Saffron in Treating Depression in Women- A Review

By

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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled “Saffron in Treating Depression in Women- A Review” submitted by Sumaiya Binte Ibrahim (ID: 20146060) of Spring, 2020 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons) on May 2, 2024.

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Ethics Statement

This study does not involve any kind of human or animal trial.

Abstract

Depression is a common psychological disorder affecting women at a greater proportion than men. The complex pathophysiology of depression makes it tougher to target the affected parts of the brain to exert antidepressant effect fully and the antidepressants which are commercially available usually comes with adverse effect exertions or longer response time. This report has detailed the information about different clinical trials that have used saffron to treat depression in women with no reporting of adverse reactions. The method of this study included the collection of relevant articles published between the year 2004 and 2024 by conducting a strategic search in PubMed and Google Scholar. After the total screening process, 4 clinical trial articles between the year 2008 and 2018 were selected relating tothe role of saffron on depression in women with specific diseases. The results depicted that saffron could effectively and safely treated depression in women including postpartum depression, depression associated with premenstrual syndrome and depression with post-menopausal hot flashes. Saffron has also demonstrated to function as efficaciously as fluoxetine in treating postpartum depression.

Keywords: Saffron; Depression; Women; Postpartum Depression; Premenstrual Syndrome; Menopause

Dedication

Dedicated to my parents and my project supervisor, Professor Dr. Hasina Yasmin.

Acknowledgement

I am grateful to the Almighty Allah for giving me the opportunity to come this far and made this project happen.

Secondly, I would like to express my special appreciation and gratitude to my supervisor, Professor Dr. Hasina Yasmin, whose ongoing generous support and direction enabled me to plan my work and execute it appropriately. Moreover, I would also like to show my sincere gratitude to the dean, Professor Dr. Eva Rahman Kabir, and to all the honorable faculties of my department.

Finally, I want to express my gratitude to my parents for constantly pushing me to pursue my goals and whose unconditional love and constant prayers have made it possible for me to progress this far. I would also like to thank my beloved friend Farhana Akter Shifa who, whenever needed, has helped me with her utmost abilities.

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List of Acronyms

5-HT	Serotonin
5-HTTLPR	Serotonin-linked polymorphic region
ACTH	Adrenocorticotropic hormone
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BDI-II	Beck Depression Inventory-Second Edition
BDNF	Brain-derived neurotrophic factor
COX-2	Cyclooxygenase-2
CREB	Cyclic AMP response element binding
CRF	Corticotropin-releasing factor
CSF	Cerebrospinal fluid
DA	Dopamine
DNA	Deoxyribonucleic acid
DSM-5	The Diagnostic and Statistical Manual of Mental Disorders-5
ERK	Extracellular regulated protein kinases
GABA	γ-aminobutyric acid
HDRS	Hamilton Depression Rating Scale
HFRDIS	Hot Flash-Related Daily Interference Scale
HPA	Hypothalamic-pituitary-adrenal

IFN- α	Interferon- α
IFN- γ	Interferon- γ
IL-1	Interleukin 1
IL-6	Interleukin 6
iNOS	Inducible nitric oxide synthase
MAOIs	Monoamine oxidase inhibitors
MDD	Major depressive disorder
MeSH	Medical Subject Headings
MMAs	Multimodal antidepressants
mRNA	Messenger ribonucleic acid
NaSSAs	Noradrenergic and specific serotonergic antidepressants
NDRI	Norepinephrine–dopamine reuptake inhibitor
NE	Norepinephrine
NF-κB	Nuclear factor-kappa B
NMDA	N-methyl-D-aspartate
PACAP	Pituitary adenylatecyclase-activating polypeptide
PPD	Postpartum depression
ROS	Reactive oxygen species
SARIs	Serotonin-2 antagonists and reuptake inhibitors

SERT	Serotonin reuptake transporter
SNRI’s	Serotonin-norepinephrine reuptake inhibitors
SSRI’s	Selective serotonin reuptake inhibitors
TCA’s	Tricyclic antidepressants
TNF- α	Tumor necrosis factor– α
TrkB	Tropomyosin-related kinase B
WHO	World Health Organization

Chapter 1

Introduction

1.1 What is Depression

Depression is one of the most prevailing psychological conditions which possess an array of detrimental outcomes with medical and societal implications with severe impairments of adaptive functioning and quality of life (Shadrina et al., 2018). Moreover, one among five individuals report of enduring at least one depressive attack and the likelihood of women to experience depression is two times higher than that of men (Hirschfeld, 2012). It is among the most common causes of suicide globally (Chatterjee et al., 2011).

