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Adulteration and Poor Quality of *Ginkgo biloba* Supplements

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Abstract

Adulteration of Ginkgo products sold as unregistered supplements within the very large market of Ginkgo products (reputedly £650 million annually) through the post-extraction addition of cheaper (e.g. buckwheat derived) rutin is suspected to allow sub-standard products to appear satisfactory to third parties, e.g. secondary buyers along the value chain or any regulatory authorities. This study was therefore carried out to identify products that did not conform to their label specification and may have been actively adulterated to enable access to the global markets.

500MHz Bruker NMR spectroscopy instrumentation combined with Topspin version 3.2 and a CAMAG HPTLC system (HPTLC Association for the analysis of *Ginkgo biloba* leaf) were used to generate NMR spectra (focusing on the 6-8ppm region for analysis) and chromatograms, respectively.

Out of the 35 samples of Ginkgo biloba analysed, 33 were found to contain elevated levels of rutin and /or quercetin, or low levels of Ginkgo metabolites when compared with the reference samples. Samples with disproportional levels of rutin or quercetin compared with other gingko metabolites are likely to be adulterated, either by accident or intentionally, and those samples with low or non-existent gingko metabolite content may have been produced using poor extraction techniques. Only two of the investigated samples were found to match with the High-Performance Thin-Layer Chromatography (HPTLC) fingerprint of the selected reference material. All others deviated significantly. One product contained a 5-hydroxytryptophan derivative, which is not a natural constituent of *Ginkgo biloba*.

Overall, these examples either suggest a poor extraction technique or deliberate adulteration along the value chain. Investigating the ratio of different flavonoids e.g. quercetin and kaempferol using NMR spectroscopy and HPTLC will provide further evidence as to the degree and kind of adulteration of Gingko supplements. From a consumer perspective the equivalence in identity and overall quality of the products needs to be guaranteed for supplements too and not only for products produced according to a quality standard or pharmacopoeial monograph.

Introduction

Ginkgo biloba L. (Ginkgoaceae) is a popular phytomedicine with a high economic value. It is used principally for the treatment of problems associated with the peripheral circulation and to improve memory and cognitive function. It is a licensed drug in some European countries, e.g. Germany. In the UK, two products hold a Traditional Herbal Registration (THR) for the treatment of Raynaud's disease although the majority of products on the UK market are sold as unlicensed food supplements (now often referred to as botanicals).

According to 'Industry Experts', the global market for the sale of *Ginkgo biloba* supplements amounts to around £650 million annually (Daniells, *2013*), typically ranging in price from 2.5 to 54 pence per individual daily dose. However, there have been frequent reports of poor quality and adulteration (Avula, et al., 2015; Edwards et al. 2015; Wohlmuth et al., 2014) .

Manufacturers of extracts complying with pharmacopoeial standards have to perform extensive testing. Besides HPTLC, for identification, the European Pharmacopeia (Ph. Eur.) requires three HPLC assays (flavonoids, terpene lactones and ginkgolic acids) and the United States Pharmacopoeia (USP) requires four HPLC assays (content of free flavonol glycosides, content of terpene lactones, limit on rutin and quercetin, and limit of ginkgolic acids) (EP 2014, USP 2015). Supplement manufacturers may however choose not to claim compliance with a pharmacopeia and thus limit their analytical work to a minimum. Such simplified conventional testing is not always able to determine which products are of good quality, particularly as it has been reported that products are often 'spiked' with buckwheat-derived rutin in order to increase their total flavonoid content and to reduce the amount of authentic drug in the preparation (Ding et al., 2006). This has important implications for both the OTC market and the practitioner led market as middlemen involved in the early stages of the supply chain (cultivation and primary processing) may cross both markets.

NMR spectroscopy is an effective tool for the quality control of medicinal plants or HMPs (Shyur and Yang, 2008). The advantages of NMR spectroscopy over other techniques for metabolomics applications include the relative ease of sample preparation, the potential to identify a broad range of compounds and provision of structural information for unknown entities (Zulak et al., 2008).

NMR spectroscopy-Metabolomics coupled with HPTLC can offer a better picture of the total metabolite profiles that can be obtained from plants and plant extracts and so may be a useful addition to other analytical methods (Liu, 2015, López-Gutiérrez, 2016), in the investigation of fake, adulterated and poor quality products (Booker et al., 2015).

Materials and methods

Test samples

35 Ginkgo products sold as food supplements were purposefully sampled from health food stores, supermarkets and pharmacies in the Central London area and from the internet. The internet search criteria used was 'Ginkgo, Ginkgo biloba, Ginkgo Products and Buy Ginkgo products'. The samples were marketed as either extracts of *Ginkgo biloba* formulated into tablets (22), hard capsules (11), or caplets (2). A detailed description of all investigated products is provided in the supplementary data.

Solvents, reagents and chemicals

Deuterated dimethyl sulfoxide D6 lot no. 14F-145 and tetramethylsilane (for NMR spectroscopy) (99.9%) were purchased from Cambridge Isotope Laboratories, Inc., Andover, MA, USA. Methanol was purchased from Carl Roth GmbH, Karlsruhe, Germany, ethylacetate (99.5%) and formic acid (98+ %) pure purchased from Acros, New Jersey, USA. Acetic acid (99.5%), toluene (99+%), acetone (pure), and dichloromethane (for HPTLC) were purchased from Sigma-Aldrich. Acetic anhydride (98.5%) was purchased from Merck. Polyethylene glycol, 2-aminoethyldiphenylborinate (Derivitisation reagents) were purchased from Aldrich chemistry.

