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

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Abstract

Introduction: The use of medicinal plants in the management of depression, also known as phytotherapy or herbal medicine for depression, is an area of growing interest in the field of mental health and complementary medicine.

Methods: This study used a systematic assessment of pertinent literature to assess the effectiveness of medicinal herbs in treating mild to severe depression. A comprehensive literature search was conducted to identify randomized controlled trials (RCTs) that reported data on the intervention, control group, adverse events, outcome measurements, and main findings. A summary and analysis were done on the included research data.

Results: We included 23 RCTs investigating the efficacy of herbal medicines, including *Crocus sativus*, *Lavandula angustifolia*, *Melissa officinalis*, and *Echium amoenum,* in treating depression. In general, saffron showed encouraging outcomes when used to treat mild to severe depression. With no discernible variations in the reported adverse effects, it proved to be equally efficacious as well-known antidepressants like imipramine and fluoxetine. However, it is noteworthy that not all trials yielded favorable results.

Conclusion: More investigation is required to fully understand the mechanisms of action, ideal dosage schedules, long-term effects, and relative efficacy of medicinal plants in depressive treatment.

Introduction

Depression is a prevalent mental health condition marked by enduring sadness, despair, and disinterest in activities.[1-3] The World Health Organization (WHO) states that depression affects people of all ages and backgrounds and is one of the significant causes of disability globally.[4,5] The epidemiology of depression is characterized by an increasing prevalence globally, with estimates suggesting that over 264 million people are affected by depression.[6] The burden of depression extends beyond individual suffering to impact families, communities, and societies at large.[7] Factors such as socioeconomic status, gender, age, genetics, and environmental stressors can influence the risk of developing depression.[8] Contemporary medicine plays a crucial role in managing depression and provides evidence-based treatments, personalized care, monitoring and follow-up, access to specialized services, and technology integration for patient support.[9-12] By leveraging the advances in contemporary medicine, healthcare providers can help individuals with depression achieve better outcomes and lead healthier, more fulfilling lives. Phytotherapy, also known as herbal or botanical medicine, is integral to contemporary medicine. It involves the use of plants and plant extracts to prevent,

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treat, and manage various health conditions, including mental health disorders like depression.[13] Many cultures have a long history of using medicinal plants to treat various ailments, including mental health conditions like depression.[14] Certain herbs and plants are frequently used in traditional medical systems, including Ayurveda, Traditional Chinese Medicine, and Indigenous healing methods, to treat mood problems. Some medicinal plants contain bioactive compounds that may influence neurotransmitter levels, neuroinflammation, oxidative stress, and other depression-related pathways.[15] For instance, it's thought that St. John's Wort (*Hypericum perforatum*), like other antidepressants, modifies serotonin levels.[16] Research studies have investigated the efficacy and safety of certain medicinal plants in treating depression. Herbs like Saffron (*Crocus sativus*), Rhodiola (*Rhodiola rosea*), and Ashwagandha (*Withania somnifera*) have shown promising results in clinical trials for improving depressive symptoms.[17,18] While herbal remedies are generally considered safe when used appropriately, it is essential to consider potential side effects, drug interactions, and contraindications. Some herbs may cause adverse reactions or interact with psychiatric medications, highlighting the importance of consulting a healthcare provider before using them. Systematic reviews comprehensively summarize existing research on a specific topic by systematically identifying, appraising, and synthesizing relevant studies. A systematic review can assist in compiling information on the effectiveness, safety, and mechanisms of action of different herbal therapies when it comes to medicinal plants for depression. By critically evaluating the methodological quality and risk of bias in individual studies, a systematic review can assess the overall strength of the evidence supporting the use of medicinal plants for depression. This method assists in identifying areas that require more investigation, discrepancies in the findings, and knowledge gaps. Therefore, our goal was to provide a thorough analysis of the body of research on the use of herbal medicine to treat depression.

Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement was followed in conducting this systematic review.[19]

Search strategy

An electronic database (PubMed) searches for and reviews the available evidence. The search time was until October 2023. Boolean operators and combinations of keywords were used to find relevant studies. The key terms used for the search include the following: Major depressive disorder, Depression, Depressive Disorder, Melancholia, Dysthymia, Mood disorder, Affective disorder, scientific names, and common names of the medical plants. The medicinal plants mentioned by Ibn Sina in the Canon of Medicine for depression, which he referred to as Mofarrehat, were collected. The list of these plants is detailed in Table 1.

