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The Potential of Saffron as an Add-on in Treating Mild to Moderate Depression in Adults: A Literature Review

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Abstract:

Depression is one of the most prevalent mental health disorders affecting five percent of the world's adults. Depression can cause suicide which is one of the top four causes of death for people aged 15-29 (World Health Organization, 2023). Due to its prevalence in the global population, the treatment of depression has received much attention. Despite advancements in treatment, current approaches often yield suboptimal results, with many medications associated with significant side effects. This has led to a global trend toward exploring natural therapies with stronger efficiency and fewer adverse effects. Saffron is a medicinal herbal and its extracts have emerged as a promising candidate due to its demonstrated antidepressant properties, especially in the treatment of mild to moderate depression. However, the application of saffron as a therapeutic option is complicated by its high cost, which led to issues with product authenticity (Raina et al., 2023), and concerns regarding long-term safety and tolerability. This literature review aims to provide a comprehensive analysis of saffron's potential as a treatment for depression by critically examining the advantages and limitations of using saffron in this context, including its efficacy, safety profile, and economic viability. It will also summarize the interesting findings from former clinical trials. In short, the review seeks to assess the feasibility of incorporating saffron as an adjunctive therapy for mild to moderate depression in adults, highlighting both its potential benefits and the challenges that need to be addressed for broader clinical use.

Keywords:- saffron, depression, herbal, antidepressant, adjunctive therapy

1. Introduction

Depression is a classic case of mental illness featuring a long period of depressed mood and lack of interest in life (World Health Organization, 2023). In addition to constant low mood, there are other signs of depression such as self-harm and suicidal tendencies. According to The American Psychiatric Association's Diagnostic Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), depressive disorder can be divided into two following categories by severity: clinical depression or major depressive disorder (MDD) and persistent depressive disorder (PDD). Besides, there are some specific forms of MDD such as seasonal affective disorder (seasonal depression) and atypical depression, and other types of depression including premenstrual dysphoric disorder (PMDD), and disruptive mood dysregulation disorder (DMDD).

Among them, PDD is common which means anyone at any age can experience it. Although PDD is not as severe as major depression, its persistence can cause a lot of pain, usually lasting at least two years or more (Cleveland Clinic, 2023). Unfortunately, the pathogenesis of depression is still not clear. Depression is a mood disease affected by a variety of factors like social factors, psychological factors, and biological factors. A genetic basis, for example, is predicted as one of the reasons for depression (Schildkraut, 1965). What's more, it can be affected by life events and even depression can be induced as a side effect of drug treatment in some cases.

1.1 Mainstream Treatment

The best-known treatment for depression is a combination of pharmacotherapy and psychotherapy according to Harvard Health Publishing (2019). In drug treatment, the two mainstream drugs are selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) (Cipriani et al., 2018). Similarly, they both function by modulating neurotransmitter activity in the brain. Serotonin, for example, is a neurotransmitter in the brain that plays a key role in helping to regulate happiness and emotional states. SSRIs specifically inhibit the reuptake of serotonin, thereby increasing its availability in the synaptic cleft, which is associated with improved mood regulation. SNRIs, on the other hand, inhibit the reuptake of both serotonin and norepinephrine, thereby enhancing both mood and arousal. These mechanisms help in restoring the balance of neurotransmitters that are often disrupted in improving moods.

1.2 Treatment Challenges

Chemical drugs like SSRIs and SNRIs do have proven efficacy, but there are still some studies that show that their ability to suppress depression is limited and has little effect on a considerable number of patients (Khalil, 2022). Based on the limited efficiency, an increase in the dosage was considered. However, this approach has only a very small effect and high doses are associated with low tolerance (Jakubovski et al., 2016).

Another problem that should not be ignored is that the side effects of chemical drugs are very strong. Side effects often manifest as a range of clinical symptoms, such as addiction, worsening depressive episodes, and tolerance for chronic antidepressant medications (Batlle et al., 2018). The problem of side effects has led to poor adherence of many patients to the drug, which affects the improvement of the condition. Hence, searching for a natural, low-side-effect adjunctive treatment has become a worldwide trend.

