Herbal Medicines, other than St. John's Wort, in the Treatment of Depression: A Systematic Review

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Abstract
OBJECTIVE: To evaluate herbal medicines, other than St. John's wort, in the treatment of depression. DATA SOURCES/SEARCH METHODS: A computer-based search of Medline, Cinahl, AMED, ALT Health Watch, Psych Articles, Psych Info, Current Contents databases, Cochrane Controlled Trials Register, and Cochrane Database of Systematic Reviews, was performed. Researchers were contacted, and bibliographies of relevant papers and previous meta-analysis were hand searched for additional references. REVIEW METHODS: Trials were included in the review if they were prospective human trials assessing herbal medicines, other than St. John's wort, in the treatment of mild-to-moderate depression and utilized validated instruments to assess participant eligibility and clinical endpoints. RESULTS: Nine trials were identified that met all eligibility requirements. Three studies investigated saffron stigma, two investigated saffron petal, and one compared saffron stigma to the petal. Individual trials investigating lavender, Echium, and Rhodiola were also located. DISCUSSION: Results of the trials are discussed. Saffron stigma was found to be significantly more effective than placebo and equally as efficacious as fluoxetine and imipramine. Saffron petal was significantly more effective than placebo and was found to be equally efficacious compared to fluoxetine and saffron stigma. Lavender was found to be less effective than imipramine, but the combination of lavender and imipramine was significantly more effective than imipramine alone. When compared to placebo, Echium was found to significantly decrease depression scores at week 4, but not week 6. Rhodiola was also found to significantly improve depressive symptoms when compared to placebo. CONCLUSION: A number of herbal medicines show promise in the management of mild-to-moderate depression.
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Introduction

Depression is one of the top five most prevalent diseases worldwide.[1] By 2020 it is expected to be the second-leading cause of disability globally.[2] Depression typically presents as lowered mood, difficulty in thinking, loss of interest, and physical complaints such as headache, disturbed sleep, loss of energy, and change in sex drive.[3,4] It incurs substantial personal, economic, and social costs for both the individuals afflicted and those close to them.[5] In Australia, 40 percent of women and 30 percent of men are estimated to experience one or more episodes of major depression during their lifetime.[1,6] The prevalence of major depression is reported as 7.5 percent in Australia, 8 percent in Canada, and 5.4-8.9 percent in the United States.[2,6]

While there are many potential precipitating factors, it is currently believed that depression is primarily the result of biochemical alterations in the brain.[3,6] Pharmaceutical treatments, including selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA), and monoamine oxidase inhibitors (MAOI), cause alterations in brain chemistry through neurotransmitter amplification and regulation and have been shown to be effective in the treatment of depression.[4] Yet, a number of adverse reactions occur with pharmaceutical antidepressant administration, including anticholinergic effects, gastrointestinal effects including nausea and constipation, orthostatic hypotension, arrhythmias, weight gain, and sexual dysfunction.[4]

In an attempt to avoid such unwanted adverse reactions, as well as being prompted by a desire to use something natural, individuals are seeking alternatives to pharmaceutical medications. Population-based studies in Australia, Europe, and

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the United States have shown that the use of complementary and alternative medicine (CAM) is widespread,[7,8] with herbal therapy the most commonly used CAM modality in the United States.[9] The need for effective and well-tolerated agents for the treatment of depression has prompted researchers to more rigorously examine herbal medicines that have traditionally been used to treat this condition.

Research has thus far focused primarily on one herb, *Hypericum perforatum* (St. John's wort) in the management of depression.[10,11] Recent Cochrane reviews have found St. John's wort (SJW) extracts efficacious and well-tolerated in the treatment of both mild-to-moderate[12] and major depression.[13] Although mild adverse effects from SJW, such as gastrointestinal complaints, tiredness, dizziness, and allergic and photosensitivity reactions are occasionally reported,[8,14] it is the herb's effect on the major drug metabolizing enzymes CYP3A and P glycoprotein that limits its widespread prescription.[8,14,15] Because of this, the purpose of this systematic review was to evaluate clinical trials investigating the efficacy of herbal medicines, other than SJW, in the treatment of depression.

Objectives

The objective of this literature search was to evaluate herbal medicines, other than St. John's wort, in the treatment of depression.