Inclusion and exclusion criteria

Studies were included if they met the following conditions: 1) Human randomized clinical trial; 2) Individuals who are diagnosed with depression with no age or gender limitation; 3) The intervention involves the use of the plant in the oral form of a drug. Excluded studies: used another study design (e.g., observational), were another publication type (e.g., systematic reviews), used another intervention or type of drug, investigated combinations of herbs, and were published in a language other than English.

Table 1. Names of plants as Mofarrehat in the Canon of Medicine

Scientific name	Family	Name in Persian medicine
Albizzia julibrissin L.	Leguminosae	Abrisham
Centaurea behen L.	Compositae	Bahman
Cinnamomum zeylanicum L.	Lauraceae	Darsini
Cinnamomum camphora J.Presl	Lauraceae	Kaphour
Cinnamomum cassia J.Presl	Lauraceae	Sazej
Citrus media L.	Rutaceae	Utruj
Corallium rubrum	Corallidae	Bosd
Coriandrum sativum L.	Apiaceae	Kozboreh
Crocus sativus L.	Iridaceae	Saffron
Curcuma zedoaria (christm) Roscoe	Zingiberaceae	Jadvar
Cyperus longus L.	Cyperaceae	Soud
Doronicum pardalianches L.	Compositae	Durunaj
Echium amoenum Fisch & C.A.Mey	Boraginaceae	Lesan-Al-Sour
Elettaria cardamomum Maton.	Zingiberaceae	Gagoleh
Ficus carica L.	Moraceae	Teen
Hyacinthus orientalis L.	Asparagaceae	Sunbul
Inula helenium L.	Compositae	Rasen
Lavandula angustifilia Mill	Lamiaceae	Ustokhodus
Malus domestica Borkh	Rosaceae	Tofah
Melissa officinalis L.	Lamiaceae	Badranjbuyeh
Ocimum basilicum L.	Lamiaceae	Badruj
Phyllanthus emblica L.	Phyllanthuceae	Amole
Pistacia vera L.	Anacardiaceae	Festeg
Polypodium vulgare L.	Polypodiaceae	Basfayej
Polyporus officinalis Laricifomes officinalis	Fomitopsidaceae	Garigon
Saccharum officinarum L.	Poaceae	Tabashir
Santalum album L.	Santalaceae	Sandal
Taxus Baccata L.	Taxaceae	Zarnub
Terminalia chebula Retz	Combretaceae	Halilaj
Zingiber zerumbet Roscoe ex Sm	Zingiberaceae	Zoronbad

Data extraction

Two members independently reviewed the studies in the first stage according to the abstract and title and, if necessary, used the articles' full text. In case of disagreement, the judgment was made by a third person. Using a Microsoft Excel spreadsheet, two reviewers independently extracted study-related data, including the author's name, year of publication, origin, sample size, outcome measurement tools, intervention type, dosage, duration of use, and other detailed information.

Quality assessment

The quality of studies was evaluated using the Cochrane risk of bias (RoB) assessment tool.[20] The Cochrane RoB assessment tool consists of several domains or criteria commonly associated with biases in research studies. These domains typically include: 1. Selection Bias: This domain assesses the methods used to select participants and assign them to different study groups, such as random sequence generation and allocation concealment. 2. Performance Bias: This domain evaluates whether participants and researchers knew the interventions being administered, which could influence outcomes or introduce bias. 3. Detection Bias: This domain examines how outcomes were assessed and whether there was blinding of outcome assessors to minimize bias. 4. Attrition Bias: This domain considers the completeness of outcome data and whether missing data or dropouts could impact the results. 5. Reporting Bias: This domain focuses on selective reporting of outcomes or analyses, which can distort the interpretation of study findings. 6. Other Sources of Bias: This area includes other possible sources of bias not addressed by the preceding domains, such as funding sources, conflicts of interest, or protocol violations in the study.[20]

Data synthesis

A meta-analysis was neither appropriate nor practicable because of the significant heterogeneity in the included studies. The studies varied significantly in terms of intervention and population. As a result, pooling the data for quantitative synthesis was deemed inappropriate, and a narrative synthesis of the findings was conducted instead.

