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Comparing the efficacy of saffron with fluoxetine for the effective management of premenstrual dysphoric disorder: A review

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Abstract

Premenstrual syndrome (PMS) significantly impacts the emotional and physical well-being of women of reproductive age. Various theories have been proposed about its etiology but still, it is unknown. The PMS starts from the luteal stage of women's menstrual cycle and affects 20% to 40% of women in their reproductive phase. The severe form of PMS is PMDD which typically affects 3% - 5% of women in their reproductive phase. Standard treatments for these conditions include selective serotonin reuptake inhibitors such as fluoxetine, paroxetine, and sertraline. Fluoxetine is mainly used for the treatment of Premenstrual syndrome and Premenstrual dysphoric disorder. Fluoxetine appears to be more effective and better tolerated for treating physical and psychological symptoms associated with severe Premenstrual syndrome and Premenstrual dysphoric disorder. Herbal remedies like saffron (crocus sativus) consist of three bioactive compounds: procrocin, safranal, and crocin. Saffron exhibits SSRIs-like actions and is also used in the management of PMS and PMDD. This review critically evaluates the comparative effectiveness of saffron and fluoxetine in the management of PMDD, aiming to provide valuable insights for treatment decisions.

Keywords: Saffron; Fluoxetine; PMDD; SSRIs; PMS

1. Introduction

There are numerous tales and stereotypes surrounding menstruation in our society. premenstrual syndrome is a frequently encountered health issue among women of reproductive age and it is a psychoneuroendocrine problem characterized by a range of emotional symptoms, with or without accompanying physical symptoms, linked to a woman's menstrual cycle[1,2]. PMS affects 20% to 40% of women during their reproductive stage which starts during the luteal phase of the menstrual cycle, but it typically resolves with the beginning of menstrual flow which starts from 7 to 10 days before the initiation of menstruation[3,4].

In the early days, the severe form of PMS was mentioned as Late Luteal Phase Dysphoric Disorder (LLPDD), as mentioned in the 3rd edition of the DSM. Later, the severe form of Premenstrual syndrome was defined as Premenstrual Dysphoric Disorder, which was diagnosed using the DSM-IV appendix with more refined and slightly different criteria, and stated that this condition was classified under "depressive disorders"[5]. Premenstrual dysphoric disorder is a condition that presents as a severe mood disorder marked by cognitive, emotional, and physical symptoms occurring in the week before menstruation, impacting women worldwide. Premenstrual dysphoric disorder (PMDD), which has recently been designated as a disorder in the Diagnostic and Statistical Manual of Mental Disorders-V, offers numerous opportunities for further research and exploration. The Diagnostic and Statistical Manual of Mental Disorders -IV and Diagnostic and Statistical Manual of Mental Disorders -V diagnoses are based on a premenstrual pattern of at least 5 physical, affective, and behavioral symptoms, with a requirement of at least 1 of the following affective symptoms, such as depression, anxiety, irritability, anger, and mood swings[6].

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Premenstrual dysphoric disorder impacts 3%-5% of women in their childbearing stage. These women are facing a decrease in overall wellness because of the detrimental effects of Premenstrual dysphoric disorder on their social, interpersonal, and occupational aspects of life[7]. Various theories regarding the etiology of PMDD have been proposed. These encompass the potential impact of reduced progesterone on neurotransmitters like serotonin, these effects increase sensitivity to prolactin, anomalies in the hypothalamic-pituitary-adrenal axis, and alterations in insulin resistance[4,7].

Table 1 Major symptoms of premenstrual dysphoric disorder

Major symptoms of PMDD
Mood swings
Depressed state
Anxiety
Insomnia / Hypersomnia
Irritability
Fatigue
Lack of concentration
Decreased interest
Changes in appetite
Agitated
Physical symptoms
At least 5 symptoms of PMDD may be present in most menstrual cycles for at least one year.

