [289] (CE:30-50V): 245, 125, 109 (Yang et al., 2015a)
	N19	337	$[M-H]^-$	191 (100%), 163 (10.21%), 173 (7.7%), 119 (6.74%), 111 (4.09%), 129 (2.45%), 143 (1.65%), 172 (1.28%), 142 (0.78%)	PHE	*p*-Coumaroylquinic acid	3-O-*p*-Coumaroylquinic acid MS^2 [337] (CE:NA) *m/z*(%): 191(7.6), 163(100), 119(3.9) 4-O-*p*-Coumaroylquinic acid MS^2 [337] (CE:NA) *m/z*(%): 191(6.4), 173(100), 163(7.2) 5-O-*p*-Coumaroylquinic acid MS^2 [337] (CE:NA) *m/z*(%): 191(100), 163(7.1) (Parveen et al., 2011)
24.72	**N20**	303	$[M-H]^-$	125 (100%), 177 (29.2%), 149 (17.35%), 151 (13.92%), 217 (8.99%), 124 (7.9%), 165 (7.78%), 213 (7.67%), 175 (7.13%), 123 (6.97%), 193 (6.77%), 285 (4.74%), 199 (4.16%), 121 (3.99%), 173 (3.31%), 303 (3.07%), 197 (2.61%), 189 (2.47%), 241 (2.43%), 133 (2.29%), 243 (2.15%), 107 (1.77%), 152 (1.75%), 145 (1.61%), 275 (1.61%), 120 (1.55%), 212 (1.27%), 147 (1.26%), 164 (1.19%), 148 (1.14%), 191 (1.1%), 172 (0.99%), 190 (0.98%)	SCU	2',3,5,6',7-Pentahydroxyflavanone (Ganhuangemin)	MS^2 [303] (CE:NA) *m/z*: 285, 276, 259, 217, 177 (Zhang et al., 2007b)

Appendix XIX Reported and percentage of fragment ions of compounds putatively identified in the HHCF by LC-MS/MS in negative ionization mode.