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classified depressive disorders in to (Bains & Abdijadid, 2023; Maina et al., 2016):

- Major depressive disorder (MDD)
- Disruptive mood dysregulation
- Persistent depressive disorder, also called dysthymia
- Premenstrual dysphoric disorder
- Depression instigated by substances or drugs
- Depression due to other medical complications

1.1.1 Prevalence

A category of depression called MDD is a highly experienced by nearly 280 million patients worldwide and as stated by the World Health Organization (WHO), depression is a major contributor of nearly 800,000 suicide occurrences (Tian et al., 2022). Moreover, over 10% of expectant mothers and women who have recently delivered

experience depressive symptoms globally (Woody et al., 2017). Shorey et al. (2021) reported that worldwide around 34% of adolescents between the age of 10 and 19 years, are prone to developing clinical depression.

According to the World Health Organization (2023), approximately 3.8% of the population endure depressive symptoms, among which adults less than 60 years old are 5% of (4% men and 6% women), and adults above 60 years old are 5.7%. World Health Organization (2023) also reported that the prevalence of depression is nearly 50% higher in women than in men. In 2022, 8.8% of adults reported experiencing a severe depressive episode in United States, while almost 20% of those between the ages of 18 and 25 reported having such disorder (Vankar, 2024). Statistical analysis of 2021 in United States reported that approximately 10.4% of women and 7% of men experienced major depressive episode (Vankar, 2024). The overall percentage of American adults experiencing a major depressive disorder episode during the year 2021 is depicted in Figure 1.

Again, Bueno-Notivol et al. (2021) reported how the COVID-19 pandemic compromised the mental health of people in 2020 and depicted the prevalence of depression to be around 25% globally which is nearly 7 times higher than the prevalence of 2017 that was 3.44%. Banna et al. (2020) reported that in Bangladesh the prevalence of depression was around 57.9% in 2020.

Moreover, Anjum et al. (2019) reported that in Bangladesh 36.6% adolescents in urban and semi-urban schools suffered from depressive symptoms (girls: 42.9%, boys: 25.7%) during the year 2018 and Hossain et al. (2019) reported in 2019 there was a 22.5% increase in the prevalence of depression (meeting provisional diagnostic criteria) among Bangladeshi university students within a 15-month period.

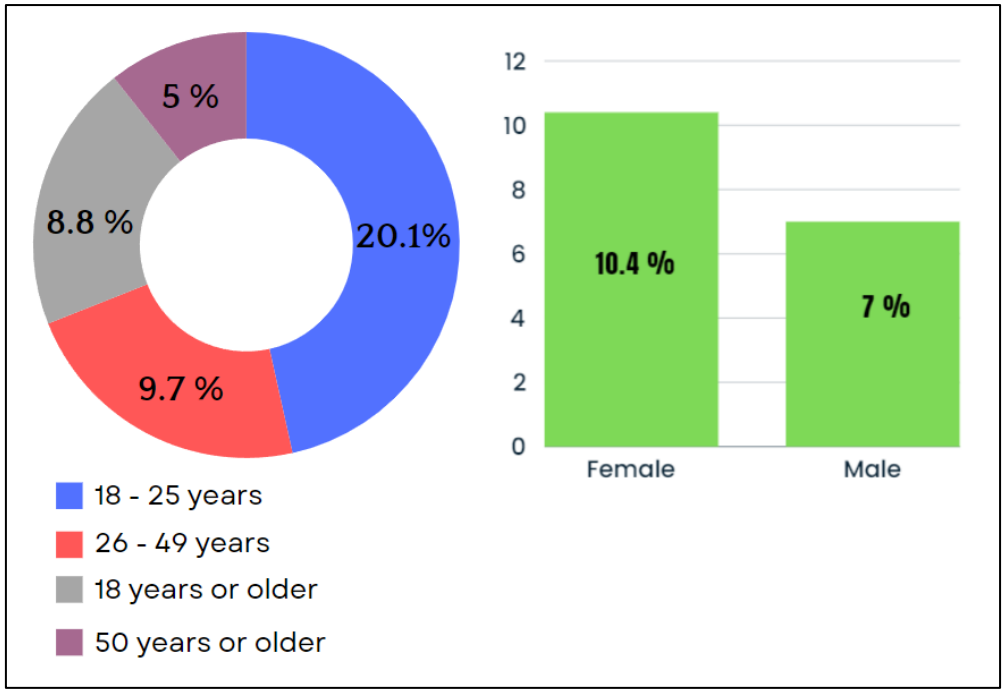

Figure 1: Percentage of American Adults Experiencing an Episode of Major Depressive Disorder in 2021 (Vankar, 2024).