Standards

Reference standard: A quantified and licensed Ginkgo extract tablet EGb 761 (Tebofortin® intense) and *Ginkgo biloba* extract tablets (LI 1370 extract) were purchased through a pharmacy. Ginkgo tablet (S1312) and *Ginkgo biloba* leaf (S1310) were obtained from the National Institute of Standards and Technology (NIST) U.S. Department of Commerce; *Ginkgo biloba* leaf samples (S11311, S15564) and powdered *Ginkgo biloba* leaf extracts (S10925 and S15571) were obtained from the American Herbal Pharmacopeia (AHP). Quercetin, chlorogenic acid, rutin, and ginkgo terpene lactones (mixture) and *Ginkgo biloba* standard supplied by The European Pharmacopoeia (EP CRS for peak identification) were obtained from Sigma-Aldrich.

^{1}H-NMR spectroscopy

Preparations of standard solutions and samples

Approximately 50 mg of solid extracts were accurately weighed and transferred to a 1.5 ml Eppendorf reaction tube, 1 ml of deuterated DMSO containing 0.05% tetramethylsilane was added. The mixture was mixed on a rotary mixer for 60 s, sonicated for 10 minutes at room temperature and centrifuged for 10 minutes at room temperature (speed; 14,000 rpm). The reference standard solutions of rutin and *Ginkgo biloba* BRM were prepared at a concentration of 20 mg/ml in deuterated DMSO. 700 µl of supernatant was transferred to a 5 mm diameter NMR tube, and the samples were submitted on the same day for ^{1}H-NMR spectroscopy analysis.

Apparatus and instrumentation

The ^{1}H-NMR spectra were acquired using 500 MHz NMR Bruker Avance spectrometer (Bruker BioSpin GmbH, Rheinstetten, Germany) equipped with a 5 mm cryoprobe head and operating at a proton frequency of 500.13 MHz. The acquisition parameters were: size of the spectra 64 k data points, line broadening factor = 0.16 Hz, pulse width (PW) = 30 degrees and the relaxation delay d1 = 1 s. The acquisition temperature was 298 K.

Topspin software version 3.2 was used for spectra acquisition and processing. AMIX Bruker Biospin multivariate analysis software version 3.0 was used for converting spectra to an ASCII file. The numbers of scans chosen was 256 for optimum strength of signal, and locked at zero on the TMS peak.

Data reduction and multivariate statistics methods

The ^{1}H-NMR spectra were phase-corrected, baseline-corrected, and zeroed to the TMS peak. The spectra were converted to an ASCII file using AMIX software for multivariate analysis.

AMIX was used to generate a number of integrated regions (buckets) of the data set in the region of 6.0 to 8.0 ppm. The size of buckets was 0.04 ppm. . The data set was imported to Microsoft EXCEL, and the samples and standards were labelled 1 to 37. The Principal Component Analysis (PCA) was carried out using SIMCA software version 13.0.

High performance thin layer chromatography (HPTLC)

Preparations of standard solutions and samples

The extraction of plant samples was performed according to a method described by the HPTLC Association for the identification of dried *Ginkgo biloba* leaf (www.hptlc-association.org). Standard solutions of rutin, chlorogenic acid and quercetin were prepared at a concentration of 0.2 mg/ml in

methanol. The terpene lactones standard was prepared at concentration of 1 mg/ml. Approximately 100 mg of solid samples (extracts/products) were weighed individually into 10 ml centrifuge tubes and 10 ml of methanol were added. The mixture was sonicated for 10 minutes at room temperature and centrifuged for 5 minutes at 5000 rpm. The supernatant solution was transferred into individual vials, and then submitted for HPTLC analysis.

Chromatography

HPTLC analysis was performed on 20 x 10 cm HPTLC glass plates silica gel 60 F_{254} (Merck, Germany). Reference solutions and samples were applied onto the plate as bands 8.0 mm wide using a CAMAG Automatic TLC Sampler (ATS 4). Bands were applied at a distance of 8.0 mm from the lower edge of plate and 20 mm from the left and right edges. The space between bands was 11 mm, and the number of tracks per plate was 15. Plates were developed in a CAMAG Automatic Developing Chamber (ADC2) to a distance of 70 mm from the lower edge of the plate. Prior to development the plates were conditioned to a relative humidity of 33 %.

Analysis of flavonoids: 3 µL of the samples and standards were applied onto the plate, which was developed with the mobile phase ethyl acetate, acetic acid, formic acid, water 100:11:11:27 (v/v/v/v). For the derivatization procedure, the plate was first heated at 100°C for 3 minutes on a CAMAG TLC Plate Heater, then dipped (speed: 3, time: 0) first into NP reagent (1 g of 2-aminoethyl diphenylborinate in 200 mL of ethyl acetate) then subsequently into PEG reagent (10 g of polyethylene glycol 400 in 200 mL of methylene chloride) using a CAMAG Chromatogram Immersion Device. The plates were documented using a CAMAG Visualizer under white light, UV 254 nm, and UV 366 nm prior derivatisation and under white light and UV 366 nm after derivatisation with visionCATS software.

Analysis of terpene lactones: Prior to sample application (3 µL of standards and 5 µL of samples), the plates were impregnated with 8 g sodium acetate in 200 mL ethanol-water (6:4) by immersion into the solution for 2 s, allowed to dry at room temperature for 5 min and then activated for 30 min at 90°C. Toluene, ethyl acetate, acetone, methanol 20:10:10:1.2 (v/v/v/v) was used as mobile phase. After development the plate was sprayed with acetic anhydride, heated at 180°C for 10min and documented under UV 366 nm for selective detection of the target compounds.