Results

Literature search

A total of 670 records were identified through the databases. According to the study type, 325 articles were excluded. Moreover, 345 studies were selected for screening. After removing the duplicate studies unrelated to the subject, one hundred and twenty-eight essays remained. One hundred five full-text articles were excluded for the following reasons: The study participants had diseases other than depression or did not have major depressive disorder criteria at the beginning of the clinical trial (n = 37). Studies whose type of intervention was different than the oral method (for example, aromatherapy and topical) (n = 32) study had a non-pharmacological intervention (n = 23), and studies that investigated the effect of a combination of herbs, at least two herbs (n = 13) The final number of 23 RCTs were selected for this review.[21-43] Fig. 1 presents a flowchart that illustrates choosing studies.

Study characteristics

Table S1 displays the characteristics of the 23 RCTs that are included. Included studies investigated the effects of phytotherapy, specifically saffron (*Crocus sativus*), in the treatment of depression. While all the included studies were RCTs, they differ in binding, having a placebo arm or a parallel group. The studies primarily focus on individuals with mild to moderate depression, although some also include patients with postpartum depression,[29,42] or depression related to specific conditions like percutaneous coronary intervention (PCI).[41] In addition, depression in type 2 diabetes patients was addressed by some studies.[34,38]

Interventions

It's important to note that the interventions' specific dosages, frequencies, and durations vary across studies. In the majority of the RCTs, the experimental group received saffron capsules. The dosage varied between 30 mg to 50 mg/d, and the duration of intervention ranged from 4 weeks to 12 weeks. Saffron capsules were administered either once daily (OD), twice daily (BD), or three times daily (TDS). In the Akhondzadeh et al study, the control group received imipramine capsules at 100 mg daily (TDS) for 6 weeks.[22] In several studies, including Noorbala et al, Moshiri et al, Talaei 2015, and Sahraian et al, the control group received fluoxetine capsules at 20 mg/d (BD) or 40 mg daily for 6 weeks.[35,37,39,43] The control group in the Moshiri et al study received placebo capsules twice daily (BD) for 6 weeks. Placebo capsules contain inactive substances and serve as a comparison to evaluate the effects of the active intervention.[35] In the Talaei 2015 study, the intervention group received one of the selective serotonin reuptake inhibitors (SSRIs), either sertraline or citalopram, in addition to a crocin tablet.[43] The dosages were 50 mg/d for sertraline or 20 mg/d for citalopram, alongside a crocin tablet at a dosage of 30 mg/d (15 mg twice daily) for a duration of 4 weeks.[43] In the Sahraian et al study, the experimental group received saffron capsules in combination with 20 mg of fluoxetine daily for 4 weeks.[39] In the Ghajar et al study, the intervention group received one of the SSRIs (citalopram, fluoxetine, or sertraline) along with placebo tablets twice daily (BID) for 4 weeks.[27]Aside from saffron, use of other phythotherapeutic agents were investigated through other RCTs, including *Lavandula angustifolia,*[23,26,30,36] *Melissa*