1.1.2 Symptoms

Some common symptoms of depression include (Pinhasov et al., 2011; Dean & Keshavan, 2017; Dudek et al., 2019; Boas et al., 2019):

- Disturbed sleep patterns
- Fatigue
- Difficulty in anger management
- Pain including headaches and back pain
- Appetite and weight fluctuation
- Constant feeling of worthlessness and guilt
- Repetitive death/suicide thoughts
- Overthinking
- Irritability
- Anhedonia
- Negative thinking

- Cognitive impairments
- Social isolation
- Constipation
- Sexual dysfunction
- Energy and motivation insufficiency
- Loss of libido

1.1.3 Etiology

Genetic Factors:

Depletion of the serotonin transporter gene expression and the involvement of apolipoprotein genes in the progression of the symptoms of depressive disorder suggest that genetic abnormalities results in depression (Kang et al., 2020; Zalsman et al., 2006).

Epigenetic Factors:

Generational transmission of traits with no alterations in the sequence of Deoxyribonucleic acid (DNA) can also contribute to the development of depression (Nestler, 2014). For instance traumatic life experiences can alter the upcoming generation's vulnerability to stress and subsequent depression (Nestler, 2014).

Environmental Factors:

Depression symptoms can also develop due to social rejection, loneliness, low birth weight, malnutrition, alcoholism, chronic stress disorders, and deficiencies in vitamin D and B12 (Zamani et al., 2022; Lima-Ojeda et al., 2017; Verduijn et al., 2015).

Stress:

Persistent stress leads to depression or deteriorate depressive symptoms by hyperactivating the Hypothalamic-pituitary-adrenal (HPA) axis and sympathetic

nervous system which leads to the excess neural secretion of glucocorticoids (Leonard, 2005; Fiori & Turecki, 2012; Lima-Ojeda et al., 2017; Li et al., 2019).

Gender:

Various clinical depicted that women endure depression at greater prevalence than men particularly, when they approach adolescence and the menopause (Van Wingen et al., 2011; Ma et al., 2019) and genetic factors might be responsible for such higher incidence in women (Kang et al., 2020).

1.1.4 Pathophysiology of Depression

Depletion of neurotransmitters:

Serotonin (5-HT):

Antidepressants including selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI) and tricyclic antidepressants (TCA) implement a significant function in the improvement of depression through the elevation of 5-HT levels in the brain which suggests that defective 5-HT neurotransmission is one of the main pathological reasons of depression (Dean & Keshavan, 2017). Additionally, constant use of antidepressant prompts the elevated secretion of 5-HT through the suppression of the presynaptic inhibitory 5-HT1A somatodendritic autoreceptors which block the release of 5-HT (Richelson, 2001; Dean & Keshavan, 2017).

Along with the 5-HT depletion, there is also reduction of tryptophan like essential amino acid which is required for the generation of 5-HT (Dean & Keshavan, 2017). Moreover, degenerated repetitions in the gene such as 5-HT-linked polymorphic region (5-HTTLPR) encoding for the 5-HT transporter (SLC6A4) induces the

declination of the amount of 5-HT in the synapse which results in the increased susceptibility to depression (Caspi et al., 2010).

Norepinephrine (NE):

Inhibition of the reuptake of NE by antidepressants including SNRI, TCA and norepinephrine-dopamine reuptake inhibitors (NDRI) and the role of mirtazapine in elevating the secretion of NE depicts the impaired norepinephrine neurotransmission as one of the main pathological reasons of depression (Leonard, 2001). Persistent stress leads to the increment of the activity of tyrosine hydroxylase which is responsible for the production of norepinephrine (Leonard, 2001).

The defective mechanism of 5-HT and NE during depression is depicted in Figure 2 and the role of SSRI and SNRI in the alleviation of such serotonergic and noradrenergic impairments is depicted in Figure 3.