Selective serotonin reuptake inhibitors are the “GOLD STANDARD” treatment for Premenstrual dysphoric disorder as well as PMS. SSRIs are chosen as first-line treatment due to their efficacy and tolerability. They show improvement in physical and emotional symptoms. Fluoxetine is one of the popular SSRIs used nowadays[7]. Saffron or crocus sativus (c.sativus) is used to treat symptoms like pain, and spasms and even used to treat mild to moderate mental abnormalities like depression[8]. 80% of females in America use herbal remedies with or without other chemical agents for PMDD treatment [7].

This review provides a comprehensive overview of the efficacy of saffron in managing PMDD by comparing it to fluoxetine, which is considered a standard drug for PMDD treatment.

2. Saffron (*C. Sativus*) – properties and its action

Saffron is yielded from the tiny, dried stigma of the lily-like Crocus sativus blossom that belongs to the Iridaceae family. In Asia, particularly in Persian traditional medicine practise, it treats menstrual disorders, throat infections, labor difficulties, vomiting, and inflammation. Recent research has revealed its promising effect as both an anti-cancer and memory-enhancing agent[9,10]. Nowadays saffron is no longer used as a medicinal purpose in the West. Saffron consists of three bioactive compounds: procrocin, safranal, and crocin. Saffron is mentioned as "red gold", is mostly cultivated in Iran, India, and Mediterranean countries. As a result, most research on the potential effects of this spice originates from these areas. 90% of the world's saffron was produced by Iran which conducts most of the research into its potential medical uses[8,11].

The saffron plant is known for its herbal medicinal properties, including anti-inflammatory and antidepressant effects. These properties make it useful in treating certain syndromes. Saffron also has antinociceptive, relaxing, and anti-inflammatory effects. In folk medicine, saffron plays a versatile role as an anti-depressant, anti-spasmodic, sedative, eupeptic, gingival, stimulant, aphrodisiac, anti-catarrhal, and expectorant[10,12]. Saffron may have an anti-depressant action by altering the levels of certain brain chemicals like serotonin. It is believed that saffron will raise serotonin levels in the brain, although the exact action is still unknown. Some studies indicate that saffron extract might restrict the

serotonin reuptake in synapses. This inhibition keeps serotonin in the brain longer, thereby improving its positive effects. Recent studies and trials have shown that saffron is potent in treating mild to moderate depression. There is ample evidence suggesting that herbal medicine, such as saffron, is helpful in mitigating the symptoms of Premenstrual syndrome and PMDD[3,11].

3. Fluoxetine in the management of PMDD

Drug treatment is the first-line treatment recommended for Premenstrual dysphoric disorder, as per the American College of Obstetricians and Gynaecologists. Selective serotonin reuptake inhibitors are considered the best practice for treating Premenstrual dysphoric disorder and severe mood-based Premenstrual syndrome[6]. SSRIs are the widely used treatment plan for Premenstrual dysphoric disorder. They have been proven to have a positive impact on a wide range of Premenstrual dysphoric disorder-based issues, including physical conditions, psychosocial status, work, and overall wellness of women[7]. During reproductive events, women are more likely to experience neuropsychiatric conditions, possibly because their hormone levels, especially sex hormones, can affect their mental health. Research has shown that the imbalance in the serotonergic system is responsible for most Premenstrual syndrome[3,8].

Non-serotonergic antidepressants are ineffective for PMDD. It is important to note that the FDA has only approved SSRIs as serotonergic medications for treating Premenstrual dysphoric disorder[13].The recommended treatment for PMS and PMDD typically includes SSRIs such as Fluoxetine, Paroxetine, and Sertraline. These drugs have proven to be impactful in alleviating symptoms like lack of energy, food urges, and sleep irregularities, and are often the primary choice for treating severe cases of PMS and PMDD[14].

