Supplementary file 1

A systematic review on the use of phytotherapy in managing clinical depression

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Table S1. The characteristics of the included RCTs.

Citation	Origin	Study design	Experimental group				Intervention (Form/dosage/duration)	Control group			Control (Form/dosage/duration)	A/E	Outcome measurement	Main Finding
			Condition	Number	Age	Sex (F/M)		Number	Age	Sex (F/M)				
Crocus sativus														

Akhondzadeh 2004	Iran	Double-blinded RCT	Mild to moderate depression	15	35.53 ± 10.28	9/6	30 mg capsule /day (TDS) for 6 weeks	15	32.53 ± 8.10	8/7	Imipramine capsule 100mg/day (TDS)-6 week	Anxiety (N=4), appetite changes (N=3), nausea (N=2), headache (N=3), dry mouth (N=1), hypomania (N=2), constipation (N=2), urinary retention (N=2)	HDRS	effective similar to Imipramine
Noorbala 2005	Iran	Double-blinded RCT	Mild to moderate depression	20	37.30 ± 8.56	9/11	30 mg capsule /day (BD) for 6 weeks	20	36.5 ± 7.27	11/9	Fluoxetine 20 capsule mg/day (BD)-6 week	Anxiety (N=3), Change in appetite (N=2), Sedation (N=5), Nausea (N=1), Headache (N=2)	HDRS	Saffron was found to be effective similar to Fluoxetine
Akhondzadeh 2005	Iran	Double-blind, placebo controlled RCT	Mild to moderate depression	20	37.30 ± 8.56	9/11	30 mg capsule /day (BD)-6 weeks	20	35.25 ± 6.12	9/11	Placebo capsule (BD)-6 week	Anxiety (N=3), Change in appetite (N=7), Sedation (N=1), Nausea (N=2), Headache (N=3), Hypomania (N=2)	HDRS	Better result than the placebo

Moshiri 2006	Iran	Double-blind, placebo controlled RCT	Major depression	20	35.45 ± 8.19	9/11	30 mg capsule/day (BD) -6 weeks	20	35.85 ± 5.63	8/12	Placebo capsule (BD)-6 week	Anxiety (N=4), Change in appetite (N=4), Stomach pain (N=4), Tremor (N=3), Nausea (N=5), Headache (N=3), Sweating (N=2), Heart pounding (N=4)	HDRS	better outcome than the placebo.
Shahmansouri 2014	Iran	Double-blind, placebo controlled RCT	Patients who were suffering from depression after performing percutaneous coronary intervention (PCI)	20	52.05 ± 8.92	11/9	30 mg capsule/day - 6 weeks	20	53.10 ± 8.47	14/6	Fluoxetine 40 mg capsule/day-6 week	Morning drowsiness (N=1), Constipation (N=1), Decreased appetite (N=4), Dry mouth (N=1)	HDRS	the same antidepressant efficacy compared with fluoxetine

Talaei 2015	Iran	Double-blind, placebo controlled RCT	MDD patients	20	35.9 ± 7.10	18/2	One SSRI (fluoxetine 20 mg/day or sertraline 50 mg/day or citalopram 20 mg/day) plus crocin tablet (30 mg/day; 15 mg BID) – 4 weeks	20	36.5 ± 7.67	16/4	1 SSRI (fluoxetine 20 mg/day or sertraline 50 mg/day or citalopram 20 mg/day) plus placebo (two placebo tablets per day, one tablet BD) - 4 weeks	Menometrorrhagia (N=1), Dyspnea (N=1), Agitation (N=1)	BDI, BAI, MDQ, side effect evaluation questionnaire,	Significantly improved scores
Sahraian 2016	Iran	Double-blind, placebo controlled RCT	MDD patients	19	NR	NR	Saffron capsule + 20 mg fluoxetine – 4 weeks	11	NR	NR	Placebo capsule + 20 mg of fluoxetine daily – 4 weeks	-	BDI, lipid profile	Improved in depression severity No change in lipid profile
Ghajar 2017	Iran	Parallel-group, double-blind RCT	Mild to moderate MDD with anxious distress	30	37.90 ± 11.56	15/15	Saffron 30 mg capsule /day-6 weeks	30	34.17 ± 10.41	19/11	Citalopram 40 mg capsule /day-6 weeks	Headache (N=2), Nausea/ Vomiting (N=2)	HDRS + Hamilton Rating Scale for Anxiety (HAM-A)	Significant improvement in scores
Mazidi 2016	Iran	Double-blind, placebo controlled RCT	Mild-to-moderate mixed anxiety and depression	30	42.8 ± 10.65	22/8	Capsule 50 mg BD-12 weeks	30	43.6 ± 8.83	20/10	Capsule placebo BD-12 weeks	-	BDI and BAI	Significant effect on scores