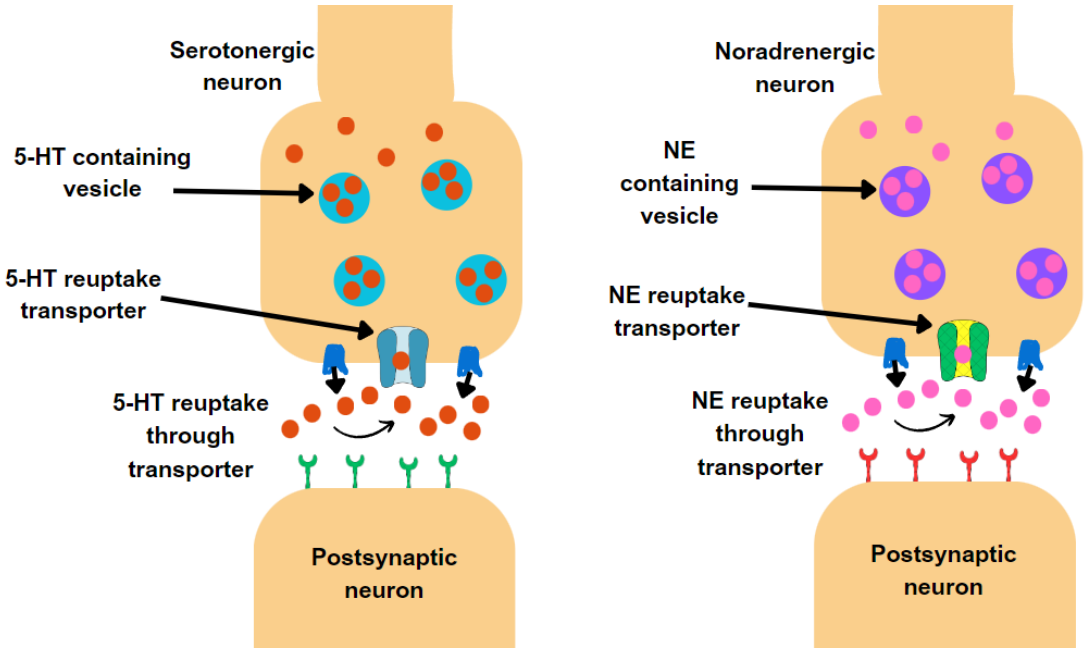

Figure 2: Impaired Mechanism of Serotonin and Norepinephrine in Depression (Goel et al., 2023).

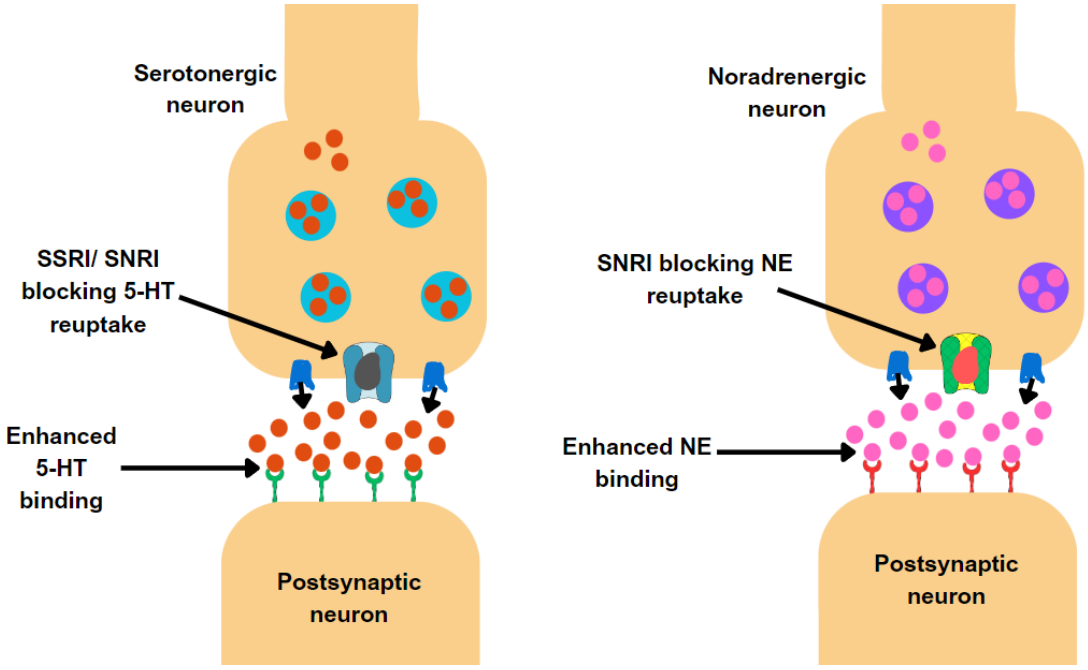

Figure 3: Role of SSRI and SNRI in Alleviating the Serotonergic and Noradrenergic Impairments (Goel et al., 2023).

Dopamine (DA):

Antidepressants such as bupropion increase DA levels which is responsible for modulating mood (Dean & Keshavan, 2017). Consistent stress induces depression through neuroadaptive alterations of the dopaminergic mesolimbic pathway that induces the fluctuations of Brain-derived neurotrophic factor (BDNF) activity resulting in impaired neuroplasticity (Nestler & Carlezon, 2006; Dean & Keshavan, 2017).

Glutamate:

Through the inhibition of N-methyl-D-aspartate (NMDA) receptors on γ-aminobutyric acid (GABA) interneurons, NMDA receptor antagonists reduce the excitation of such inhibitory interneurons which results in the disinhibition of glutamatergic neurons. Elevated glutamate by binding to the postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors helps in conducting Na+ and Ca2+ into the cell which subsequently activates voltage-gated calcium

channels. Further increment of the intracellular concentration of Ca2+ trigger the vesicular release of the BDNF into the synaptic space which results in synaptogenesis that contribute to the persistent antidepressant effects (Sanacora & Schatzberg, 2014; Aleksandrova et al., 2017).