Data Sources/Search Methods

Two of the authors (A.V.D. and J.A.H) independently performed a computer-based search of Medline, Cinahl, AMED, ALT Health Watch, Psych Articles, Psych Info and Current Contents databases (inception to April 2009). The Cochrane Controlled Trials Register and the Cochrane Database of Systematic Reviews were also searched (April 2009). The herb search term list was formulated from texts by Blumenthal et al,[16] Mills,[17] Mills and Bone,[18] and Weiss,[19] and comprises the herbs each author discussed under the headings of antidepressant, adaptogen, anxiolytic, nervine, nervous system tonic, nervous system restorative, nervous system trophorestorative, relaxant, sedative, thymoleptic, and stimulant. The authors' personal knowledge of herbs with the above actions were also included when formulating the search term list. Complete keyword list and search criteria are described in the accompanying sidebar.

The keywords and exact search criteria used were: 'depress', 'dysthymic disorder', 'dysthymia', 'dysthymic mood', 'affective disorder', 'mood disorder', 'melancholia' and 'unipolar', using AND as the combination term with 'herb*', 'botanic*', 'phyto*', 'chinese medicine', 'plant extract*', 'plant preparation*', 'complementary medicine', 'thymoleptic', 'nervine', 'adaptogen', 'asafoetida', 'ferula', 'ashwagandha', 'withania', 'astragalus', 'bacopa', 'betony', 'stachys', 'bitter orange', 'citrus', 'californian poppy', 'eschscholzia', 'catnip', 'catmint', 'nepeta', 'chamomile', 'matricaria', 'clove', 'syzygium', 'codonopsis', 'corydalis', 'yan hu suo', 'cowslip', 'primula', 'cramp bark', 'viburnum', 'damiana', 'turnera', 'dong quai', 'angelica', 'ginseng', 'panax', 'goldenrod', 'solidago', 'gotu kola', 'centella', 'green tea', 'camellia', 'guarana', 'paullinia', 'happiness bark', 'albizia', 'hoelen', 'poria', 'hops', 'humulus', 'indian snakeroot', 'rauvolfia', 'jamaican dogwood', 'piscidia', 'kava', 'piper', 'kola nut', 'cola', 'korean ginseng', 'lady's slipper', 'cypripedium', 'lavender', 'lavandula', 'lemon balm', 'melissa', 'licorice', 'glycyrrhiza', 'linden', 'tilia', 'lotus', 'nelumbo', 'magnolia', 'mistletoe', 'viscum', 'motherwort', 'leonurus', 'nutmeg', 'mystica', 'oat', 'avena', 'passionflower', 'passiflora', 'peppermint', 'mentha', 'pulsatilla', 'anemone', 'rehmannia', 'reishi', 'ganoderma', 'rhodiola', 'rosemary', 'rosmarinus', 'saffron', 'crocus', 'sceletium', 'schisandra', 'siberian ginseng', 'eleutherococcus', 'skullcap', 'scutellaria', 'squaw vine', 'mitchella', 'sutherlandia', 'tulsi', 'ocimum', 'valerian', 'valerian', 'vervain,' 'verbena', 'wild cherry', 'prunus', 'wild lettuce', 'lactuca', 'wild yam', 'dioscorea', 'yarrow', 'achillea', 'yellow jasmine', 'gelsemium', 'zizyphus', 'pukeweed', 'lobelia', 'white horehound', 'marrubium', 'black horehound', 'ballota', 'deadly nightshade', 'atropa', 'henbane', 'hyoscyamus', 'thornapple', 'jimson weed', 'datura', 'lily', 'convallaria', 'opium poppy', 'papaver', 'nux vomica', 'borage' and 'borago', all with OR as the combination term. NOT was used with the search terms 'animal', 'murine', 'rodent', 'mouse', 'mice', 'dog', 'hypericum', 'guinea pig', 'st. johns wort, 'st johns wort', 'st. john's wort', 'st john's wort', 'saint john's wort', 'saint johns wort', and 'in vitro', to eliminate irrelevant papers.

Researchers in the field were contacted, and bibliographies of papers discussing herbs for the treatment of depression, as well as previous systematic reviews and meta-analyses, were hand searched for additional references. Due to language restrictions only papers published in English were considered for analysis.