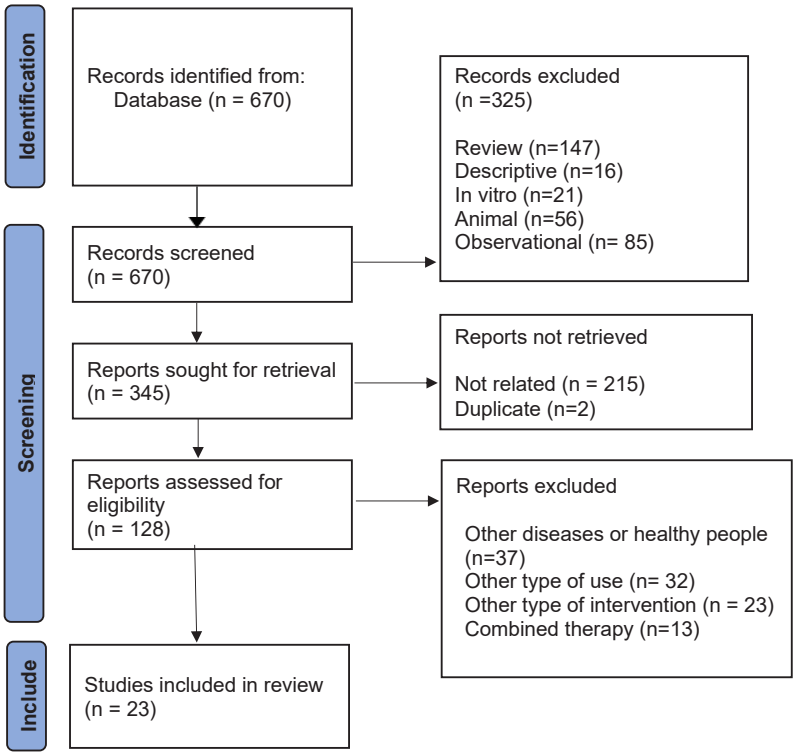

Fig. 1. Study flow diagram.

officinalis,[26,38] and *Echium amoenum.*[40]

Outcome measures

In order to evaluate how effectively the treatments worked in lowering depressed symptoms and enhancing general mental health, several outcome measures were employed. The choice of outcome measures may vary across included RCTs. Based on the frequency with which these tools were used, they will be addressed in the following paragraphs.

A. Hamilton Depression Rating Scale (HDRS): The HDRS consists of several items related to mood, sleep, anxiety, weight loss, and other symptoms of depression. The scale is scored based on the presence and severity of symptoms, with higher scores indicating more severe depression.[21-23,25-27,29,35-37,40,41]

B. Beck Depression Inventory (BDI): This is a self-report tool that gauges how severe depression symptoms are. It consists of multiple items assessing various aspects of depression, including mood, guilt, irritability, and physical symptoms. Based on their experiences throughout the last two weeks, participants rank each item, and the total score on the BDI indicates the level of depressive symptoms, with higher scores indicating more severe depression.[24,28,33,39,43]

C. Beck Depression Inventory-II (BDI-II): The BDI-II is a self-report questionnaire designed to measure depression severity, much like the BDI. It contains things about physical, emotional, and cognitive symptoms of depression. The total score on the BDI-II indicates the severity of depressive symptoms.[38,42]

Further details on the study measures are available in Table S1 (see Supplementary file 1).

Therapeutic effects

Based on the information in the table, the studies suggest that saffron (*Crocus sativus*) may have therapeutic effects in managing depression. The main therapeutic effect observed in the studies is reducing depressive symptoms. Participants who received saffron intervention showed improvements in their depressive symptoms compared to baseline and/or the control groups. The reduction in symptoms was assessed using rating scales such as the HDRS, BDI, and BDI-II. According to specific research, saffron can be just as beneficial as prescription antidepressants, such as fluoxetine or imipramine. The saffron intervention showed comparable or similar reductions in depressive symptoms compared to the control groups receiving these medications. This suggests that saffron may have a similar therapeutic impact on depression as conventional antidepressants. Some studies investigated the use of saffron as an adjunctive therapy alongside standard antidepressant medications like fluoxetine, sertraline, or citalopram. The results indicated that the combination of saffron with these medications may have additional benefits in reducing depressive symptoms compared to medication alone.

Safety profile

The reported side effects in the studies. Here are the common side effects that were mentioned:

- Anxiety: Reported in multiple studies, including Akhondzadeh et al, Noorbala et al, and Moshiri et al.[22,35,37]
- Change in appetite: Reported in multiple studies, including Akhondzadeh et al, Noorbala et al, Moshiri et al, and Ghajar et al.[22,27,35,37]
- Nausea: Reported in multiple studies, including Akhondzadeh et al, Moshiri et al, Talaei 2015, and Ghajar et al.[22,27,35,43]
- Headache: Reported in multiple studies, including Akhondzadeh et al, Noorbala et al, Moshiri et al, and Ghajar et al.[22,27,35,37,43]
- Sedation: Reported in studies like Noorbala et al and Ghajar et al.[27,37]
- Dry mouth: Reported in Akhondzadeh et al.[22]
- Hypomania: Reported in Akhondzadeh et al and Moshiri et al.[22,35]
- Constipation: Reported in Akhondzadeh et al and Moshiri et al.[22,35]
- Urinary retention: Reported in Akhondzadeh et al.[22]
- Stomach pain: Reported in Moshiri et al.[35]
- Tremor: Reported in Moshiri et al.[35]
- Sweating: Reported in Moshiri et al.[35]
- Heart pounding: Reported in Moshiri et al.[35]
- Menometrorrhagia: Reported in Sahraian et al.[39]
- Dyspnea: Reported in Sahraian et al.[39]
- Agitation: Reported in Sahraian et al.[39]
- Morning drowsiness: Reported in Shahmansouri 2014.[41]
- Decreased appetite: Reported in Shahmansouri 2014.[41]
- Vomiting: Reported in Ghajar et al.[27]

Methodological quality

Based on the Cochrane risk of bias tool, one study in random sequence generation and three studies in allocation concealment were high risk. Two studies did not explain how participants were blinded. One study specified Detection bias as high risk, but it was unclear in four studies. Attrition bias was determined as high risk in six studies, unclear in one study, and low risk in the remaining studies. Regarding reporting bias, one study was specified as high risk because of incomplete reporting of outcome data, and four studies were classified as unclear. Fig. 2 and Fig. 3 show the risk of bias summary and risk of bias graft respectively.

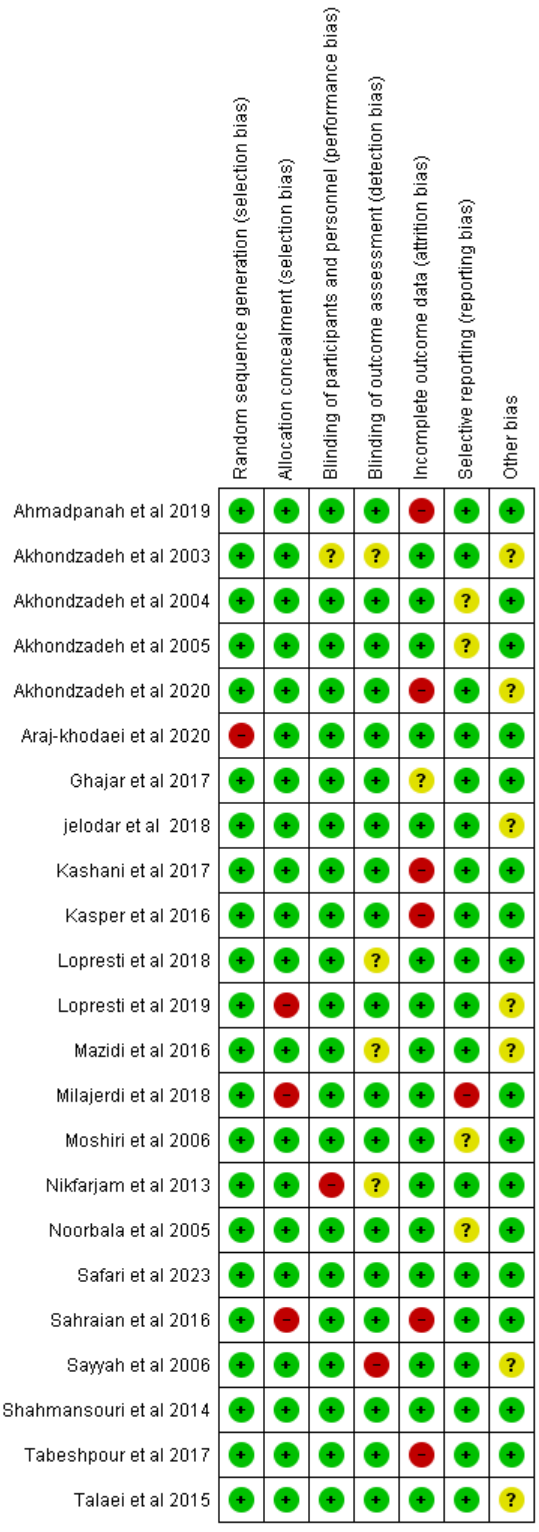

Fig. 2. Risk of bias summary.