Gamma-Aminobutyric Acid (GABA):

GABA neurons help in alleviating chronic stress by modulating the impaired HPA axis (Fogaça & Duman, 2019) which suggests that lower levels of GABA results in the development of depressive symptoms (Tian et al., 2022). Moreover, dysfunctional GABA signaling, expression of GABA transporter and enzymatic activity in the metabolism of GABA results in the development of depressive disorders (Godfrey et al., 2018).

Altered HPA Axis:

Defectiveness in the function of the HPA axis triggers the hypothalamus to excessively secrete corticotropin-releasing factor (CRF) which subsequently stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH) that bind to the receptors on adrenocortical cells to trigger adrenal gland to secrete cortisol (Mucci et al., 2020). The cortisol's negative feedback towards the pituitary, hypothalamus as well as immune system gets disturbed leading to the consistent HPA axis activation that induces the secretion of excessive cortisol which subsequently results in the development of chronic stress that is one of the vital causes of depression (Mikulska et al., 2021; Mucci et al., 2020). The abnormal activities of HPA axis in depression is depicted in Figure 4.

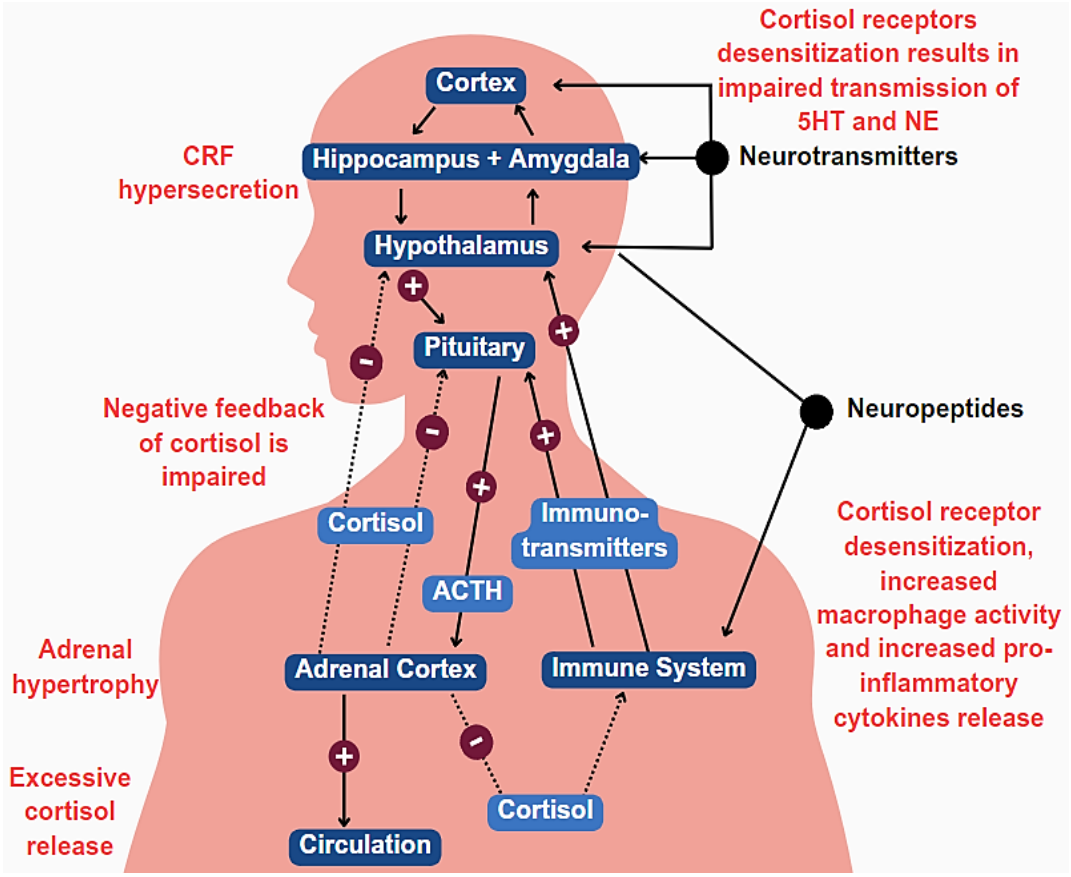

Figure 4: Impaired HPA Axis in Depression (Mucci et al., 2020).

Reduced Neuroplasticity of BDNF:

Due to the depletion of hippocampal BDNF by chronic stress which is one of the primary triggers of depression, insufficient binding of BDNF with the tropomyosin-related kinase B (TrkB) receptor takes place, for which neuroprotective cell signaling cascades cannot get initiated (Begni et al., 2016). Moreover, imbalance between the mature BDNF and proBDNF which is the bioactive precursor protein of BDNF leads to depression (Philpotts et al., 2023).

