Table 1. Adjunctive use of herbal products and antidepressants and adverse events

Drug	Drug dosage	Condition(s) (N analysed in group taking both)	Herbal product used adjunctively	Duration of use	Serious adverse events	Adverse events
Selective serotonin reuptake inhibitors (SSRIs)						
Sertraline (n=5 studies). All administered to both treatment and control groups.	100mg/day	Major depressive disorder (n=23)	Cinnamon capsules (500mg/day) – leaves of *C.tamala* purchased from herbal shop, powdered and standardised on total essential oil (1.2%) and ash (4.6%) (Ghaffari 2019) [17]	6 weeks	None	No significant difference in frequency of AEs vs placebo + sertraline group. AEs reported in both groups included morning drowsiness, constipation, dizziness, stiffness, nervousness, increased appetite, loss of appetite, dry mouth, and tachycardia.
	1 capsule/day (dose not reported)	Mild-moderate depressive disorder (n=33 high dose, n=34 low dose)	Rhodiola capsules (*Rhodiola rosea* root 0.6g/day high dose or 0.3g/day low dose) manufactured according to GMP by Tibet Gao Yuanan Biotechnology company) (gao 2020) [16]	12 weeks	None	More patients reported study-related adverse events using sertraline with placebo (n=19) versus sertraline with Rhodiola capsule at high (n=3) and low (n=6) dose (p=0.008). No clinically meaningful differences BP, pulse rate, weight or laboratory values in any group. 14-day post-study safety follow-up: no subsequent adverse effects.
	All patients controlled by sertraline for >3months	Major depressive disorder (n=26)	Nigella sativa oil capsules (1x1000mg capsule/day), generated under provision of professors according to established protocols. (Zadeh) [18]	10 weeks	NR	No complications reported in the study or 2 weeks after.
	50mg for 2 weeks then 100mg/day for 2 weeks	Generalised anxiety disorder (n=14)	Passionflower (species NR) (Pasipy ® drops – standardised hydroalcoholic extract of passionflower), 15 drops three times daily (Noujoumi 2016) [19]	4 weeks	None	Most common AEs were somnolence (23.5% Pasipy vs 20.6% placebo drops, p=0.481), nausea (20.6% vs 8.8%, p=0.319) and dizziness (14.7% vs 5.9%, p=0.155). Other AEs ≤3/ either group (allergy, asthma, sinus irritation, dermatitis, tachycardia, vomiting, excessive sedation, abnormal bleeding)
	50mg/day	Generalised anxiety disorder (n=20)	Saffron (*Crocus sativus* L. stigma) 450mg capsules 1/day (prepared in Faculty of Pharmacy, manufacturing details NR) (Jafarnia 2017) [10]	6 weeks	None	4 saffron patients reported: constipation (1 patient), polydipsia (1 patient), and headache (2 patients). All tolerable and treatment not discontinued. AEs in placebo group NR.
Fluoxetine (N=2)	20mg/day	Major depressive disorder (n=20)	Saffron (*Crocus sativus*) stigma capsules (30mg/day). High quality saffron collected	4 weeks	NR	No significant differences between saffron and placebo regarding side effects (details NR).