Fluoxetine, with seven trials involving 398 participants, and sertraline, with five trials involving 364 participants, were the most extensively studied SSRIs. The findings demonstrate that fluoxetine was the most effective. Fluoxetine appears to be more effective and better tolerated for treating somatic and functional symptoms associated with severe Premenstrual syndrome and Premenstrual dysphoric disorder. Fluoxetine enhances central serotoninergic activity, leading to significant improvement in physiological symptoms compared to physical symptoms[15]. It's crucial to note that upon discontinuation of fluoxetine, all symptoms of PMDD reoccur. This quick resurgence of symptoms strongly supports the idea of Premenstrual dysphoric disorder as a clinical condition that responds well to SSRI treatment. Fluoxetine is more effective than bupropion, a non-serotonergic antidepressant, and desipramine, a tricyclic antidepressant. This suggests that the antidepressant action is not the specific factor at work in treating PMDD[16].

4. Efficacy comparison between saffron and fluoxetine

A trial has been conducted on saffron showing that implementation of saffron is a different approach for the management of Premenstrual syndrome[3]. The efficacy of saffron on PMDD is more similar to the standard treatment with fluoxetine. Many research studies have been conducted based on the efficacy of saffron in the treatment of PMDD with fluoxetine.

In a recent study, 120 female participants identified with PMDD were assigned to three different treatment groups. These groups received either 20mg of fluoxetine twice daily, 15mg of saffron twice daily, or a placebo for a duration of two weeks during the luteal stage of two menstrual cycles. Fluoxetine clearly demonstrates a significantly higher rate of undesirable effects compared to saffron or placebo agents. Following the outcomes of this investigation, saffron demonstrated noteworthy efficacy as an herbal intervention for the management of Premenstrual dysphoric disorder, exhibiting minimal side effects[7]. Another clinical trial was conducted on employed women and their family members. Initially, 164 individuals with PMS were chosen and randomly divided into 2 groups, with 82 participants in each group. One group received fluoxetine while the other received saffron. Both groups underwent a two-month treatment period. The figure 1,2,3 compares fluoxetine and saffron action. The trial shows that saffron has a similar action to fluoxetine and it reduces symptoms like abdominal pain, mood swings, and depression[14].

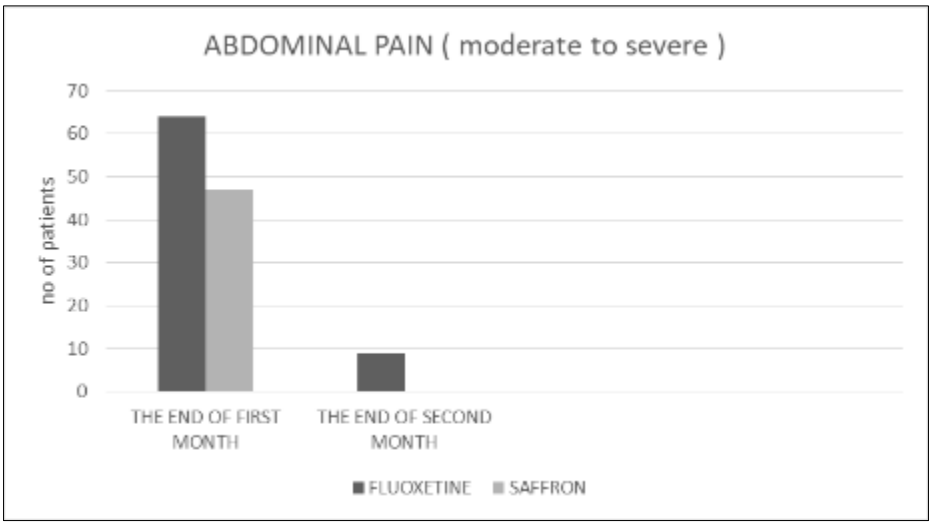

Figure 1 Compares the action of fluoxetine and saffron relating to abdominal pain [14]