Inflammatory Response:

Interleukin 6 (IL-6), interleukin 1 (IL-1) andtumor necrosis factor– α (TNF- α)like proinflammatory cytokines play a vital role in elevating the generation of corticotropin-releasing factor (CRF) which subsequently hyperactivate the HPA axis that causes depression (Saveanu & Nemeroff, 2012). Moreover, interferon- α (IFN-

α), interferon- γ (IFN- γ), and TNF- α increase the levels of serotonin reuptake transporter (SERT) which subsequently deplete the serotonin concentration in the synapse resulting in decreased serotonergic transmission and IFN- α also reduces the level of DA in cerebrospinal fluid (CSF) (Saveanu & Nemeroff, 2012).

1.1.5 Pharmacological Treatment Approaches of Depression

The primary treatment options of depression are antidepressants which are usually accompanied with serious side effects as depicted in table 1.

Table 1: Antidepressants with Associated Side Effects (Tian et al., 2022).

Class of Antidepressant	Function	Side Effects
TCAs (Imipramine, Doxepin, Amitriptyline, Desipramine)	Inhibit the reuptake of NE and 5-HT.	Dizziness, hypotension, impaired memory and drowsiness.
MAOIs (Monoamine oxidase inhibitors) (Phenelzine, Isocarboxazid, Selegiline)	Inhibit the monoamine oxidase enzyme, thus corrects the neurotransmitter imbalances commonly occurs during depression.	Food-drug interactions results in hypertensive crisis
SSRIs (Citalopram, Fluoxetine, Paroxetine, Sertraline)	Increase 5-HT level by inhibiting its reuptake	Nausea, insomnia, and sexual dysfunction,
SNRIs (Venlafaxine, Desvenlafaxine, Duloxetine)	Increase NE and 5-HT levels by inhibiting their reuptake with little or no pharmacological action at other receptors	Nausea, headache, sexual dysfunction, sedation, constipation and high dose induced increased blood pressure and heart rate
SARIs (Serotonin-2 antagonists and reuptake inhibitors) (Trazodone, Nefazodone)	Inhibit the reuptake of NE and 5-HT and bind with α1-adrenoceptors with no effect on other receptors.	Dry mouth, drowsiness, headache, dizziness, blurred vision
NDRI (Norepinephrine–dopamine reuptake inhibitor) (Bupropion)	Shows stronger binding affinity towards dopamine transporter than norepinephrine transporter with little or no affinity for serotonin transporters or other receptors.	Dry mouth, nausea, and insomnia.

NaSSAs (Noradrenergic and specific serotonergic antidepressants) (Mirtazapine)	Blocks α2 adrenoceptors along with the selective inhibition of 5-HT2 and 5-HT3 receptors for elevating noradrenergic and serotonergic function.	Weight gain
MMAs (Multimodal antidepressants) (Vortioxetine, Vilazodone)	Possess high binding affinity towards 5-HT1A, 5-HT1B, 5-HT3A, 5-HT7 receptors and 5 HT transporters and also increases the level of norepinephrine, dopamine, serotonin, acetylcholine, glutamate and GABA	Nausea and headaches

1.1.6 Women and Depression

Various studies consistently depicted that women experience depressive disorders more than men (De Graaf et al., 2013). As 30-40% heritability is responsible for the development of major depressive disorder, some conflicting evidences suggest that women are more genetically predisposed to the depression than men (Flint & Kendler, 2014). Moreover, women are more prone to depression due to the fluctuations of different sex hormones that occur during thetransition in puberty and other hormone associated transitions (Kuehner, 2017). Studies have shown that women possess greater independent and dependent interpersonal stressors than man, and these stressors substantially regulate the relationship between gender and depression (Kuehner, 2017).

Postpartum depression (PPD), the most common mental health disorder experienced by 10% to 30% women is associated with the mother's impairment in functional ability, maintenance of constructive interpersonal relationships, providing attention to the baby and it can also affect the health and development process of the infant (Als & Butler, 2008; Tabeshpour et al., 2017). It appears two weeks to one month following delivery (O'Hara & McCabe, 2013) with the depiction of symptoms including deteriorated mood, irritability, tearfulness, difficulty in concentrating, difficulty in baby nursing, loss of appetite, sleep disorder and including weight gain and

hypersomnia (Wisner et al., 2013). Risk factors include poor parent confidence, issues with the health of the newborn, and difficulties during labor and/or delivery (Als & Butler, 2008). Despite being the primary pharmacotherapy in postpartum depression, SSRIs result in low remission rate and high relapse and recurrence risk (Pearlstein et. al., 2009; Molyneaux et. al., 2014). Moreover, multiple adverse reactions including orthostatic hypotension, anticholinergic reactions, arrhythmias, and sexual dysfunction, are prompted by these antidepressant medications which many mothers cannot tolerate (Moshiri et. al., 2006). Besides lack of effective response and development of tolerance throughout the treatment course can result in deteriorating the condition (Ferguson, 2001). Furthermore, due to the secretion of antidepressants in breast milk and exertion of subsequent negative effects, mothers express reluctance in taking such antidepressant while they breastfeed their child (O'Hara et al., 2000; Burt et al., 2001; Pearlstein et al., 2006).