Review Methods

Inclusion and Exclusion Criteria

Study selection criteria were defined *a priori*. Study outcomes, methods, and methodological quality were evaluated independently by two investigators (A.V.D. and J.A.H.); a third investigator resolved discrepancies (D.L.W.). Trials were included if they: (1) were prospective human trials assessing the effect of herbal medicines other than SJW in the treatment of mild-to-moderate depression, (2) utilized a validated instrument to assess participant eligibility (e.g., the Diagnostic and Statistical Manual of Mental Disorders), and (3) used a validated instrument to assess clinical endpoints. All prospective study types were eligible for inclusion, including less rigorous designs (i.e., open-label, non-randomized, and uncontrolled studies).

Validity Assessment

Methodological quality was assessed according to quality criteria published by Jadad et al.[20] Reports were also assessed for evidence of allocation concealment.[21]

Data Abstraction

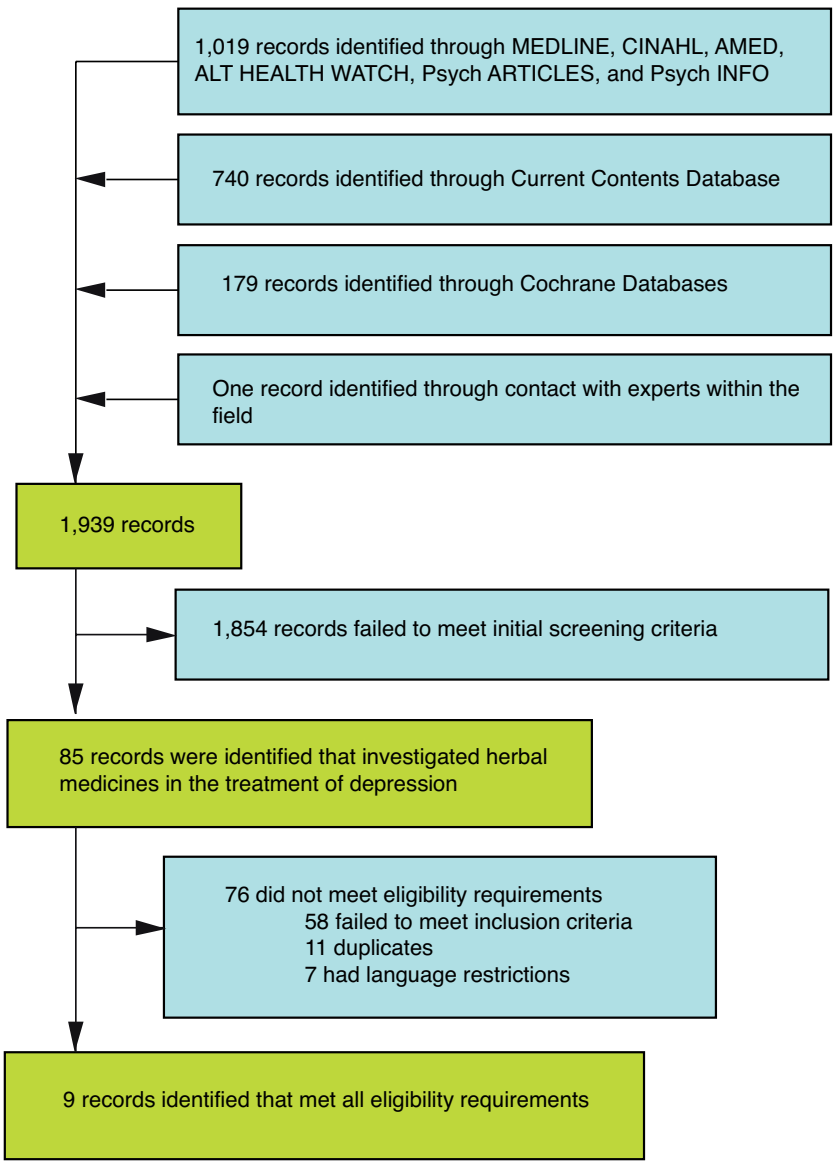
Key data taken for analysis included sample size and subject characteristics, methodological quality, and study design of individual trials, including treatment regimens, trial duration, comparators, and main outcomes. Endpoints included changes in Hamilton Rating Scale for Depression (HAM-D) scores in comparison to the comparator.