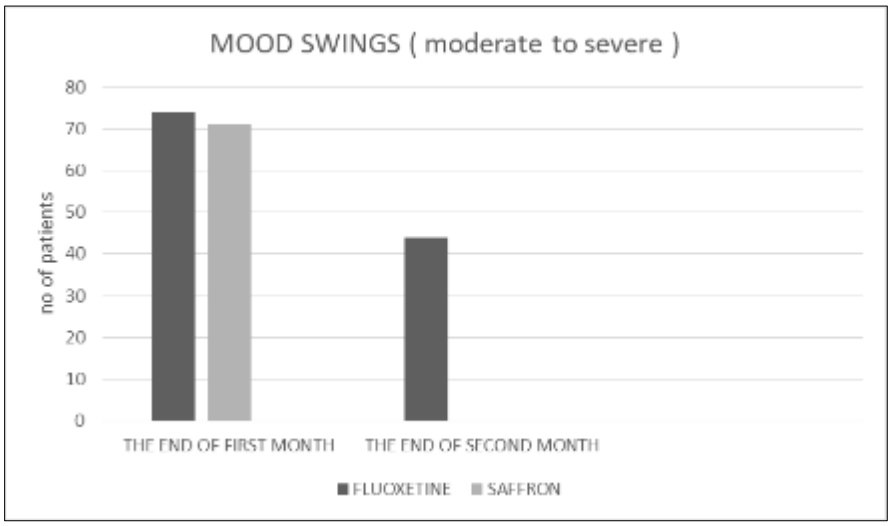

Figure 2 Compares the action of fluoxetine and saffron relating to mood swings [14]

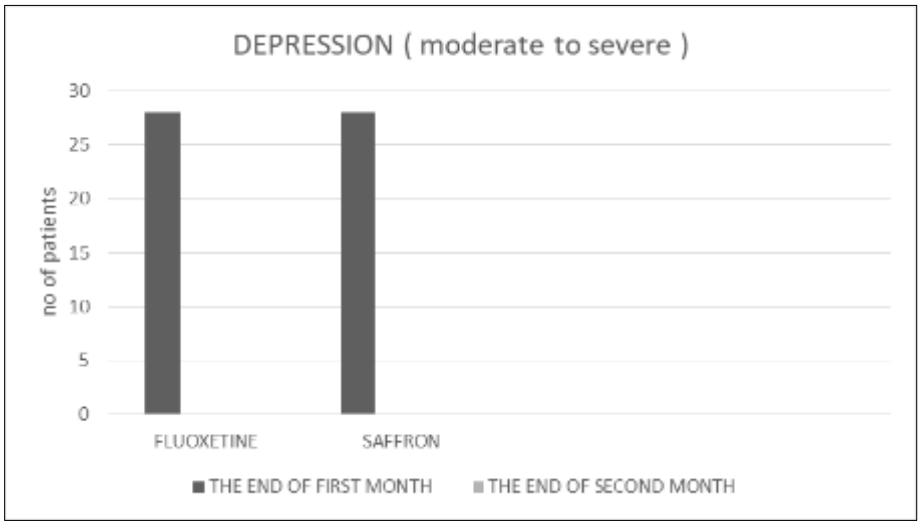

Figure 3 Compares the action of fluoxetine and saffron relating to depression [14]

The mechanism of both saffron and fluoxetine are similar in the treatment of PMDD but the adverse effect produced by saffron is much more tolerable than fluoxetine. This leads to the use of herbal plants or herbal remedies to treat severe forms of PMS and PMDD. In a recent research study, findings indicate that saffron plays an alternative drug treatment for depressive symptoms associated with PPD. These results imply that saffron may offer a promising option for individuals seeking alternatives to traditional medication for managing postpartum depression[9]. Their effectiveness surpasses that of other pharmacologic options, establishing them as the emerging gold standard in the medical management of PMDD. However, it is important to note that cognitive behavioral therapy (CBT) can be just as effective as SSRIs. CBT offers a non-pharmacologic approach that helps patients develop coping strategies and cognitive techniques to manage the symptoms of PMDD, providing a viable alternative or complement to pharmacologic treatment [17].

5. Conclusion

To the best of our knowledge, it has been found that saffron is as potent as fluoxetine in treating premenstrual dysphoric disorder (PMDD). Moreover, saffron exhibits even greater efficacy than fluoxetine while causing fewer adverse drug reactions (ADRs), making it a more tolerable option for patients. These findings highlight the potential use of saffron as a viable alternative to traditional SSRI treatments like fluoxetine, providing a combination of high efficacy and improved tolerability.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

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