Results and Discussion

^{1}H-NMR spectroscopy analysis

On visual inspection, the ^{1}H-NMR raw data suggests that there is considerable variation between products (Fig.1).

A closer examination of the NMR spectra shows the typical chemical shift for rutin more clearly and moreover many samples appear to contain mainly rutin (Fig.2).

However, the information that can be derived visually from the raw data is limited so SIMCA multivariate software offers a suitable tool to analyse the variation in the data. The SIMCA scores plot (Fig. 3) confirms that there is wide variation in the chemical composition of the samples. This is likely due in part to the samples being formulated into different dosage forms, e.g. capsules and tablets, but also different excipients are typically used in the manufacture of different brands of product. Consequently, in order to avoid variations in the samples due to excipients, we have focused the SIMCA scores plot on the 6 – 8 ppm chemical shift region (where mainly aromatic compounds, e.g. flavonoids give signals) and so the scores plot reflects the variation in the phytochemistry of the *Ginkgo biloba* leaf and not any added excipients.

The scores plot indicates that some samples are similar in chemical composition to the selected *Ginkgo biloba* reference (CRS for peak Identification) and some samples appear similar to the rutin standard. This can be seen clearly from the contribution plot (Fig. 4) where, for example, samples 23, 32 and 33 are very similar in composition to the rutin standard (36) and are weaker in all metabolites when compared with the average fingerprint of the other samples, apart from those metabolites that correspond in chemical shift to rutin. This observation is further confirmed using the HPTLC data where we see that some samples purporting to be *Ginkgo biloba* only show a band for rutin (Rf 0.38) (Fig.6).

Moreover, the NMR spectroscopy scores plot shows some supplements that are very different in chemical composition to that of *Ginkgo biloba* e.g. sample 7, and again this can be clearly seen on the HPTLC analysis. Examination of the NMR spectroscopy raw data for this supplement suggests some similarity in structure to 5-hydroxytryptophan (5-HTP). This product was manufactured by the same company that our group identified in connection with rhodiola products adulterated with 5-HTP (Booker et al., 2016).

HPTLC analysis

All 35 samples were analysed using the HPTLC Association's methods for identification of dried Ginkgo leaf based on flavonoids and terpene lactones. The fingerprints obtained were compared to 3 samples of Ginkgo leaf and 4 samples of extracts, which are compliant with the respective Ph. Eur. monograph (Ph. Eur. 8.8, monographs 1827 and 1828) and USP monographs (Ginkgo and powdered Ginkgo extract) (Fig. 5.a and 5.b). One of the extract samples (on Track 5) is a tablet containing a special extract (EGb 761).

Flavonoid fingerprint of the reference material: the fingerprint of the leaf and extract are similar in intensity, colour and number of zones except for the reddish zone below the solvent front due to chlorophyll, which is only seen in leaf samples. Some of the leaf samples and all extract samples show a greenish/brownish zone at the position of quercetin.

Terpene lactones fingerprint of the reference material: In the fingerprint of the leaf samples (tracks 2-6) the zones of ginkgolides c, b and bilobalide are not clearly seen due to a matrix interference (greenish zone), while in the extracts (tracks 7-9) all zones are well separated. Additionally a red zone due to chlorophyll, just below the solvent front, is only seen in leaf samples. The intensity of the main four zones seen in the extracts' fingerprint is equivalent to 6% of the sum of ginkgolides a, b, c and bilobalide.

Evaluation of the products: The visual inspection of the HPTLC chromatograms of the 35 products reveals a large variation in the intensity and composition of the chemical fingerprint (Fig. 6). Only two samples (20 and 33) show a flavonoid fingerprint equivalent to the one of quantified Ginkgo reference special extract EGb 761 (track 5, fig. 5.a). However, the fingerprint of sample 33 is significantly weaker. The drug extract ratio of this sample was not specified on the label. Therefore the weak fingerprint is likely associated to an insufficient amount of material used during sample preparation.

Four samples (14, 23, 30 and 32) show a predominant zone due to rutin and one sample (7) shows just a dark blue zone. 26 out of 35 samples show an intense yellow zone at the position of quercetin, just below the solvent front (1, 2, 4, 5, 6, 8, 9, 10, 11, 12, 13, 15, 16, 17, 18, 19, 21, 22, 24, 25, 27, 28, 29, 31, 34 and 35). Despite the high amount of quercetin, the fingerprints of these samples, except for sample 4, match those of the reference materials shown in Fig. 5.a. Some are just weak. The same observation has been made by (Chandra et al, 2011), who classify the samples with high content of quercetin but a profile similar to that of Ginkgo extract in the HPLC fingerprint as category of intermediate quality.

All samples were also tested for the content of bilobalide, ginkgolides a, b and c (Fig. 7). Four samples (7, 23, 30, and 32) showed no zone for terpene trilactones. Those zones were very faint in sample 14 and slightly stronger in sample 33 but still weaker than in all other samples. However, on their label the samples 7, 14 and 23 claimed to contain 6% of terpene lactones, which should produce an intensity equivalent to these of the reference extracts (Fig 5.b, tracks 5-7). Samples 30, 32 and 33 did not provide any specification about the content of terpene lactones on their labels.