Rt (min)	No.	*m/z*	Adduct ion(s)	MS/MS fragment ions (*m/z*)	Source	Identity	Reported MS/MS fragments (CE=collision energy)
26.26	**N21**	367	$[M-H]^-$	191 (100%), 173 (41.26%), 193 (18.5%), 134 (11.18%), 111 (8.15%), 155 (4.26%), 178 (3.62%), 149 (3.53%), 143 (3.1%), 175 (2.27%), 113 (2.05%), 137 (1.84%), 160 (1.78%), 129 (1.77%), 127 (1.74%), 101 (1.33%), 117 (1.25%), 192 (1%), 136 (0.64%), 116 (0.63%), 115 (0.58%), 171 (0.36%)	PHE	5-*O*-Feruloylquinic acid	MS^2 [337] (CE:NA) *m/z*(%): 193(6.0), 191(100), 173(2.2), 134(4.5) (Parveen et al., 2011) MS^2 [337] (CE:NA) *m/z*: 367, 193, 191, 176, 173, 147 (Hu et al., 2010)
26.65	**N22**	389	$[M-H]^-$	NA	RHE	Resveratrol-4'-O-β-D-glucoside OR Resveratrol 3-O-β-glucoside (Pieceid)	MS^2 [389] (CE:15-35V) *m/z*: 227, 185, 143 (Liu et al., 2016)
		435	$[M+FA-H]^-$	227 (100%), 191 (9.41%), 389 (3.8%), 225 (2.18%), 173 (1.57%), 367 (1.44%), 374 (1.42%), 185 (1.08%), 193 (0.64%), 228 (0.43%)			
		779	$[2M-H]^-$	NA			
		825	$[2M+FA-H]^-$	NA			
28.16	**NA**	229	NA	229 (100%), 185 (45.31%), 139 (33.76%), 183 (28.24%), 167 (20.83%), 137 (18.63%), 211 (9.9%), 165 (9.23%), 155 (8.91%), 117 (7.3%), 149 (4.12%), 113 (3.63%), 111 (2.36%)	PHE	NA	NA
30.42	**NA**	385	NA	NA	PHE	NA	NA
32.06	**N23**	301	$[M-H]^-$	125 (100%), 149 (66.53%), 151 (64.68%), 148 (35.07%), 301 (29.63%), 175 (26.33%), 283 (24.01%), 107 (22.49%), 147 (18.18%), 152 (14.15%), 201 (8.59%), 171 (8.31%), 192 (8.15%), 121 (8.09%), 135 (7.67%), 229 (7.09%), 213 (6.53%), 187 (6.25%), 215 (5.98%), 119 (5.9%), 177 (5.81%), 257 (5.67%), 163 (5.57%), 105 (5.44%), 109 (5.24%), 211 (5.21%), 239 (5.12%), 205 (4.94%), 227 (4.85%), 176 (3.14%), 161 (2.76%), 153 (2.62%), 159 (2.53%), 189 (2.48%), 195 (2.44%), 203 (2.43%), 273 (2.42%), 120 (2.41%), 272 (2.37%), 185 (2.29%), 214 (2.26%), 137 (2.21%), 233 (1.79%), 245 (1.73%), 216 (1.6%), 255 (1.56%), 160 (1.55%), 186 (1.49%), 133 (1.44%), 173 (1.33%)	SCU	3,5,7,2',6'-Pentahydroxyflavone (Viscidulin I)	MS^2 [301] (CE:NA) *m/z*: 383, 273, 257, 229, 151 (Zhang et al., 2007b) MS^2 [301] (CE:35eV) *m/z*: 283, 257, 193, 151, 125 (Qiao et al., 2016)
34.57	**N24**	441	$[M-H]^-$	169 (100%), 289 (50.74%), 125 (35.13%), 245 (17.94%), 271 (12.85%), 203 (12.14%), 137 (8.9%), 253 (8.3%), 193 (7.68%), 205 (7.38%), 331 (7.28%), 179 (6.31%), 151 (6.2%), 441 (6%), 124 (5.44%), 303 (5.34%), 166 (4.44%), 288 (4.14%), 287 (3.83%), 168 (3.31%), 227 (2.89%), 175 (2.76%), 259 (2.65%), 145 (2.65%), 109 (2.41%), 123 (2.38%), 221 (2.19%), 204 (1.99%), 397 (1.82%), 150 (1.82%), 167 (1.81%), 184 (1.77%), 185 (1.39%), 165 (1.31%), 315 (1.22%), 192 (1.04%), 188 (1.04%), 161 (0.91%), 164 (0.87%)	RHE	Epicatechin 3-O-gallate	MS^2 [441] (CE:50%) *m/z*(%): 289(100), 109(Jin et al., 2007) MS^2 [441] (CE:30-50 V) *m/z*: 289, 271, 169, 125 (Yang et al., 2015a)
	N25	477	$[M-H]^-$	477 (100%), 169 (40.95%), 313 (35.4%), 125 (11.02%), 151 (7.41%), 124 (5.6%), 289 (3.44%), 123 (3.28%), 168 (3.05%), 441 (2.8%), 161 (2.22%), 163 (1.95%), 245 (1.95%), 241 (1.89%), 211 (1.36%), 167 (1.25%), 101 (1.16%), 295 (1.01%)	RHE	Isolindleyin	MS^2 [477] (CE:30-50 V) *m/z*: 313, 211, 169, 125 (Yang et al., 2015a) MS^2 [477] (CE:50%) *m/z*(%): 313(100), 169(55), 125(25) (Jin et al., 2007)
	N26	547	$[M-H]^-$	547 (100%), 337 (30.32%), 457 (14.43%), 427 (13.69%), 367 (12.56%), 487 (6.97%), 280 (5.16%), 409 (2.45%), 529 (1.42%), 349 (1.42%)	SCU	Chrysin-6-C-arabinosyl-8-C-glucoside	MS^2 [547] (CE:NA) *m/z*: 529, 487, 457, 427, 367, 337 (Zhang et al., 2007b)

Appendix XIX Reported and percentage of fragment ions of compounds putatively identified in the HHCF by LC-MS/MS in negative ionization mode.