Results

Trial Flow

Overall the search of Medline, Cinahl, AMED, ALT Health Watch, Psych Articles, and Psych Info found 1,019 citations. Search of Current Contents database provided an additional 740 citations and the Cochrane Controlled Trials Register and the Cochrane Database of Systematic Reviews provided 179 citations. Communication with expert informants provided one additional paper. Hand searching and sponsoring organizations provided no new articles. In total, 1,939 reports were

Figure 1. Flow of Citations and Articles through the Phases of Screening and Eligibility Evaluation



screened, from which 85 clinical trials on herbal medicines in the treatment of depression were identified. These 85 reports were further assessed, with 76 of these records not meeting eligibility requirements: 58 failed to meet inclusion criteria, 11 were duplicates, and seven had language restrictions. Figure 1 depicts this trial flow.

Table 1. Characteristics of Subjects in the Nine Trials Included in the Systematic Review

Trial	Number of Subjects	Sex Ratio (female:male)	Age (mean)
Akhondzadeh et al (2003)	48	21:24	33.0 years
Akhondzadeh et al (2004)	30	17:13	34.0 years
Noorbala et al (2005)	40	1:1	36.9 years
Akhondzadeh et al (2005)	40	18:22	36.3 years
Sayyah et al (2006)	35	2:3	31.9 years
Moshiri et al (2006)	40	17:23	35.7 years
Basti et al (2007)	40	21:19	34.8 years
Darbinyan et al (2007)	91	53:36	45.9 years
Basti et al (2008)	44	1:1	34.8 years

Study Characteristics

Nine randomized, controlled trials were included in the review. Descriptive data for each is summarized in Tables 1, 2, and 3. Methodological quality of the included trials is outlined in Table 4.

Publication Bias

The authors cannot exclude the possibility of publication bias, as some negative trials may not have been published.

Discussion

This systematic review identified nine studies that investigated herbal medicines, other than SJW, in the treatment of mild-to-moderate depression. Three studies investigated *Crocus sativus* (saffron) stigma, two investigated saffron petal, and one compared saffron stigma to petal. Individual trials evaluating *Lavandula angustifolia* (lavender), *Echium amoenum*, and *Rhodiola rosea* were also located.

Saffron

Saffron has long been revered as both spice and medicine by a number of cultures. Frescos uncovered in Akrotiri, Greece clearly depict the use of saffron stigma as a medicine over 3,600 years ago.[22] In the Middle East, where it was originally cultivated, saffron is considered an antispasmodic, thymoleptic, carminative, cognition enhancer, aphrodisiac, and emmenagogue.[23] Several historical texts suggest an antidepressant effect. A traditional Chinese medicine (TCM) text from the Mongol dynasty mentions that "...long-term ingestion causes a person's heart to be happy."[24] In 1862, an English herbalist, Christopher Catton, was quoted as remarking: "Saffron hath power to quicken the spirits, and the virtue thereof pierceth by and by to the heart, provoking laughter and merriness...."[25]

The results of the trials included in this systematic review (Table 2) support the traditional use of saffron as a thymoleptic.[26-31] In the Akhondzadeh et al[28] study, saffron stigma was found to be significantly more effective than placebo in reducing HAM-D scores in individuals suffering from mild-to-moderate depression. The saffron group showed a considerable improvement in symptoms by week 2 of the trial, in comparison to placebo, illustrating the short amount of time taken to influence clinical outcomes.[28] When saffron stigma was compared to pharmaceutical antidepressant agents it was found to be equally effective as fluoxetine (Prozac) and imipramine in improving depression scores, and significantly better tolerated than imipramine.[26,27]

While not appearing to be traditionally used as an herbal medicine, saffron petals are significantly less expensive than the stigmas, which prompted researchers to examine their potential in the treatment of depression. When compared to placebo, administration of saffron petal resulted in significant reductions in HAM-D scores, with a decrease in depression symptoms reported by week 2 of the trial.[29] When compared to fluoxetine, saffron petal was found to be equally efficacious,