R_F

A careful evaluation of the samples' label claims was performed and it was observed that they fell into seven general categories, from standardised extracts to no information about the content (see table 1). Some samples belong to one or more categories at the same time. Additionally, all samples declare to contain Ginkgo (extract or leaf), thus it is expected that their HPTLC fingerprints are similar to those obtained for the reference images in Figs 5.a and 5.b.

Type 1: Of 35 products 18 declare to contain a standardised extract (24% of flavone glycosides and 6% of terpene lactones). Similar specifications are described in the USP and Ph. Eur. monographs for Ginkgo extracts. *Therefore, these samples must comply with the amounts of flavone glycoside and terpene lactones stated on the product label (minimum content) and comply with the quantitative assays as detailed in the pharmacopoeias.* However the assay is not able to show the differences in the samples' composition. Consequently official methods require combining the assay with an identification test (e.g. HPTLC identification). In this context, the fingerprints of only 15 samples are in compliance with the reference image, even though the yellowish-brown fluorescent zone at the position of quercetin in the flavonoid fingerprint is of much higher intensity than that in the reference images (Fig. 5a). Three samples from this category (7, 14 and 23) show a very poor fingerprint.

In the identification by TLC/HPTLC neither the intensity of the quercetin is described in the USP and Ph. Eur. monographs, nor is it explicitly stated that the yellowish-brown zone describe in the upper part of the chromatogram is not quercetin. The intensity of the quercetin zone in the samples of this group can therefore not be used as quality criterion. However, from a consumer's perspective it may still be questioned whether a Ginkgo product with high quercetin amount is of equivalent quality to a product with low quercetin amount.

A second group only declares to be standardized to contain 24% of the flavone glycoside (type 2, table 1). The fingerprint of all four samples of this group comply with the acceptances criteria for identification.

Of the products which declare the drug extract ratio (DER) equivalent to 50:1 (type 3), eight provide no additional information (type 3.a), 12 declare to be standardized (type 3.b), one declares to contain 24% of flavone glycosides (type 3.c) and one declares to contain leaf powder and extract (type 3.d). Once the amount of powdered leaf used to produce the extract is declared, it is expected that the intensity of the product's fingerprint is similar to that of the reference material (EGb 761; track 7, figs 5.a and b). However none of the samples of type 3 is equivalent. Therefore those samples can be considered to contain lower than declared amounts of Ginkgo, based on the flavonoids fingerprint.

Samples 3 and 27 declare to contain Gingko leaf and Ginkgo leaf extract (type 4). The first sample shows additional zones on its flavonoid fingerprint, 2 blue fluorescent zones in the upper third of the chromatogram, which are neither found in leaf powder nor in the reference extract. Both samples show a reddish zone due to chlorophyll in the terpene lactones and flavonoids fingerprints (present in the leaf powder). Four samples provided no relevant information about the extract but just the amount of extract in the tablet/capsule (type 5). One sample declares to contain an extract enhanced with rutin, however its fingerprint has an additional strong zone at the position of quercetin (type 6). The samples of type 7 declare to contain only Gingko leaf but their fingerprints are different from those of the reference drug (Fig. 5)

Our study suggests that the main problems are poor concentrations of Ginkgo metabolites, addition of marker compounds (rutin) and addition of other compounds e.g. 5-hydroxytryptophan type derivatives.

No sample claims compliance with any pharmacopoeial method but, aside from the pharmacopoeias, there are no definitions for Ginkgo leaf and extract. Therefore, it is difficult to assign a good or bad quality to label to those samples. Only deviation from the label claim can be used for such qualification. On this basis and their HPTLC fingerprints, we may classify the samples to have a quality similar to that described in the Pharmacopoeias (samples 20 and 33), bad quality (no ginkgo at all) or not in compliance with their label (samples 7, 34, and 28) and a quality different from that described in Pharmacopoeias (remaining 30 samples).

The underlying reason for why there is so much variation in samples is likely to be complex. It may be in some cases that the extraction processes are insufficient. . However for the addition of marker compounds in order that they may satisfy basic analytical limit tests and the addition of substances such as 5-hydroxytryptophan type derivatives, there seems little other recourse than to draw the conclusions that these companies are either being sold sub-standard material from third parties or are using poor quality and adulterated material intentionally in order to maximise profits.

The THR scheme was introduced to ensure that herbal medicinal products are of good quality and comply with what is claimed on the label. It came under some criticism when it came into force claiming that it took away consumers rights to choose. This may be true, but it seems obvious that a right to choose a poor quality or fake product is not a right that's of much value to the general consumer of these products. It was further argued that THR products would be too expensive for consumers. Our research suggests that THR products are generally mid-price range (comparison of our samples against THR products sold on the UK market), with most of the very cheap products showing to be of poor quality but in some instances the very expensive products were also adulterated or of poor quality. It therefore seems that price is not always a reliable indicator of quality.

Conclusions

From a regulatory perspective, five samples (7, 14, 23, 28 and 34) are not in compliance with their label specification. The other 28 samples can be considered to be in compliance with their label claim but their quality is different from that described in pharmacopoeias. This means that these samples show different fingerprints with different levels of rutin, quercetin and other additional zones. Only two samples (20 and 33) show a fingerprint similar to that described in the Ph.Eur. and USP monographs for ginkgo extract. From a consumers perspective it may be legitimate to assume that a Ginkgo supplement contains the "same" extract as a registered herbal medicine. However, this is not the case. Future investigations into the ratio of different flavonoids e.g. quercetin and kaempferol using NMR spectroscopy and HPTLC will provide further evidence as to the kind and degree of adulteration of gingko supplements and provide a measure of product quality that helps overcoming supplement adulteration.