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			from Khorasan province, powdered and packed into capsules. (Jelodar 2018) [11]			
	20mg/day Oxetine® (note: in case of insomnia 10mg oxazepam could be given)	General anxiety disorder (n=19)	*Echium amoenum* 3x250mg capsules/day. Fresh flowers collected from northern mountains and authenticated (voucher specimen 628). 10mg flowers boiled with 300ml water for 15min, filtered and concentrated to 4.6g aqueous extract (Sayyah 2012) [20]	8 weeks	None	No significant differences in frequency of side effects vs placebo (talcum powder only). Most common AE in the extract group was headache (p=0.41). No further details reported.
Citalopram (N=1)	2x20mg/day	Depression diagnosis (n=40)	Lavender (*Lavandula angustifolia* Mill.) – 2 cups of tea (5g packages made by researchers in boiling water with sugar) daily. Source and manufacture of lavender NR (Nikfarjam 2012) [21]	8 weeks	NR	No significant difference in side effects vs citalopram only. Most common lavender side effects were nausea (12.8%) and confusion (10%), citalopram only group dry mouth (8.9%) and confusion (8%).
Escitalopram (N=1)	Doses ranged from 5-15mg, no difference in plasma concentration between groups (44 placebo vs 37ng/ml curcumin)	Diagnosis of unipolar depressive disorder (n=50)	Curcumin 2x500mg capsules/day. Powder (>95% purity, 70% curcumin, 20% demethoxycurcumin and 10% double demethoxycurcumin) purchased from Shijiazhuang Lvchuan Biological Technology Co, Ltd (Yu 2015) [14]	6 weeks	None	No significant AEs in curcumin group except mild nausea (frequency NR).
SSRIs (mixed) (N=4)	SSRI maintained at stable dose throughout	Multiple sclerosis with depressive symptoms (n=26)	Syrup (10ml 2/day). Saffron, St John's Wort, Cinnamon and grape juice (*Crocus sativus* L., *Hypericum perforatum* L., *Cinnamomum verum* J.Presl, and *Vitis vinifera* L). All purchased from a traditional herbal store and identified and quality controlled at School of Pharmacy. (64mg saffron, 357mg cinnamon, 857mg St John's Wort in 4.3ml grape syrup, increased to 10ml using sugar and distilled water) prepared in university pharmacy lab. (Adalat 2019) [26]	4 weeks	None	NR (compared to placebo syrup)
	Sertraline (11R, 11P), fluoxetine (1R, 1 P), citalopram (4R, 1 P),	Major depressive disorder (n=26)	Rosemary (*Rosmarinus officinalis* L.) 2x 350mg capsule/day, purchased from market and authenticated (voucher	8 weeks	NR	Significant differences in heartburn (11 (42%) vs 0, p=0.0001) and increased memory (21 (81%) vs 3 (12%), p=0.0001) in rosemary group

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	escitalopram (10R, 11P), fluvoxamine (0R, 1P) (p=0.587)		number KF-1245). Dried, powdered and placed into capsules. Total phenolic content 4.25w/w% and rosmarinic acid content 21.13 mg/g. (Azizi 2022) [22]			compared to placebo. No differences in nausea (23% vs 16%), headache (4% vs 4%), diarrhoea (8 vs 24%), constipation (15% vs 0%), drowsiness (51% vs 28%), increased libido (19% vs 8%) or increased appetite (15% vs 4%).
	"Under SSRI treatment with adequate dose and duration"	Generalised anxiety disorder (n=18)	Ashwagandha (*Withania somnifera* root) capsules 1x1g/day, increased to 2 or 3g at week 2 or 6 if needed. Gathered from Saravan mountain and prepared as treatment capsules according to previous protocols in university pharmacy lab (Fuladi 2020) [23]	6 weeks	NR	No significant differences in side effects between Ashwagandha and placebo. Patients monitored for common adverse effects, including gastrointestinal upset and vomiting, headache, fatigue and drowsiness, only rare side-effects were reported (no further details). A small number of patients dropped out due to dyspepsia or intolerance (sedation) but group NR.
	Fluoxetine 20mg/day or sertraline 50mg/day or citalopram 20mg/day	Major depressive disorder (n=20)	Crocin tablet (2x15mg/day). Saffron stigmas were purchased from Novin Saffron Company, and extraction and crystallisation performed according to previous protocols in a university lab and formulated into tablets. (Talaei 2015) [12]	4 weeks	None	No statistically significant difference in frequency of side effects between groups. AEs included urinary incontinence (Crocin 0, placebo 1), menometrorrhagia (crocin 1, placebo 0), dyspnoea (crocin 1, placebo 1) and agitation (crocin 1, placebo 0). Side effects in both groups caused dropout.
Serotonin and noradrenaline reuptake inhibitors (SNRIs)						
Venlafaxine (N=1)	75mg/day (could be increased to a max of 225mg/day) Lower average venlafaxine doses were required in Gingko patients (6037mg vs 6930mg per patient, p=0.007)	Post-ischaemic stroke depression (n=40)	Gingko biloba 3x40mg/day (no further details) (Liang 2019) [24]	8 weeks	None	Gingko group had fewer AEs (significance NR). AEs included constipation (n=3), dizziness (n=2), nausea (n=1), headache (n=2), drowsiness (n=3), and insomnia (n=1). AEs in control (venlafaxine only) included abdominal distension (n=3), dizziness (n=4), nausea (n=2), headache (n=5), drowsiness (n=6), insomnia (n=4), and fatigue (n=3). All AEs mild and disappeared quickly.
Tricyclic antidepressants (TCAs)						
Combination of nortriptyline,	Nortriptyline 75-100 mg/day, imipramine &	MDD (mild-moderate) (n=20)	St John's Wort (*Hypericum perforatum*). Perforan pills (300mcg total hypericin) (Paksereshat 2012) [25]	6 weeks	NR	Quality of sleep: significantly increased in perforin group vs placebo. GI complications: significantly lower than in placebo group.