Rt (min)	No.	*m/z*	Adduct ion(s)	MS/MS fragment ions (*m/z*)	Source	Identity	Reported MS/MS fragments (CE=collision energy)
							MS^2 [547] (CE:NA) *m/z*: 487, 457, 427, 409, 367, 337, 309, 281 (Seo et al., 2013)
36.56	**N27**	477	$[M-H]^-$	313 (100%), 477 (22.45%), 169 (17.33%), 151 (6.47%), 124 (6.44%), 123 (6.14%), 168 (4.76%), 163 (4.52%), 125 (4.31%), 167 (3.65%), 113 (3.28%), 107 (2.31%), 211 (2.14%), 433 (1.87%), 223 (1.16%), 268 (1.09%), 101 (1.06%), 253 (1.03%), 269 (0.89%), 153 (0.54%), 209 (0.52%), 165 (0.43%), 251 (0.4%), 162 (0.39%), 193 (0.32%), 179 (0.32%)	RHE	Lindleyin	MS^2 [477] (CE:30-50 V) *m/z*: 313, 211, 169, 125 (Yang et al., 2015a) MS^2 [477] (CE:50%) *m/z*(%): 313(100), 169(55), 125(25) (Jin et al., 2007)
		955	$[2M-H]^-$	477 (100%), 313 (56.56%)			
	N28	545	$[M-H]^-$	NA	RHE	Rhein-8-O-D-[6'-O-(3"-methoxylmalonyl)] glucoside	NA
37.25	**N29**	547	$[2M-H]^-$	547 (100%), 427 (13.87%), 457 (8.35%), 337 (6.72%), 479 (5.77%), 367 (5.04%), 265 (2.76%), 529 (2.12%), 101 (1.98%), 281 (1.6%), 309 (1.19%), 379 (0.82%), 349 (0.73%), 308 (0.68%), 397 (0.6%), 307 (0.57%), 511 (0.51%), 266 (0.5%), 278 (0.5%), 439 (0.5%), 279 (0.48%), 469 (0.45%), 291 (0.41%), 409 (0.41%), 335 (0.41%), 377 (0.41%), 336 (0.4%)	SCU	Chrysin-6-C-glucosyl-8-C-arabonoside	MS^2 [547] (CE:NA) *m/z*: 529, 487, 457, 427, 367, 337 (Zhang et al., 2007b) MS^2 [547] (CE:NA) *m/z*: 457, 427, 367, 337, 309, 281 (Seo et al., 2013)
38.43	**N30**	541	$[M-H]^-$	313 (100%), 227 (20.57%), 169 (18.22%), 541 (17.99%), 151 (9.27%), 312 (4.29%), 123 (3.42%), 124 (2.09%)	RHE	Resveratrol-4'-O-β-D-(2"-O-galloyl) glucoside	MS^2 [541] (CE:50%) *m/z*(%) 313(100), 227(25), 169(40), 125(10) (Jin et al., 2007)
39.20	**N31**	541	$[M-H]^-$	541 (100%), 313 (25.58%), 169 (12.97%), 227 (6.46%), 125 (2.62%), 124 (2.14%), 123 (1.46%), 151 (1.22%), 181 (1.07%), 241 (1.02%), 168 (0.74%), 540 (0.69%), 211 (0.62%)	RHE	Resveratrol-4'-O-β-D-(6"-O-galloyl) glucoside	MS^2 [541] (CE:50%) *m/z*(%) 313(100), 227(25), 169(40), 125(10) (Jin et al., 2007)
45.08	**N32**	301	$[M-H]^-$	139 (100%), 124 (44.12%), 133 (28.08%), 135 (25.92%), 107 (23.4%), 161 (17.74%), 273 (3.81%), 268 (3.35%), 283 (3.32%), 165 (3.24%), 240 (3.04%), 269 (2.94%), 151 (2.73%), 251 (2.55%), 179 (2.35%), 160 (2.3%), 134 (2.27%), 255 (2.08%), 117 (1.99%), 178 (1.72%), 224 (1.71%), 201 (1.32%)	SCU	Trihydroxy-methoxyflavanone	MS^2 [301] (CE:35eV) *m/z*: 161, 139 (Qiao et al., 2016)
46.91	**N33**	431	$[M-H]^-$	269 (100%), 431 (84.39%), 240 (14.94%), 225 (3.77%), 268 (2.54%), 283 (1.82%), 293 (1.06%), 280 (1%), 281 (0.93%)	RHE	Emodin-1-O-β-D-glucoside OR Emodin-8-O-β-D-glucoside OR Aloe-emodin 8-O-β-D-glucoside OR Aloe-emodin-3-CH_2-O-β-D-glucoside.	Aloe emodin 8- O-β-D-glucoside MS^2 [431] (CE:15-35V): 269, 240 (Liu et al., 2016) Aloe-emodin-3-CH_2-O-β-D-glycoside MS^2 [431] (CE:15-35V): 269, 268 (Liu et al., 2016) Emodin 1-O-β-D-glucoside MS^2 [431] (CE:15-35V): 269, 240, 225 (Liu et al., 2016)

Appendix XIX Reported and percentage of fragment ions of compounds putatively identified in the HHCF by LC-MS/MS in negative ionization mode.