Table 2. Study Design and Primary Results of Saffron (*Crocus sativus*) Trials

Author	Extract Description	Daily Dose	Study Design	Comparator	Results	Tolerability	Industry Sponsored
Akhondzadeh et al (2004)	*Crocus sativus* (dried stigma) from Novin Zaferan Co; TIC; ethanolic (80%) extraction evaporation dried; extract not characterized	30 mg	R; DB; AC; 6 wks	Imipramine (100 mg)	Both groups showed improvement in mean HAM-D scores compared to baseline (~55% ↓ in saffron grp vs. ~58%↓ in imipramine grp; Both p<0.0001); no significant differences between treatment groups	Dry mouth observed significantly more often in imipramine group (n=7; p=0.03), as was sedation (n=6; p=0.01)	No
Noorbala et al (2005)	*Crocus sativus* (dried stigma) from Novin Zaferan Co; TIC; ethanolic (80%) extraction evaporation dried; capsules standardized to 0.3-0.35 mg safranal	30 mg	R; DB, AC; 6 wks	Fluoxetine (20 mg)	Both groups showed improvement in mean HAM-D scores compared to baseline (~54%↓ in saffron grp vs.~65%↓ in fluoxetine grp); no significant differences between treatment groups	Not significant difference between groups; trend toward a decreased incidence of sexual dysfunction (p=0.10) and tremor (p=0.10) in the saffron group	No
Akhondzadeh et al (2005)	*Crocus sativus* (dried stigma) from Novin Zaferan Co; TIC, ethanolic (80%) extraction evaporation dried; extract not characterized	30 mg	R; DB; PC; 6 wks	Placebo	Mean HAM-D scores for the saffron group lower at week 6, compared to placebo (~54%↓ in saffron grp vs. ~23% ↓ in placebo grp; p<0.001)	Not significantly different between groups; trend toward increased appetite in the saffron group (p=0.18)	No
Moshiri et al (2006)	*Crocus sativus* (dried petal) from Novin Zaferan Co; TIC; ethanolic (80%) extraction evaporation dried; extract not characterized	30 mg	R; DB; PC; 6 wks	Placebo	Improvement in mean HAM-D scores in saffron group by week two (p=0.01 compared to placebo); mean HAM-D scores in saffron group lower at week 6 compared to placebo (~60% ↓ in saffron grp vs. ~22% ↓ in placebo grp; p<0.001)	No significant difference in frequency of side effects between groups	No
Basti et al (2007)	*Crocus sativus* (dried petal) from Novin Zaferan Co; TIC; ethanolic (80%) extraction evaporation dried; capsules standardized to 0.3-0.35 mg safranal	30 mg	R; DB; AC; 8 wks	Fluoxetine (20 mg)	Improvement in mean HAM-D scores for both groups compared to baseline (~54% ↓ in saffron grp vs. ~59% ↓ in fluoxetine grp; both p=<0.001); no significant difference between groups at endpoint; no significant difference in treatments in terms of percentage of responders (≥ 50% decrease in HAM-D scores; 85% in fluoxetine grp vs. 75% in saffron grp; p=0.69) or remission rate (25%)	No significant difference in frequency of side effects between groups	No
Akhondzadeh Basti et al (2008)	*Crocus sativus* (dried petal). TIC; ethanolic (80%) extraction evaporation dried; capsules standardized to 0.3-0.35 mg safranal	30 mg	R; DB; AC; 6 wks	*Crocus sativus* (dried stigma) (30mg)	Improvement in mean HAM-D scores for both groups compared to baseline (~60% ↓ in stigma grp vs. ~54% ↓ in petal grp; both p<0.0001); no significant difference between groups at endpoint; no significant difference in treatments in terms of percentage of responders (≥ 50% decrease in HAM-D scores – 77% in stigma grp vs. 68% in petal grp) or remission rate (18%)	No significant difference in frequency of side effects between groups	No

Abbreviations: grp = group; TIC = taxonomic identity confirmed; R = randomized; DB = double-blind; PC = placebo-controlled; AC = active-control; wks = weeks; HAM-D = Hamilton Rating Scale for Depression; ↓ = decrease

with improvement in symptoms reported in both groups at week 1.[30] One trial comparing the efficacy of saffron petal to the stigma, suggests they are equally effective in the treatment of mild-to-moderate depression.[31]

The effects of saffron stigma and petal in mild-to-moderate depression compare favorably to results observed in SJW trials. Administration of both the stigma and petal resulted in reductions in HAM-D scores over a six-week period (~54% reduction in stigma group; ~56% reduction in petal group). In the positive SJW trials, reductions in HAM-D scores varied from 37-62 percent over similar time periods.[32] Thus, clinical effectiveness could be expected to be similar among these agents, although no comparative trials have been conducted.