Discussion

Depression is a prevalent mental health disorder that poses significant challenges in terms of effective treatment and management. While conventional pharmacological approaches, such as antidepressant medications and psychotherapy, are commonly utilized, there is growing interest in exploring alternative treatment options, including phytotherapy.[44-46] This systematic review aimed to evaluate the use of phytotherapy in the management of depression, with a particular focus on the effectiveness and safety of herbal interventions. The included studies primarily focused on the use of *Crocus sativus* (saffron) as an herbal intervention for depression. Saffron showed encouraging therapeutic benefits, reducing depression symptoms in a way that was on par with typical

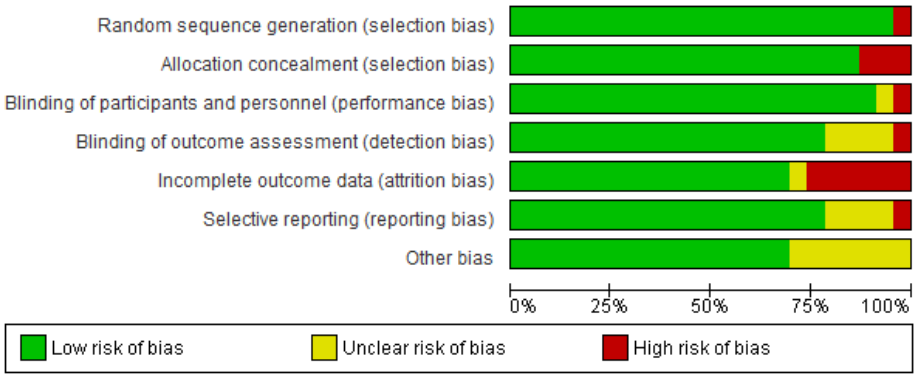

Fig. 3. Risk of bias graph.

antidepressant drugs like imipramine and fluoxetine. These results suggest that saffron may be a viable alternative or adjunctive treatment option for individuals with depression. Moreover, saffron was generally well-tolerated, with only mild and transient side effects reported. This favorable safety profile is encouraging, as it suggests that saffron may provide a potentially safer option compared to some conventional antidepressant medications, which can be associated with side effects and tolerability issues.[47] However, it is essential to note that the studies reviewed had relatively small sample sizes and varied dosages and treatment durations, warranting caution in generalizing the findings. Another central point to discuss is that patients with depressive symptoms may prefer phytotherapeutic approaches over conventional treatments for several reasons. For instance, phytotherapeutic approaches often involve using natural herbs and plants, which some patients may find more appealing than synthetic medications. They may feel that a holistic approach that addresses their mental health through natural remedies aligns more with their values and beliefs.[48] Also, many conventional antidepressant medications can have significant side effects, such as weight gain, sexual dysfunction, and insomnia.[49] Patients may be drawn to phytotherapeutic treatments because they are perceived to have fewer side effects and be gentler on the body.[50] While scientific evidence supporting the effectiveness of phytotherapeutic treatments for depression is limited, some patients may believe that these natural remedies are just as effective as conventional medications. Placebo effects and the power of belief can also affect how patients perceive the effectiveness of different treatment approaches.[51,52] Therefore, the present review clearly emphasizes the necessity of more study in this area. In addition, although phytotherapy has been getting more recognition worldwide as a complementary and alternative medicine to treat depression, the underlying mechanism of its effectiveness is not well understood yet. When it comes to depression symptoms, several mechanisms are believed to be involved in how phytotherapy can help:

- Neurotransmitter modulation: Some herbs used in phytotherapy for depression, such as St. John's Wort, may act on neurotransmitters like serotonin, dopamine, and norepinephrine. These herbs can help regulate these neurotransmitters, which are essential for mood regulation.[53]
- Anti-inflammatory effects: Chronic inflammation has been linked to depression, and some herbal remedies have anti-inflammatory properties. By reducing inflammation in the body, these herbs may help alleviate depressive symptoms.[54]
- Antioxidant effects: Oxidative stress is another factor that can contribute to depression. Certain antioxidant-rich herbs may lessen oxidative stress and shield brain tissue from harm, which may elevate mood.[55]
- Adaptogenic effects: Adaptogens are a class of herbs that help the body adapt to stress and maintain balance. Adaptogenic herbs can strengthen resistance to depressive symptoms and lessen the adverse effects of stress on mental health by assisting the body's stress response system.[56]
- Anxiolytic effects: Some herbs used in phytotherapy have calming and anxiety-reducing effects, which can be beneficial for individuals experiencing symptoms of anxiety along with depression. These herbs may help improve overall mood by promoting relaxation and reducing anxiety.[17,54]

It's crucial to remember that even while phytotherapy might be a proper adjunctive strategy for treating depressive symptoms, it cannot take the place of expert medical guidance and care. Hence, it's essential to consult with a healthcare provider to develop a comprehensive treatment plan that may include phytotherapy and other interventions such as therapy and medication.

Strengths and limitations

Identifying gaps in the existing literature through a systematic review can help prioritize future research directions, such as conducting well-designed clinical trials, mechanistic studies, or long-term follow-up

Research Highlights

What is the current knowledge?

- Medicinal plants are increasingly being used in the management of depression, known as phytotherapy or herbal medicine for depression.
- A study assessed the effectiveness of medicinal herbs in treating depression through a systematic review of relevant literature.

What is new here?

- 23 RCTs were included in the study, focusing on herbs like Crocus sativus, Lavandula angustifolia, Melissa officinalis, and Echium amoenum.
- Not all trials yielded positive results, indicating the need for further research to understand mechanisms of action, optimal dosages, long-term effects, and overall efficacy of medicinal plants in treating depression.

investigations on promising medicinal plants for depression. This process contributes to advancing the scientific understanding of phytotherapy in mental health. Transparency and Reproducibility: Systematic reviews follow a transparent and reproducible methodology to ensure the reliability and validity of their findings. Another limitation of this systematic review is the inability to perform a meta-analysis due to substantial heterogeneity among the included studies. Significant variability in study designs, populations, interventions, and outcomes across the included studies hindered the ability to synthesize the data quantitatively. As a result, the findings were synthesized narratively, which may limit the precision and generalizability of the conclusions drawn from this review. It is worth noting that this systematic review focused primarily on saffron, and limited information was available on other herbal interventions for depression. Future research should explore the potential of other herbal remedies, such as *Lavandula angustifolia* (English lavender), St. John's wort, and others, to provide a comprehensive understanding of the efficacy and safety of phytotherapy in depression. Future studies should aim to elucidate the specific pharmacological mechanisms through which saffron exerts its antidepressant effects. Additionally, large-scale randomized controlled trials with standardized protocols are warranted to establish the optimal dosages, treatment durations, and long-term safety profile of saffron in depression management.

Saffron may offer therapeutic advantages and be a viable therapy choice for those with depressive symptoms, according to the systematic review's findings. The studies utilized different study designs, including double-blinded RCTs and placebo-controlled RCTs. Comparable results were seen with saffron and traditional antidepressants such as imipramine and fluoxetine, with no significant differences in terms of observed side effects. It is crucial to remember that not all trials had excellent results, and further investigation is required to thoroughly understand the possible advantages and restrictions of saffron as a depression cure. Overall, for those with mild to severe depression, the results of this systematic review offer early evidence in favor of using saffron as an alternative or complementary treatment.

Conclusion

Medicinal plants are being progressively explored for managing depression through phytotherapy or herbal medicine. Numerous clinical trials evaluated the effectiveness of medicinal herbs in treating depression. Some plants appeared promising in treating depression, comparable to conventional antidepressants. Further studies are required to understand the mechanisms of action, optimum doses, and longer-duration effects.

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Authors' Contribution

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Writing-Review & Editing: Fateme Tahmasbi, Mohammad Reza Mirzaei, Solmaz Asnaashari.

Competing Interests

Authors declare no conflict of interests.

Ethical Statement

All data generated or analyzed during this study are included in this article and the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Supplementary files

Supplementary file 1 contains Table S1.

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