In view of the therapeutic claims for Ginkgo, the reported potential side effects / interactions (Abad et al. 2010) and the problems identified in this study, it seems appropriate to cover Ginkgo preparations with an appropriate *medical* regulation. Alternatively, a regulatory scheme needs to be introduced for food supplements. In addition it is essential to firstly study the value chains of *Ginkgo biloba* products and to clearly identify the crucial points responsible for such poor quality or adulteration (Heinrich 2015). In a next step best practice along the value chains needs to be established requiring first of all, all producers of final products to gain a detailed understanding of the value chains of their products.

These quality problems have important implications for all healthcare practitioners prescribing, dispensing or recommending ginkgo-based products. A full verification of the composition and quality of the products needs to be ascertained and practitioners will need to implement quality assurance measures either on the basis of using fully certified material or implementing such steps themselves. In addition patients should be advised accordingly about problems with potentially adulterated OTC preparations.

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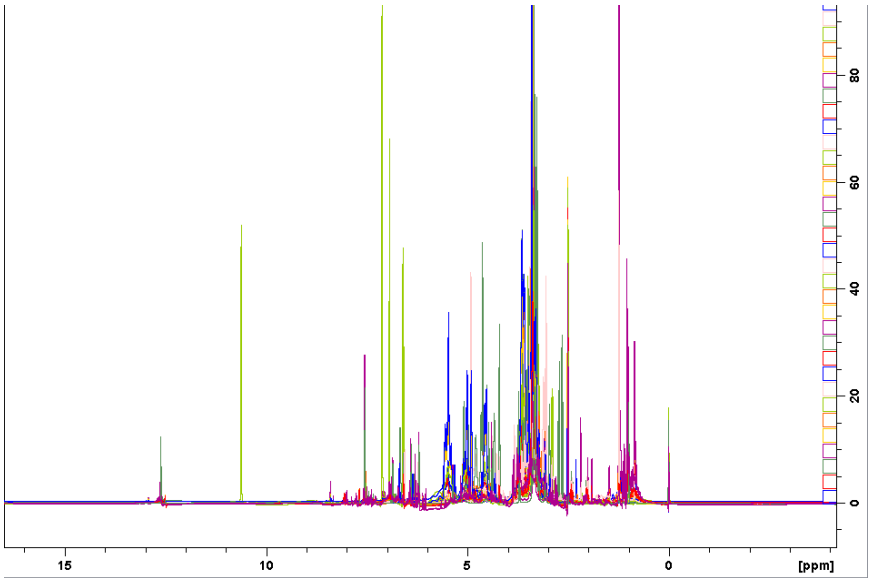

Figure 1, Raw NMR spectra from 35 Ginkgo supplement samples plus rutin reference and *Ginkgo biloba* botanical reference material.

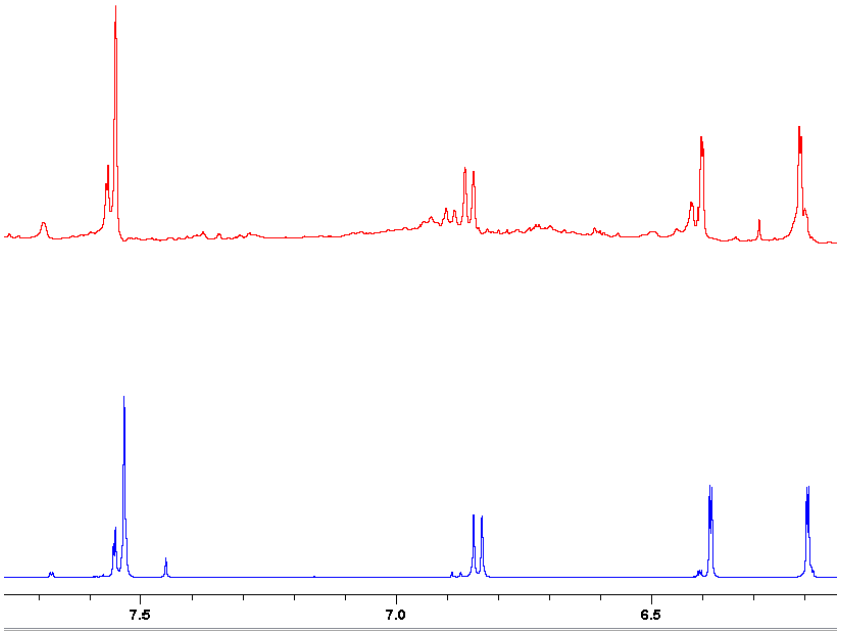

Figure 2, Comparison of rutin reference standard bottom against one of the samples (top)