Findings of six studies investigating saffron in both its stigma and petal form have reported positive results for its use as a treatment for mild-to-moderate depression. Studies comparing saffron to pharmaceutical antidepressants have demonstrated its beneficial therapeutic effect and its safety profile in comparison to certain antidepressants. Saffron's advantage in terms of tolerability is likely to result in improved patient compliance and provide a major clinical benefit of saffron in the treatment of depression.

Although studies have revealed positive therapeutic effects of saffron, limitations for its clinical application include taxonomic identification and adulteration issues, a widely noted concern since the time of Dioscorides.[33,34] This is an unfortunate consequence of the herbs cost.[34] As saffron stigma is one of the world's most expensive spices, positive studies demonstrating the effectiveness of saffron's much more affordable petal may give rise to an increased harvesting of saffron petal, as well as its stigma, resulting in reduced cost of the herb, possibly leading to greater utilization of saffron by herbal medicine practitioners.

Lavender

Lavender has had a long tradition of use in the treatment of conditions afflicting the digestive and nervous systems. Its traditional uses are similar to current usage – as a carminative, to promote appetite, and to relieve spasm, flatulent colic, and nausea.[35] Gerard spoke of "conserves of Lavender" served with meals "to comfort the stomach."[36] Lavender's nervine properties were employed as a remedy against faintness, nervous debility, palpitations, hysteria, and weak giddiness.[36,37] Culpeper speaks of lavender being of "…special good use for all the griefs and pains of the head and brain…."[38] This statement, along with Grieves' "…in lack of nerve power lavender will act as a powerful stimulant,"[36] suggests its long use as a treatment against lowered mood and depression.

Akhondzadah et al investigated lavender alone, imipramine alone, and a combination of lavender and imipramine in the treatment of mild-to-moderate depression in a three-arm, comparative study. Both the lavender-only and the imipramine-only treatment groups showed significant improvements in depression scores from baseline, although the improvements observed in the imipramine group were significantly greater than in the lavender-only group (Table 3).[39]

These findings suggest that lavender at this concentration, although less effective than imipramine, potentially exerted a beneficial effect in the treatment of depression. This is further supported by the findings of the lavender and imipramine combined group, where the combination was found to be significantly more effective than imipramine alone. These results suggest that lavender is an effective adjuvant therapy in combination with imipramine, resulting in a superior and quicker improvement in depressive symptoms.

Anticholinergic side effects were significantly more common in the imipramine-only group, but headache was reported more often in the lavender-only group.[39] This is an interesting side effect, given lavender's long tradition of use in the treatment of headache and migraine.[38,40-42]

Limitations of this study included short trial duration and the absence of a placebo comparator. In addition, the low dose of lavender used in this trial may have limited the degree of clinical benefits observed. The currently recommended daily dose of lavender is 2-4.5 mL per day of a 1:2 alcoholic tincture[40-42] or 6-12 mL per day of a 1:5 tincture.[42] Only 3 mL of a 1:5 tincture was investigated in this study,[39] which is only half the minimum recommended dose. Future clinical trials should evaluate larger doses of lavender.

It is also noteworthy that the dried lavender flowers used in this trial were sourced from a local herb store. Although taxonomic identification was confirmed, without quantification of key constituents the quality of the herbal product may be questionable.