1.3 The rise of natural treatments for depression

Natural treatments for depression have been around for two decades and are still being developed. Various herbs experiments have been carried out, including St. John's wort and Rhodiola rosea L. extract for MMD (Clement et al., 2006; Darbinyan et al., 2007). Previous literature reviews listed seven herbs that have certified efficacy, and saffron extracts and hypericum are the only two that have demonstrated efficacy in controlled clinical trials.

2. Advantages and Challenges of Saffron Extract

2.1 Function and Benefits of Saffron

Saffron (Crocus sativus L.) is one of the world's most expensive spice which is mainly grown and produced in Iran. The stigma of saffron was once used as a food additive and the petals with distinctive purple color can be used as pigment. Apart from its traditional functions, saffron has high medicinal value. There is evidence that saffron can also regulate neurotransmitter levels in the brain, maintaining higher levels of serotonin and thus improving depression (Bertagna, 2023).

Saffron has several obvious benefits as an adjunctive treatment for depression. First of all, saffron itself is very safe. The daily safe dose range reported in studies on saffron toxicity is in measured grams (Marrone et al., 2024). The existing experimental design took cost into account, which means the saffron daily intake in the trial was measured in milligrams - well below the maximum safe dose and well within the safe dose range. Second, Saffron has been used in medicine for about 4,000 years (Raman, 2023). Adapted by our ancestors for a long period, saffron acts as a natural

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antidepressant and is well tolerated by the human body (Seyedeh Farzaneh Omidkhoda & Hosseinzadeh, 2022). Third, saffron is cholesterol-free and calorie-free which means depression patients with metabolic and obesity abnormalities can also take it safely. Previous studies have shown that saffron can be a promising intervention for metabolic syndrome including obesity, high cholesterol levels, and cardiovascular disease (CVD) (Razavi & Hosseinzadeh, 2017). Although the exact relationship between depression and metabolic disease is unclear, depression is a risk factor for cardiovascular and other diseases. As a result, the potential target group for saffron antidepressant therapy also includes people with metabolic diseases, and it is even possible to cure multiple diseases in a patient at the same time.

2.2 Active Ingredients in Saffron and Cost Problem

As an independent intervention, saffron has proven antidepressant efficiency for mild-to-moderated depression. Of all the parts of saffron, the red filamentous stigma is the most useful. Three chemicals, named picrocrocin, crocin, and safranal (standardized saffron extract), respectively, determine the taste, color, and odor, in turn. The above three active ingredients are almost extracted from the stigma which means their total amount is very limited (Jelodar et al., 2018). It is estimated that 110,000 and 170,000 flowers need to be lost to obtain one kilogram of dried stigma (Vignolini et al., 2008; Gracia et al., 2009; Jéssica Serrano-Díaz et al., 2014). The petals, which make up most of the volume and mass of saffron, are missing and discarded, resulting in a large amount of waste, which is one of the reasons saffron is expensive. Other reasons for its high cost include manual labor for picking and separation after picking (Li et al., 2023; Marrone et al., 2024). The high cost increases the risk of fraud, which makes it difficult to put saffron into clinical use even if it has a good safety, tolerability, and therapeutic effect. Saffron quality cannot be guaranteed after adulteration leading to public health issues (Kumari et al., 2021).

2.3 Possible Economic Approach

To deal with this problem, Previous studies have tried to investigate the effects of combining saffron and chamomile, another medicinal plant with metabolic benefits and antidepressant effects (Keefe et al., 2016; Rengasamy et al., 2019). In a randomized, double-blind, placebo-controlled trial in 2023, researchers conducted a one-month study of adults with moderate to mild depression or with metabolic disorders such as diabetes, hyperlipidemia, and hypertension who were rated primarily using the Patient Health Questionaire-9 (PHQ-9) scale. During the trial period, patients in the experimental group were given tea bags mixed with saffron and chamomile and consumed twice a day. To control the consumption of the expensive saffron, a tea bag containing only one milligram of saffron and 20 milligrams of chamomile was prepared and the results showed a significant reduction in scores compared to the control group. In addition to demonstrating the efficacy of chamomile and saffron tea bags as an additive for depression in adults, the trial provides a good idea for controlling the cost of treatment by combining two natural herbs, so that the required dose of both herbs is significantly lower than using only one, making the treatment regimen more economical. At the same time, some additional benefits such as reduced the high-density lipoprotein (HDL) levels may regulate metabolic abnormalities (Ahmad et al., 2023).