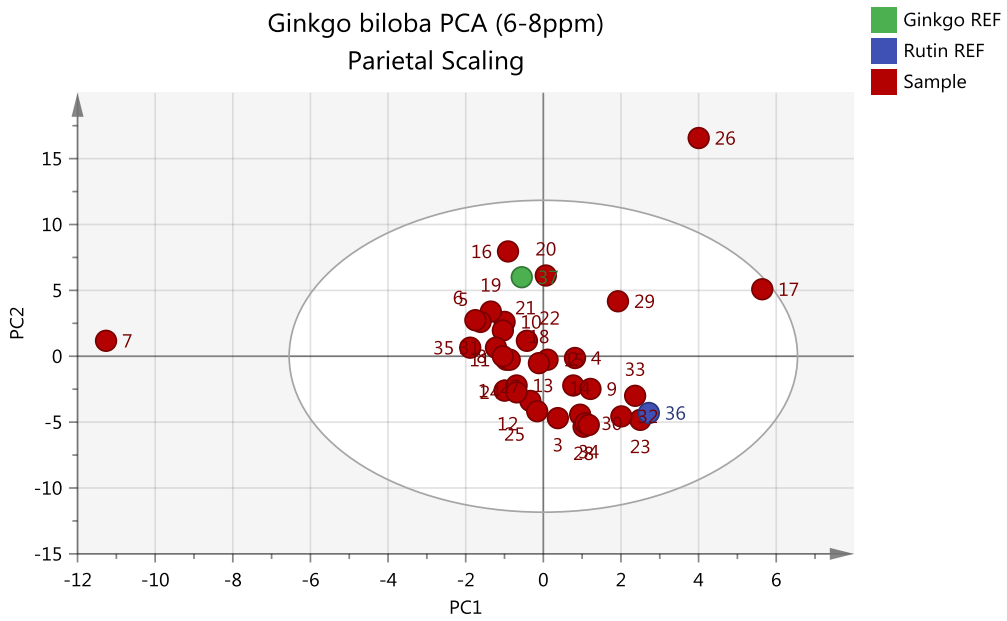

Figure 3, SCORES plot of 35 Ginkgo supplement samples as well as Rutin and *Ginkgo biloba* reference samples.

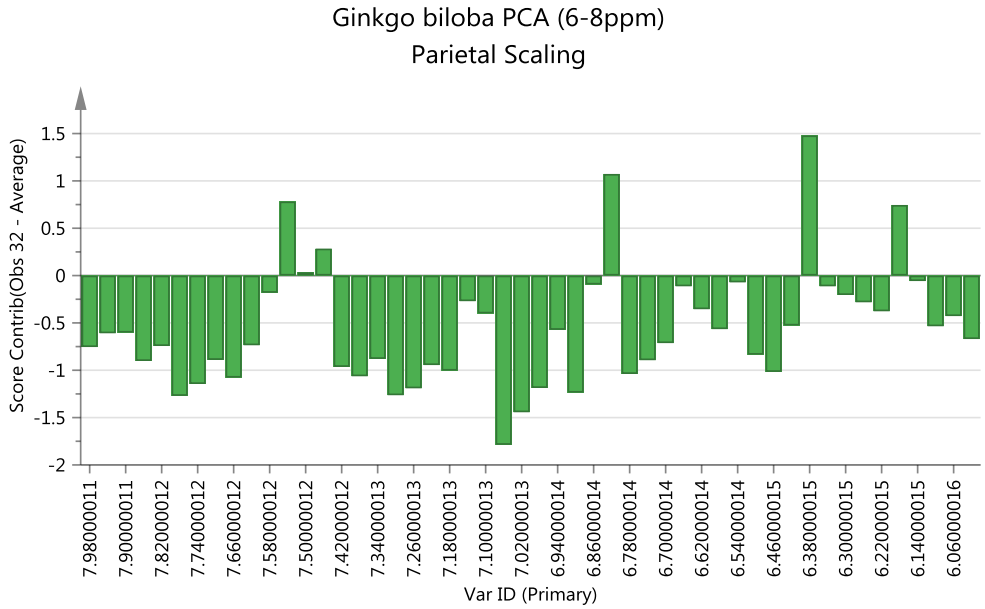

Figure 4, Contributions plot showing the variation in data between sample 32 (top) which shows mainly peaks for pure rutin and the average metabolite content for the rest of the samples showing a wide range of ginkgo metabolites.

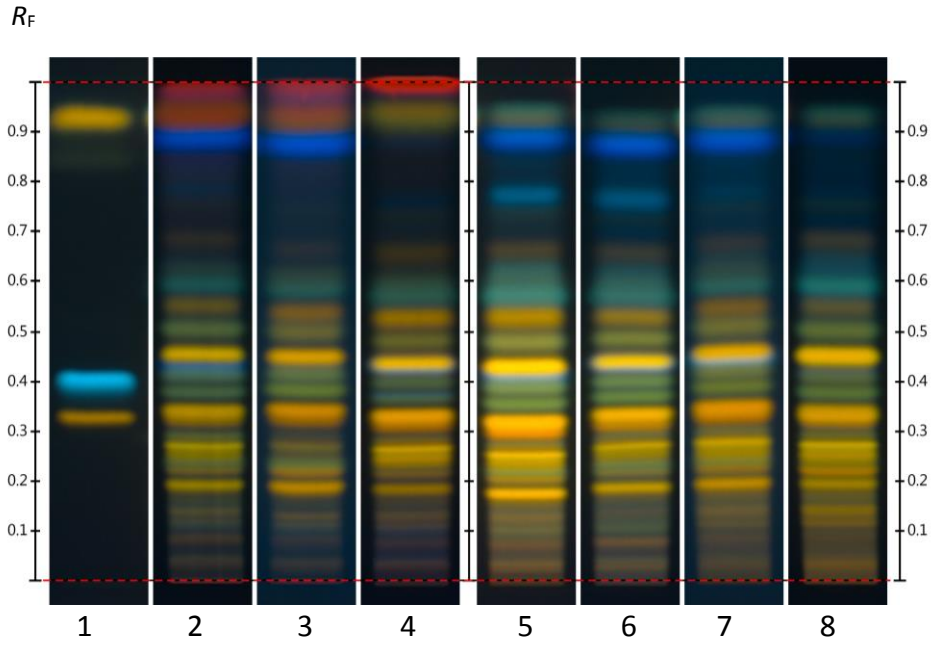

Fig. 5.a, HPTLC chromatograms of the reference tracks under UV 366 nm after derivatisation with NP. Track 1: SST (rutin, chlorogenic acid and quercetin with increasing RF values); Track 2: Ginkgo leaf sample (S1310); Track 3: Ginkgo leaf sample (S11311); Track 4: Ginkgo leaf sample (S15564); Track 5: tablet with quantified Ginkgo leaf extract EGb 761; Track 6: Ginkgo leaf extract (S15571); Track 7: Ginkgo leaf extract (S1312); Track 8: Ginkgo leaf extract (S10925);