Table 3. Study Design and Primary Results of Lavender, Rhodiola and Echium Trials

Author	Extract Description	Daily Dose	Study Design	Comparator	Results	Tolerability	Industry Sponsored
Akhondzadeh et al (2003)	*Lavandula angustifolia* (dried flower) sample from local Iranian herbal store; TIC; 1:5 alcoholic tincture; extract not characterized	60 drops	R; DB; AC; 4 wks	Imipramine (100 mg); imipramine (100 mg) and Lavandula combined	Lavandula tincture vs. imipramine groups both showed significant improvement in HAM-D scores compared to baseline (~39% ↓ in Lavandula grp vs. ~50% ↓ in imipramine grp; both p<0.0001); mean HAM-D scores for Lavandula group higher at week 4 (p<0.0001); Lavandula plus imipramine vs imipramine group both showed significant improvement in HAM-D scores compared to baseline (~58% ↓ in Lavandula grp vs. ~50% ↓ in imipramine grp; both p<0.0001); mean HAM-D scores for imipramine group higher at week 4 (p<0.0001)	Dry mouth observed more often in imipramine group (n=9; p=0.029), as was urinary retention (n=8; p=0.047); headache observed more often in Lavandula group (n=7; p=0.03)	No
Sayyah et al (2006)	*Echium amoenum* (dried flower) sample wildcrafted in Iran; TIC; decoction, extract concentrated with water bath; extract not characterized	375 mg	R; DB; PC; 6 wks	Placebo	Mean HAM-D scores lower in Echium group compared to placebo at week 4 (~30% ↓ in Echium grp vs. ~16% ↓ in placebo grp; p=0.02), but not week 6 (~32% ↓ in Echium grp vs. ~21% ↓ in placebo grp; p=0.07)	No significant difference between groups	No
Darbinyan et al (2007)	*Rhodiola rosea* (Dried rhizome) from Swedish Herbal Institute; TIC; standardized to 170 mg Rhodiola SHR-5 extract per tablet	340 mg and 680 mg	R; DB; PC; 6 wks	Placebo	Improvement in mean HAM-D scores in both the 340-mg and 680-mg groups compared to baseline (~35% ↓ in 340-mg grp vs. ~30% ↓ in 680-mg grp; both p=0.0001), but not in placebo group (~3% ↓); Reduction in mean HAM-D scores after 6 weeks in combined Rhodiola groups, compared with placebo group (p<0.001)	No serious adverse side-effects reported in any group	Yes

Abbreviations: grp = group; TIC = taxonomic identity confirmed; R = randomized; DB = double-blind; PC = placebo-controlled; AC = active-control; wks = weeks; HAM-D = Hamilton Rating Scale for Depression; ↓ = decrease

Echium

Echium is an herb native to Iran, where it is more commonly referred to as "ox-tongue." The tea of Echium flowers is a beverage frequently drunk by Iranian locals, where it is believed to possess mood enhancing and anxiolytic effects.[43] In line with Iranian usage, Culpeper also remarked on this herb's use in lowered mood, stating it "…is thought to be most effectual to comfort the heart and expel sadness, or causeless melancholy."[38] The study by Sayyah et al aimed to further investigate this aspect of Echium in a randomized, double-blind, clinical trial.[43]

Echium was evaluated in comparison to placebo in the treatment of mild-to-moderate depression. Although at week 4 of the six-week trial, there was a significant lowering of depression symptoms in the Echium group compared to placebo, at week 6 no significant difference between the two groups was observed; the difference, however, was close to having statistical significance (Table 3).[43] This study illustrates that Echium may have some

antidepressant activity. It was well tolerated as there was no significant difference in side effect profiles observed between the two groups. Due to Echium's long tradition of use and good safety profile, further studies using higher doses of the herb, a larger participant sample size, and longer trial duration are warranted to further assess this herb's traditional use as an antidepressant.

Rhodiola

For several centuries, *Rhodiola rosea* (golden root) has been used as an herbal medicine in Russia and Scandinavia.[44] In keeping with its modern reputation as an adaptogen,[45] it has a long history of use for increasing physical endurance, work productivity and longevity, enhancing energy levels, resisting high altitude sickness, and in the treatment of fatigue, depression, impotence, and infection including tuberculosis.[44] The Vikings are said to have used this herb to improve physical endurance. Dioscorides includes *R. rosea* in *De Materia Medica* written in 77 AD where he describes its use topically.[33] It is also described in the *Swedish Pharmacopoeia* published in 1755.[44] The use of *R. rosea* to treat depression is in line with its traditional use, particularly in regard to its role in managing fatigue and improving endurance.