Again, depression is associated with premenstrual syndrome which refers to a collection of menstrually associated cyclic or chronic problems with the manifestation of emotional, behavioral, and physical symptoms affecting patient's functional ability and which occur during the second half of the menstrual cycle particularly in the luteal phase (Milewicz & Jędrzejuk, 2006). It has been found that throughout the luteal phase, the exertion of significant effects by serotonergic system takes placein women suffering from premenstrual syndrome (Andrus, 2001). Furthermore, sex hormones are involved inthe uptake, binding, and transportation of 5-HT which depicts the impact of the dysfunctional serotonergic system in the development of majority of premenstrual syndrome symptoms (Andrus, 2001; Agha-hosseini et al., 2008). Additionally, similarity exists between the premenstrual syndrome symptoms and depressive symptoms (Agha-hosseini et al., 2008).

Besides, depression has been correlated with one of the most significant vasomotor menopausal symptom known as hot flashes which is manifested by intensive warmth feeling across the upper part of the body that occurs due to the alterations in estrogen level reflecting defective thermoregulatory center (Pinkerton et al., 2009; Shanafelt et al., 2002). Various clinical trials depicted the efficacious role of SSRIs as well as SNRIs like antidepressants in improving the symptoms of hot flashes (Stearns et al., 2005; Freeman et al., 2011; Davari-Tanha et al., 2015). The reduction of 5-HT levels in synaptic clefts are attributed to the increased expression of SLC6A4 gene that encodes for the transporters of 5-HT and NE, which subsequently stimulate the feedback mechanism of presynaptic autoreceptor for the production of more 5-HT and such excess 5-HT levels play protective role in the management of hot flashes (Montasser et al., 2015). This also suggests that reduction in the 5-HTlevel can deteriorate the condition of hot flashes (Kashani et al., 2018).

1.2 Saffron (*Crocus sativus* L.)

One of the autumn-blooming flowering plants that is herbaceous in nature is the Iridaceae family's *Crocus sativus* L. whose red-colored stigmas are dried to yield one of the oldest spices called Saffron (Cardone et al., 2020). Large amount of saffron's cultivation take place in Iran, Morocco, Afghanistan, Greece, India, Italy and Spain (Cardone et al., 2020) and among them, Iran possesses 50000 hectares area belonging to saffron that represent around 90% of the total global harvest of saffron (Mortazavi et al., 2012). Saffron exerts beneficial effects because of crocin, crocetin, picrocrocin and safranal which are regarded as the bioactive constituents of saffron (Cardone et al., 2020).

The taxonomy of *Crocussativus* L. is as follows (Anand et al., 2022):

Kingdom: Plantae

Division: Magnoliophyta

Class: Liliopsida

Order: Asparagales

Family: Iridaceae

Genus: *Crocus*

Species: *C. sativus*

1.2.1 Saffron Plant Parts

Saffron, a perennial plant grows to a maximum height of 25 to 30 cm, with erectile leaves containing ciliated margins and possesses corm having thin brown coats (Dar et al., 2017). A flowering stem emerges from the center of the corm bearing one to three flowers and each flower contains six petals, three stamens which the male part of the flower and a three-pronged style which terminate into three stigmas of reddish-orange tone (Salehi et al., 2022). Furthermore, white-colored bracts coat the flowers (Mzabri et al., 2019). Moreover, saffron has two types of roots; contractile roots which are thick and short developed as single by narrowing the corm and absorbing roots which are thin, fibrous and long originating from the base of the corm (Rashed-Mohassel, 2020). Different parts of saffron plant are depicted in Figure 5.