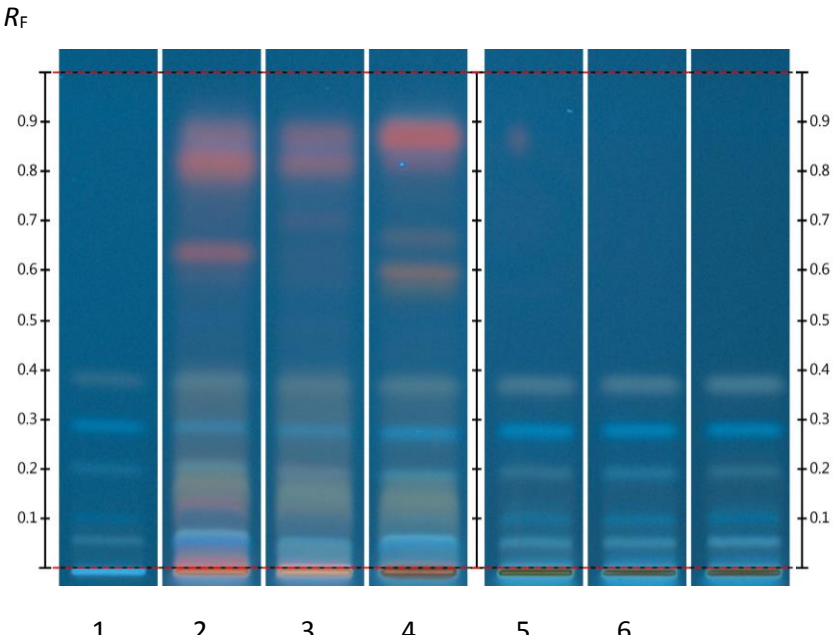

Fig. 5.b, HPTLC chromatograms of the reference tracks under UV 366 nm after derivatisation with acetic anhydride. Track 1: SST (Ginkgolides c, j, b and a and bilobalide with increasing RF values); Track 2: Ginkgo leaf sample (S1310); Track 3: Ginkgo leaf sample (S11312); Track 4: Ginkgo leaf sample (S15564); Track 5: tablet with quantified Ginkgo leaf extract EGb 761; Track 6: Ginkgo leaf extract (S15571); Track 7: Ginkgo leaf extract (S10925);