The one study that investigated the effects of *R. rosea* in depression tested two doses (340 mg and 680 mg) of *R. rosea* (extract SHR-5). There were significant improvements in HAM-D scores in both active groups, but not the placebo group. Interestingly, significant improvements in depression, insomnia, emotional instability, and somatization were reported in both Rhodiola groups, but only the higher dose Rhodiola group reported significant improvements in the symptom of low self-esteem – suggesting a dose response. No serious adverse side effects were reported in any group (Table 3).[46] Further research will aid in determining the place of Rhodiola in the treatment of depression.

Conclusions

For this systematic review, trials of varying methodologies were sought, including open-label and nonrandomized trials; however, only randomized, controlled trials were found in the literature search. Although the methodological quality of the nine studies was excellent, with high Jadad scores[20] (five points for five trials, four points for three trials, and three points for one trial), and there was adequate allocation concealment for seven of the nine trials (Table 4), there were study limitations. All of the trials were of short duration and utilized relatively small numbers of participants. Future studies should utilize larger numbers of participants, have a longer follow-up period, and ideally use varying doses of each herb. It is recognized, however, that it is more challenging to find positive results when utilizing a smaller sample size, as only large effect sizes are noted; and, therefore, the authors believe the positive findings of each of the nine trials are more compelling due to their smaller number of subjects.

Another issue facing herbal medicine research in general, as well as many of the trials included in this review specifically, is extract characterization. Variations in environmental conditions, harvesting and cultivation practices, processing techniques, and storage can cause considerable variation in the chemical constituent profile of herbal medicines. This creates a challenge when it comes to the generalizability of trial results. Limited funds and lack of access to appropriate technology can be barriers to obtaining extract characterization. Of the nine trials included in this review, only three studies[27,30,31] reported phytochemical characteristics of the extract used.

Table 4. Methodological Quality of Trials

Trial	Jadad Score	Allocation Concealment
Akhondzadeh et al (2003)	3	Unclear
Akhondzadeh et al (2004)	5	Adequate
Noorbala et al (2005)	4	Adequate
Akhondzadeh et al (2005)	4	Adequate
Sayyah et al (2006)	5	Unclear
Moshiri et al (2006)	4	Adequate
Basti et al (2007)	5	Adequate
Darbinyan et al (2007)	5	Adequate
Basti et al (2008)	5	Adequate

The limitations of randomized controlled trials (RCTs) also need to be considered. For example, findings from controlled trials may not necessarily be extrapolated to an individual patient, due to differences in age, gender, ethnicity, and medical history, as findings of trials are derived from mean effects on a group basis.[47-50] RCTs also will not necessarily extrapolate to CAM clinical practice, where treatment plans are individualized and often include dietary and lifestyle modifications, nutritional supplements, and body work, in addition to herbal medicines. Further, some natural therapies and their modes of administration (e.g., herbal infusions or decoctions) are impossible to adequately blind. In light of these limitations, evidence from RCTs needs to be considered in the context of all available evidence. It is one source of information to be used alongside traditional evidence and clinical experience.

This systematic review has several limitations. Despite a broad literature search, it is possible the authors failed to locate all trials that investigated herbal medicines other than St John's wort in the treatment of depression. While studies on saffron (both stigma and petal) were consistently positive, since none of the trials on lavender, Echium, or Rhodiola have been replicated, it is impossible to make definitive statements regarding the efficacy of these three herbal medicines for depression. Another point worth noting is that the same research group from Tehran University of Medical Sciences, Iran, authored eight of the nine trials assessed in this systematic review. Replication by other investigative groups would be advantageous to further clarify findings detailed in these trials.

Future research could examine other herbs that have been used traditionally for melancholy and depression. This might include herbs such as *Verbena officinalis* (vervain), *Avena sativa* (green oats), *Eleutherococcus senticosus*, and *Schisandra chinensis*, for example.[16-19] *Leonurus cardiac* (motherwort) is another example of an herb with a long tradition of use for such ailments. As detailed by Culpeper in 1653, "There is no better herb to take melancholy vapours from the heart, to strengthen it, and make a merry, cheerful, blithe soul than this one."[38]

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