In another double-blind randomized trial investigating the efficacy of co-administration of curcumin and saffron in treating MDD, combination therapy improved depressive symptoms compared with placebo significantly (Lopresti & Drummond, 2017). The highlight of this article is that the trial period is long enough to have 12 weeks to avoid the bias caused by too short a course of treatment. Secondly, it consisted of four groups that received different treatment regimens: the placebo group, the low-dose curcumin group (250mg b.i.d.), the high-dose curcumin group (500mg b.i.d.), and the group with low-dose curcumin extract and saffron (15mg b.i.d.). All three experimental groups experienced relief from depression, and there was no difference in effectiveness between different doses of curcumin. In addition, the combined group performed better on The Spielberger State-Trait Anxiety Inventory (STAI), a scale with measures highly correlated with measures of depression (Kennedy et al., 2001).

In order to make saffron therapy more affordable, the increase in the extraction of effective antidepressant ingredients will boost the realization of this therapy. In the latest comprehensive review, researchers are trying to explore biosynthesis of crocin and picrocrocin molecules. Synthetic biology is promising to improve saffron production (Kumari et al., 2021).

All in all, the efficiency of co-administration of saffron and another herbal is being actively explored by several researchers recently. Future research on alternative herbal options besides saffron should continue to focus on medicinal plants that are more affordable and available than saffron in pursuit of reducing side effects in the treatment process. At the same time, the development of technologies that can synthesize saffron gives us hope of getting enough effective antidepressant ingredients.

3.Review of Clinical Studies

3.1 Summery for Placebo-controlled Studies

The potential and effectiveness of saffron adjuvant therapy has been continuously tested recently, and this literature review selects several representative clinical trials over the past ten years using Google Scholar, Scopus and PubMed for comparison and review. The studies chosen are mainly double-blind, randomized and placebo-controlled.

A clinical study carried out in 2015 mainly examine the effect of co-administration of SSRIs and saffron. During the 4 weeks treatment, total number of 46 MDD patients receive either SSRIs (fluoxetine 20 mg/day or sertraline 50 mg/day or citalopram 20 mg/day) with crocin tablets (15mg/day) or SSRIs with placebo. Result from filled beck depression inventory (BDI), beck anxiety inventory (BAI) and general health questionnaire (GHQ) all show a significant drop in scores occurred in the experimental group. Although evidence supported the efficiency of saffron as adjunctive method, there are 6 patients dropped out and cases with agitation were found in both groups. Other symptoms leading to discontinuous treatment includes agitation and menometrorrhagia in crocin group. Researchers attributed these conditions to the side effects of SSRIs (Talaei et al., 2015). Also, in this study, patients receive only one SSRIs (fluoxetine or sertraline or citalopram) but there is no report on the effect among different SSRIs.

To test the efficiency of saffron therapy for woman with postpartum depression, scientists began a two-mouth experiment in 2017. The reason for choosing saffron is that mothers are more receptive to natural medicines. Since many new mothers with mild to moderate postpartum depression are resistant to synthetic antidepressants, fearing they will have an adverse effect on their breast milk (Tabeshpour et al., 2017). The complete response rates (66% for saffron and only 6% for placebo) based on Beck Depression Inventory-II (BDI-II) scores give the supporting results.

In 2018, a treatment involving saffron and fluoxetine was launched for adults with MDD. Although the Beck questionnaire value used in the trial showed that saffron did not enhance fluoxetine, the saffron group had a greater improvement in homocysteine levels, a physiological marker that has been reported to be associated with the pathogenesis of depression (Plante, 2005; Jelodar et al., 2018).