Kashani 2017	Iran	Double-blind RCT	Mild to moderate postpartum depression	32	29.21 ± 7.69	All F	Saffron 15 mg capsule BD-6 weeks	32	32.09 ± 4.99	All F	Fluoxetine 20 mg capsule BD-6 weeks	Headache (N=1), Dry mouth (N=2), Nausea (N=4), Daytime drowsiness (N=1), Constipation (N=2), Sweating (N=1)	HDRS	No significant effect for time ×treatment interaction
Tabeshpour 2017	Iran	Double-blind, placebo controlled RCT	Mild-to-moderate postpartum depressive disorder	30	28	All F	Saffron tablet 15mg/ BID-8 weeks	?	28.1	All F	An equivalent dose of placebo -8 weeks	Gastrointestinal disorders (N=2), Lack of sleep (N=1), Oversleeping (N=1), Low breast milk (N=2), Bleeding gums (N=1)	BDI-II	More significant impact than placebo
Jelodar 2018	Iran	Double-blind RCT	Severe depression	20	NR	NR	Fluoxetine 20 mg/day and saffron 30 mg /day - 4 weeks	20	NR	NR	Placebo and fluoxetine 20 mg/day -4 weeks	-	BDI	Lower level in both groups

Lopresti 2018	Australia	Double-blind, placebo controlled RCT	Teenagers with mild-to-moderate anxiety or depressive symptoms	36	14.08 ± 0.21	?	Tablet 14 mg-BD-8 weeks	32	13.93 ± 0.24	?	Tablet placebo -8 weeks	nausea and stomach pain in placebo group (N=1) increased frequency of headaches in the placebo (N=5) compared to saffron group (N=1)	The youth and parent versions of the Revised Child	Improved anxiety and depressive symptoms.
Milajerdi 2018	Iran	Double-blind, placebo controlled RCT	Mild to moderate Comorbid Depression-Anxiety (CDA) in type 2 diabetic patients	25	54.57 ± 6.96	20/6	Capsule 30mg/day-8 weeks	25	55.42 ± 7.58	20/6	Capsule placebo-8 weeks	-	RCADS	No significant effect on depression Significant reduction in depression +anxiety
Ahmadpanah 2019	Iran	Double-blind, RCT	MDD in older people	22	64.48 ± 2.63	6/19	Capsule 60 mg/day- 6 weeks	20	66.72 ± 5.34	9/16	Capsule sertraline 100mg/day- 6 weeks	Tiredness (N=1)	HDRS	Symptoms of depression decreased