Rt (min)	No.	*m/z*	Adduct ion(s)	MS/MS fragment ions (*m/z*)	Source	Identity	Reported MS/MS fragments (CE=collision energy)
							Emodin 8-O-β-D-glucoside MS^2 [431] (CE:25%): 311, 293, 269, 268; MS^3 [431 à 269]: 269, 241, 225; MS^4 [431 à 269 à 225]: 210, 182 (Zhao et al., 2013a)
55.48	**N34**	481	$[M+Cl]^-$	NA	SOP	(-)-Maackiain-3-O-glucoside (Trifolirhizin)	NA
		483	$[M+K-2H]^-$	NA			
		491	$[M+FA-H]^-$	283 (100%), 255 (10.61%), 254 (4.06%)			
58.94	**N35**	431	$[M-H]^-$	269 (100%), 431 (38.42%), 268 (11.89%), 311 (4.38%), 225 (2.53%), 293 (2.48%), 265 (1.93%), 240 (1.6%), 241 (1.29%), 239 (0.87%), 224 (0.68%), 270 (0.63%), 181 (0.57%), 282 (0.54%), 310 (0.5%)	RHE	Emodin-1-O-β-D-glucoside OR Emodin-8-O-β-D-glucoside OR Aloe-emodin 8-O-β-D-glucoside OR Aloe-emodin-3-CH_2-O-β-D-glycoside.	Aloe emodin 8- O-β-D-glucoside MS^2 [431] (CE:15-35V) *m/z*: 269, 240 (Liu et al., 2016) Aloe-emodin-3-CH_2-O-β-D-glycoside MS^2 [431] (CE:15-35V) *m/z*: 269, 268 (Liu et al., 2016) Emodin 1-O-β-D-glucoside MS^2 [431] (CE:15-35V) *m/z*: 269, 240, 225 (Liu et al., 2016) Emodin 8-O-β-D-glucoside MS^2 [431] (CE:25%) *m/z*: 311, 293, 269, 268; MS^3 [431 à 269] *m/z*: 269, 241, 225; MS^4 [431 à 269 à 225] *m/z*: 210, 182 (Zhao et al., 2013a)
63.95	**N36**	233	$[M-H]^-$	191 (100%), 233 (74.34%), 147 (16.22%), 175 (13.72%), 173 (9.55%), 190 (5.6%), 149 (5.1%), 217 (5.08%), 215 (4.04%), 123 (3.6%), 145 (2.65%), 189 (2.07%), 172 (2.05%), 148 (1.99%), 158 (1.92%), 129 (1.9%), 132 (1.19%), 131 (1.12%)	RHE	(5Z)-6-Hydroxy-3,4-dioxo-6-phenyl-5-hexenoic acid	MS^2 [233](CE:30-50V): 189, 175, 147 (Jin et al., 2007)
71.02	**N37**	269	$[M-H]^-$	269 (100%), 223 (11.25%), 241 (9.54%), 251 (7.35%), 169 (7.09%), 195 (6.82%), 197 (5.46%), 137 (5.03%), 167 (4.17%), 139 (3.69%), 179 (3.12%), 141 (2.68%), 171 (2.6%), 213 (2.35%), 207 (2.16%), 225 (2%), 151 (1.89%), 153 (1.52%), 183 (1.48%), 143 (1.46%), 185 (1.34%), 224 (1.28%), 145 (1.25%), 123 (1.24%), 240 (1.05%), 212 (0.98%), 199 (0.95%), 155 (0.92%), 157 (0.92%), 196 (0.9%), 165 (0.88%), 181 (0.86%), 111 (0.83%), 268 (0.72%), 164 (0.64%), 101 (0.61%), 127 (0.57%), 109 (0.51%), 184 (0.51%), 168 (0.47%), 192 (0.45%), 150 (0.41%), 239 (0.4%), 182 (0.38%), 222 (0.37%), 198 (0.36%), 252 (0.36%), 125 (0.35%), 180 (0.33%), 129 (0.31%), 221 (0.28%), 178 (0.27%), 211 (0.26%), 152	SCU	Trihydroxyflavone [i.e. 5,6,7-Trihydroxyflavone (Baicalein) OR 5,7,8-Trihydroxyflavone (Norwogonin)]	Trihydroxyflavone: MS^2 [269] (CE:35eV) *m/z*: 225, 151, 117/269, 169 (Qiao et al., 2016) Baicalein: MS^2 [269] (CE:45% of maximum) *m/z*: 251(100), 241(40), 225(40), 223(40); MS^3 [269 à 251]: 223(100) (Han et al., 2006)

Appendix XIX Reported and percentage of fragment ions of compounds putatively identified in the HHCF by LC-MS/MS in negative ionization mode.

Rt (min)	No.	*m/z*	Adduct ion(s)	MS/MS fragment ions (*m/z*)	Source	Identity	Reported MS/MS fragments (CE=collision energy)
				(0.25%), 117 (0.24%), 270 (0.24%), 122 (0.24%), 121 (0.2%), 227 (0.19%), 138 (0.18%), 149 (0.17%)			Norwogonin: MS^2 [269] (CE:NA) *m/z*: 251, 241, 223, 197, 195, 179, 169, 167, 151, 137, 123, 117 (Seo et al., 2013) MS^2 [269] (CE:45% of maximum) *m/z*: 251(60), 241(10), 169(5) (Han et al., 2007)
89.37	**NA**	176	NA	NA	SOP	NA	NA

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