In 2019, a clinical study set out the purpose to investigate the antidepressant effects of saffron in a group of adults taking a single antidepressant and suffering from persistent depression. Patients who used other herbs or had severe suicidal tendency or self-harm behaviors were excluded. The outcomes are measured by Aberg Depression Rating Scale (MADRS) and Aberg Depression Rating Scale, self-report (MADRS-S). MADRS clinical credibility and reliability and MADRS-S is recommended as a good complement to MADRS (Williams and Kobak, 2008). Nine symptoms were evaluated on these scales: sadness, tension, sleep, appetite, concentration, initiative, interest, pessimism and suicidal ideation. During the eight weeks experiment, a total of 160 participants were given either a placebo or a saffron pill twice a day in addition to their original medication, and the results were collected by Posting online questionnaires or telephone interviews. After statistical analysis, MADRS showed a significant difference between the two groups, which means the degree of depression in the experimental group and control group decreased 41 and 21% respectively ($p=0.001$) from base line to week eight. But the results of MADRS-S were less supportive, giving the similar score reduction in both groups (26 and 27%, $p=0.831$) (Lopresti et al., 2019). The non-supportive or non-significant results given in MADRS-S is worth paying attention to for future researchers.

Another study, continued for 12 weeks and completed in 2020, also noted that saffron has a healing effect on moderate to mild depression in overweight women. The participants are women with body mass index (BMI) equal or greater than 25. By using BDI-II, the study found that saffron has greater efficiency then placebo ($p=0.007$). But saffron shows no impact on patients' appetite through repeated analysis of variance.

4. Discussion

From the previous analysis, saffron alone has a good effect, but as an auxiliary intervention, some scholars pointed out that the current clinical research is not enough (Dai et al., 2020). By increasing serotonin, saffron as a whole or its derivatives may act alone in the treatment of moderate and mild depression, but the uncertainties regarding saffron as an additional tool for use with other synthetic antidepressants require further research. In conclusion, recent clinical trials and meta-analysis have shown that saffron as an additional treatment for moderate and mild depression is more effective than placebo and even not weaker than SSRI (Tóth et al., 2019).

The only experiment conducted by 2019 Lopresti et al., which gave statistically contradictory conclusions, could be explained by the methodological problems of the paper, because they all measured the results in the form of scales, especially the patient-self-report form from which the contradictory conclusions were derived. In addition to the low sensitivity of the self-rating scale to certain depressive symptoms the certain negative objectionability that exists in the cognition of depressed patients makes

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the self-rating scale biased to some extent (Gotlib & Joormann, 2010). In addition, due to the current lack of understanding of the diagnosis and management of depression at the pathophysiological level, the measures of severity of depression in most trials relies on psychiatric scales. Although those scales are widely followed and have proven rigor and reliability, the single evaluation system is not conducive to accuracy. Future studies should consider an evaluation system that combines physiological indicators with psychiatric scales like HDL level.

On the other hand, there are few studies that focus on one specific chemical. And based on the fact that the mechanisms by which natural medicines such as saffron interact with both the chemical and another herb are unclear, perhaps more depression drugs need to be tested separately with saffron avoiding side effects within two drugs. So far, the longest duration of clinical is two mouths, the feasibility of longer term use and the optimal duration of medication remain to be studied.

At the same time, the synthesis or the heterologous expression methods of the active substances in saffron also needs to be further explored, and the artificial synthesis of those ingredients may reduce the cost of breeding saffron.

5.Conclusion

Saffron is famous for its medicinal value for quite a long time. But because of the small amounts of the extracts and high cost, saffron therapy can't be widely used in the clinic until now. Fortunately, Co-administration of different kinds of herbals and synthetic saffron may solve these problems in the future. This article explores the potential of saffron as an herbal remedy in the treatment of mild-to-moderate depression. Efficacy and adverse reactions are two thorny issues in the treatment of depression at present, and scientists all over the are actively seeking herbal regimens as adjuvant or even alternative treatment regimens.

The persistence of MDD and its risk of causing other illnesses have prompted ongoing research but there have been limited clinical studies on MDD with saffron as an add-on. So, several relevant clinical studies helping us explore saffron as a potential adjuvant to help with treatment are selected, and they the generally accepted result is that saffron adjuvant has a significantly positive effect over placebo. Further research may be needed to further investigate the mechanism of action or the synthetic synthesis of active ingredients to make saffron therapy a practical option.

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