Drug	Drug dosage	Condition(s) (N analysed in group taking both)	Herbal product used adjunctively	Duration of use	Serious adverse events	Adverse events
imipramine & amitriptyline (n=1)	amitriptyline 100-150 mg/day (n=1)					Energy: increased energy and lower fatigue in perforin group. Photosensitivity: developed in 3 patients (drug continued with sunscreen). Sexual side effects: none in either group. Autonomic NS problems: none in either group. Drowsiness and fatigue: none in either group. Frequency and further details NR.
Mixed (N=2)						
	Stable dose for previous 4 weeks Antidepressants used by 64% LDC (SSRI 44%, other 20%), 48% high dose curcumin (32% SSRI, 16% other), 50%LDC+S (35% SSRI, 15% other) and 42% placebo (32% SSRI, 10% other)	Major depressive disorder (HDC 30, LDC 26, LDC+S 24)	High dose curcumin (500mg BCM-95® 2/day), Low dose curcumin (250mg BCM-95® 2/day), low dose curcumin-saffron combination (250mg BCM-95® + 15mg saffron, 2/day) All supplied by Dolcas-Biotech LLT. BCM-95 contains total curcuminoids 88% and volatile oils 7% from *Curcuma longa* Linn. rhizomes. Saffron (Affron®) derived from *Crocus sativus* L. stigma and standardised to >3.5% Lepticrosalides. (Lopresti 2017) [15]	12 weeks	None	No significant differences between placebo and active drug treatment groups (N AEs HDC 19, LDC 11, LDC+S 10, placebo 16). AEs included diarrhoea (7 HDC, 2 LDC, 2 LDC+S, 1 P), headache/migraine (2 HDC, 3 LDC, 0 LDC+S, 1 placebo),hot flush (1 HDC only), stomach ache (2 HDC, 2 P), spicy aftertaste (5 HDC, 4LlDC, 2 LDC+S, 1 P) m constipation (1 LDC, 1P), nausea (1 LDC, 1 LDC+S. 1 P), vivid dreams (1 LDC+S, 3 P), dizziness (2 LDC+S. 3 P), dry eyes (1P), weight gain/increased appetite (2 HDC, 2 LDC+S, 2 P).No treatment withdrawals.
	Stable dose ≥8 weeks. Escitalopram (19 S, 20 P), sertraline (11 S 7 P), desvenlafaxine (8 S, 14 P), venlafaxine (8 S, 8 P), duloxetine (7 S, 6 P), citalopram (7 S, 5 P), fluoxetine (7 S, 9 P), amitriptyline (6 S, 0 P), mirtazapine (4 S, 1 P), paroxetine (0 S, 2 P), vortioxetine (0 S, 2 P), deptran (0 S, 1 P), agomelatine (2 S, 5 P), moclobemide (1 S, 0 P)	Mild-moderate depressive symptoms (n=72)	Saffron 2x14mg tablets/day Affron® extract from *Crocus sativus* L. stigma, standardised to >3.5% Lepticrosalides. Saffron stigmas cultivated in Alborea (Spain) and extracted in Pharmactive Biotech products factory. (Lopresti 2019) [13]	8 weeks	None	No significant AEs reported by participants, similar dropout rates. Antidepressant side effect checklist showed significant group x time interaction between weeks 4 and 8 but not weeks 0 to 4 with reductions in the saffron group (not significant when baseline ASEC scores adjusted for).

AEs = adverse events, NR=not reported, SAEs= Serious adverse events