R_F

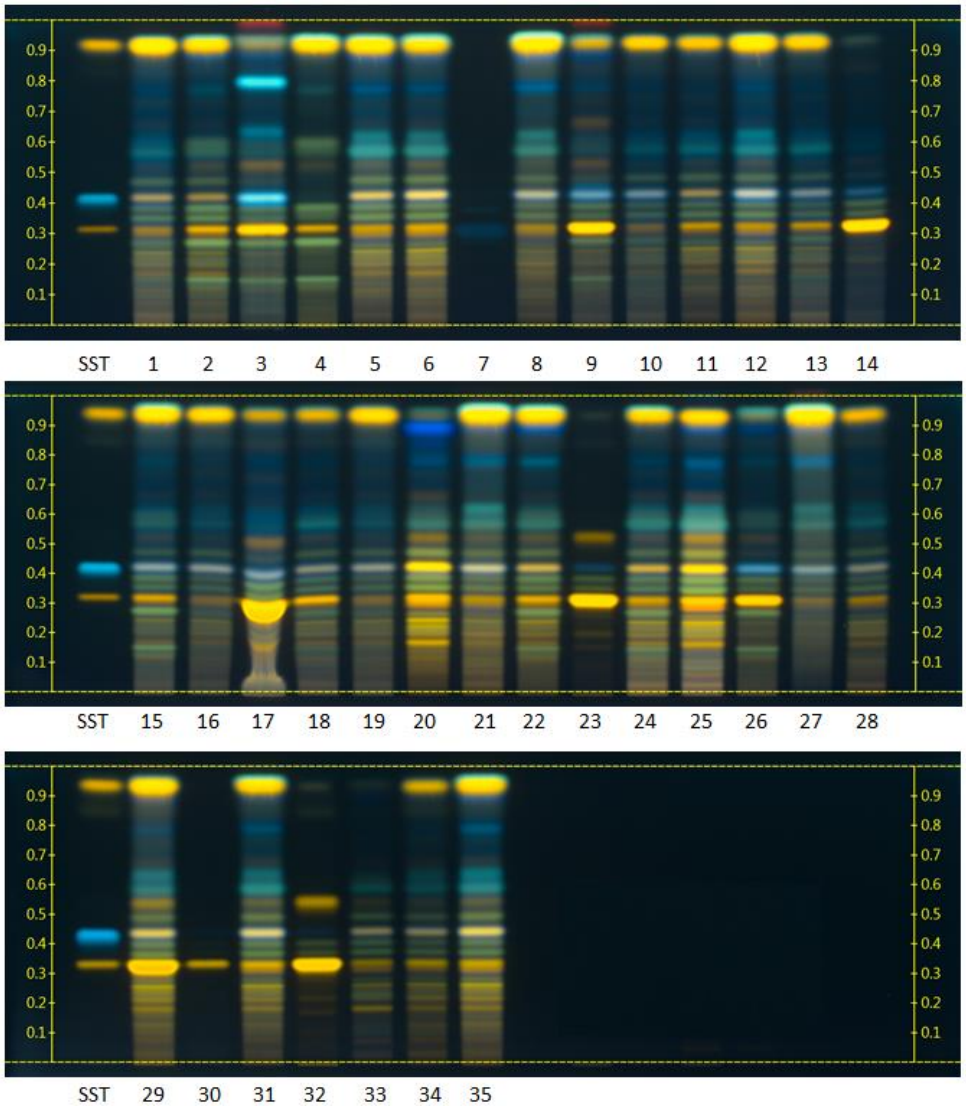

Figure 6, HPTLC chromatograms of products 1-35 under UV 366 nm after derivatisation of the 35 Ginkgo products evaluated with flavonoids method. SST: rutin, chlorogenic acid and quercetin with increasing R_F values

R_F

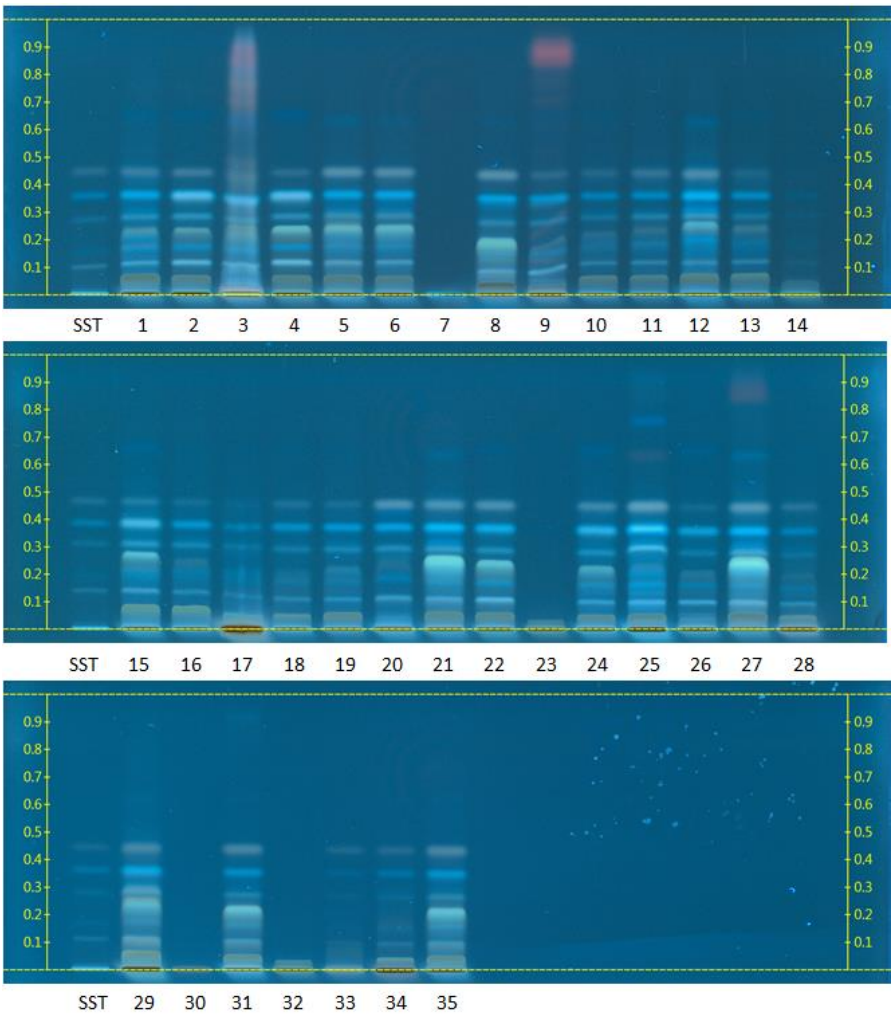

Figure 7, HPTLC chromatograms of products 1-35 under UV 366 nm after derivatization of the 35 Ginkgo products evaluated with terpene trilactones method. SST: Ginkgolides c, j, b, a, and bilobalide with increasing R_F values.

Table 1: classification of the products according to their label claim

Type	Label claim	total	Sample(s) number
1	Extracts standardised to contain 24% of flavone glycoside and 6% of terpene lactones	18	1, 2, 4, 6, 7, 9, 11, 12, 14, 17, 21, 22, 23, 25, 24, 29, 31, 35
2	Extracts standardised to contain 24% of flavone glycoside (solely)	4	5, 8, 20, 27
3.a	Provide the drug extract ratio (50:1) but no additional information	19	10, 13, 15, 16, 18, 19, 26, 30
3.b	provide the drug extract ratio (50:1) and declare to contain 24% of flavone glycoside and 6% of terpene lactones		1, 7, 11, 14, 17, 21, 22, 29, 31
3.c	Provide the drug extract ratio (50:1) and declare to contain 24% of flavone glycoside		5
3.d	Provide the drug extract ratio (50:1) and to contain both leaf powder and extract		3
4	Declare to contain Ginkgo leaf powder and extract	2	3 (?), 27
5	No specification about the extract	4	28, 32, 33, 34
6	Extract enhanced with Rutin	1	29
7	Only leaf powder (no extract)	2	34, 28