Akhondzadeh 2020	Iran	Double-blind, placebo controlled RCT	Overweight women with mild to moderate depression	27	37 ± 10.3	All F	Saffron 15 mg capsule - BD-12 weeks	25	39.8 ± 9.2	All F	1 placebo capsule - BD-12 weeks	One subject in the saffron group reported the side effect "hives"	BDI	Mean depression scores decreased.
Lopresti 2019	Australia	Double-blind, placebo controlled RCT	Adults with persistent depression	68	40.4 ± 1.44	57/23	Saffron 14 mg tablet-BD-8 weeks	65	39.65 ± 1.31	56/24	Placebo tablet -8 weeks	No significant adverse events	MADRS, MADRS-S, ASEC, SF-36 subscale scores	AImprovement symptoms in MADRS but not in MADRS-S.
Lavandula angustifolia														
Kasper 2016	Germany	Double-blind, placebo controlled RCT	MADD	141	47.7 ± 12.6	105/54	Silexan (an active substance produced from Lavandula angustifolia) 80 mg capsule/day-10 weeks	128	47.9 ± 12.6	113/43	Capsule placebo - 10 weeks	Eructation (n=16), Headache (n=4), Nasopharyngitis (n=3), Diarrhea (n=2), Nausea (n=3)	HAMA, MADRS	Better clinical outcomes
Nikfarjam 2013	Iran	RCT	Depressed patients taking Citalopram.	40	40.6	13/17	2 cups of Lavandula angustifilia infusion + tablet Citalopram 20 mg (BD)-8 week	40	40	24/16	Citalopram 20 mg tablet (BD)-8 week	In the experimental group were nausea and confusion. In the control group were dry mouth and confusion	HDRS	decreased mean depression scores

Akhondzadeh 2003	Iran	Double-blind RCT	Mild to moderate depression	Group A: 15 Group B: 15	Group A: 33.53 ± 8.81 Group B: 31.53 ± 10.22	Group A: 7/8 Group B: 6/9	Group A: Lavandula tincture- 60 drops/day-4 weeks Group B: Imipramine 100 tablet mg/day+ tincture- 4 weeks	15	33.93 ± 11.38	8/7	Imipramine100 mg tablet /day + placebo drop - 4 weeks	In the imipramine group, anticholinergic effects such as dry mouth and urinary retention headache in the lavandula tincture group	HDRS	Significant improvement
Other														
Araj-khodaei 2020	Iran	Double-blind RCT	Mild to moderate depression	Group A: 15 Group B: 15	Group A: 37.9 ± 2.4 Group B: 37.4 ± 3.3	Group A: 11/4 Group B: 10/5	Group A: L. angustifolia 1g capsule-BD-8 weeks Group B: M. officinalis 1g capsule -BD-8 weeks	15	33.4 ± 2.7	11/4	Fluoxetine 10mg capsule – BD - 8 weeks	diarrhea in placebo group (N=1) drowsiness in group A (N=1)	HDRS	The effect is similar to Fluoxetine
Safari 2023	Iran	Double-blind RCT	Type 2 diabetes patients with depression	23	52.65 ± 6.14	14/9	700 mg/day M. officinalis hydroalcoholic extract - 12 weeks	21	54.19 ± 5.99	11/10	700 mg/day toasted flour - 12 weeks	-	BDI-II, BAI, PSQI	significant decrease in depression and anxiety severity

Sayyah 2006	Iran	Double-blind, parallel-group RCT	Mild to moderate MDD	19	29.5 ± 10.1	7/12	E. amoenum 375 mg capsule/day-4 weeks	16	34.7 ± 13.6	7/9	Placebo capsule-4 week	Headache (N=9), Nausea (N=3), Dry mouth (N=7), Blurred vision (N=2), Constipation (N=2)	HDRS	Significant in reducing depressive symptoms

Abbreviations (In alphabetical order):
Adverse event (A/E); Antidepressant Side-Effect Checklist (ASEC); Anxiety and Depression Scale (RCADS); Beck anxiety inventory (BAI); Bis in die, twice per day (BID) Beck Depression Inventory (BDI); Hamilton Anxiety Rating Scale (HAMA); Hamilton depression rating scale (HDRS); Montgomery Asberg Depression Rating scale (MADRS); Mixed anxiety and depressive disorder (MADD); Mood disorder questionnaire (MDQ); Pittsburgh Sleep Quality Index (PSQI); Randomized controlled trial (RCT); Short Form-36 Health Survey (SF-36); Ter die sumendum, three times per day (TDS)