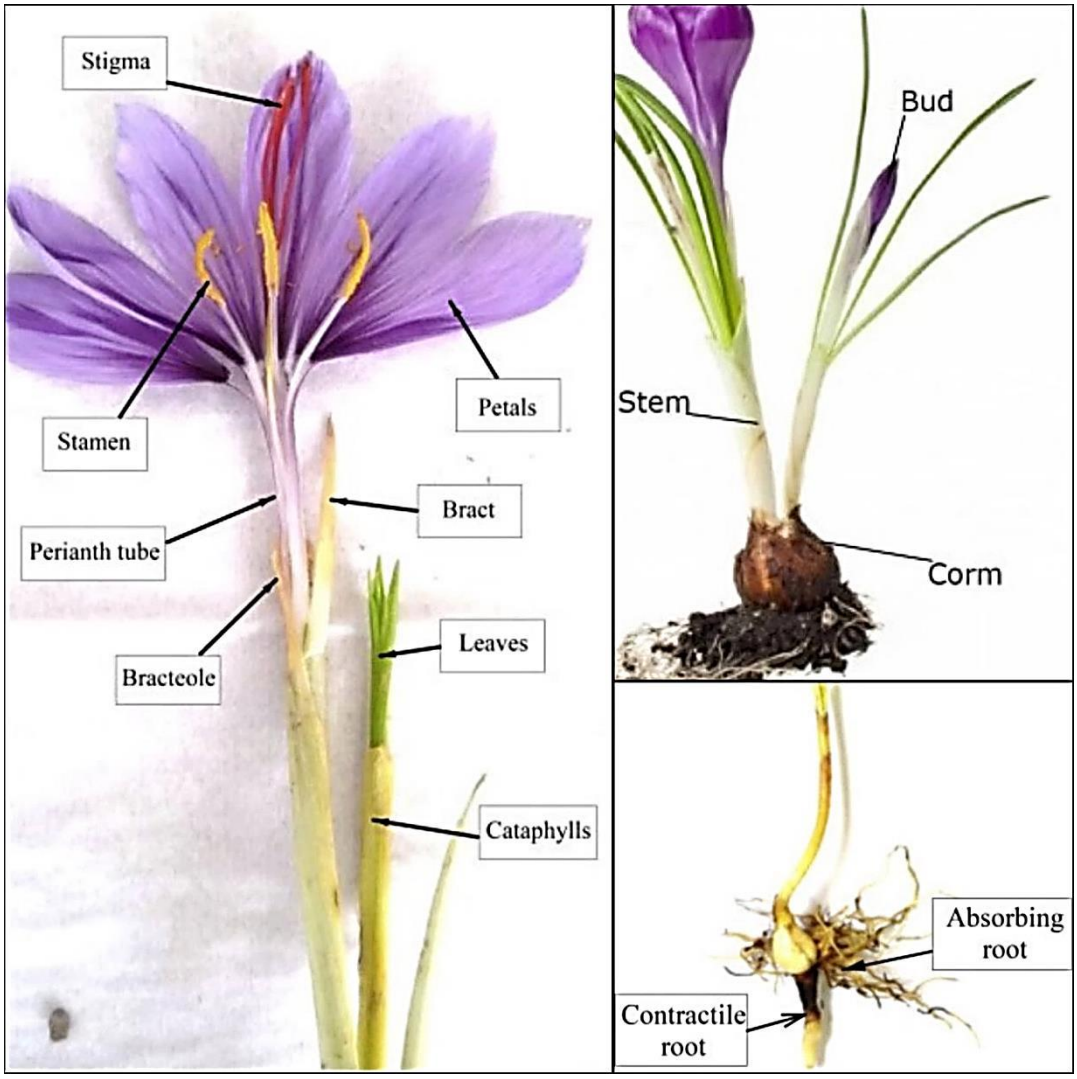

Figure 5: Parts of Saffron Plant (Salehi et al., 2022; Rashed-Mohassel, 2020).

1.2.2 Depiction of Chemical Constituents of Saffron

There are about 150 volatile and non-volatile components isolated from saffron including carotenoids, polyphenols, flavonoids, and terpenes, whose quantity vary according to the place of origin (Al-Snafi, 2016; Hosseini et al., 2017; Mykhailenko et al., 2019; Jarukas et al., 2020). The chemical constituents of saffron include:

- Zeaxanthin, lycopene along with several α- and β-carotenesare regarded as the carotenoids which are non-volatile in nature (Mzabri et al., 2019).
- Terpenes along with their alcohols and esters cover majority of the saffron's 34 volatile components (Mzabri et al., 2019).

- Some other components with approximate composition are (Al-Snafi, 2016; Hosseini et al., 2017): 10% water, 12% proteins and amino acids, 5% lipids, 5% minerals, 63% sugars, 5% fibers, and some vitamins including vitamin B1 (riboflavin) and vitamin B2 (thiamine).

Saffron possesses the four major compounds which are biologically active including; crocin and crocetin which are zeaxanthin derived carotenoids responsible for exerting the color (Rameshrad et al., 2017; Hashemi & Hosseinzadeh, 2019; Song et al., 2021), picrocrocin derived from apocarotenoid responsible for exerting the flavor, and safranal which is basically terpenes with aldehyde functional group responsible for providing the odor (Nanda & Madan, 2021; Midaoui et al., 2022). Additionally, the other major compounds include anthocyanins and kaempferol like flavonoids (Mzabri et al., 2019). The chemical structures of four major constituents of saffron including crocin, crocetin, picrocrocin and safranal are depicted in figure 6.

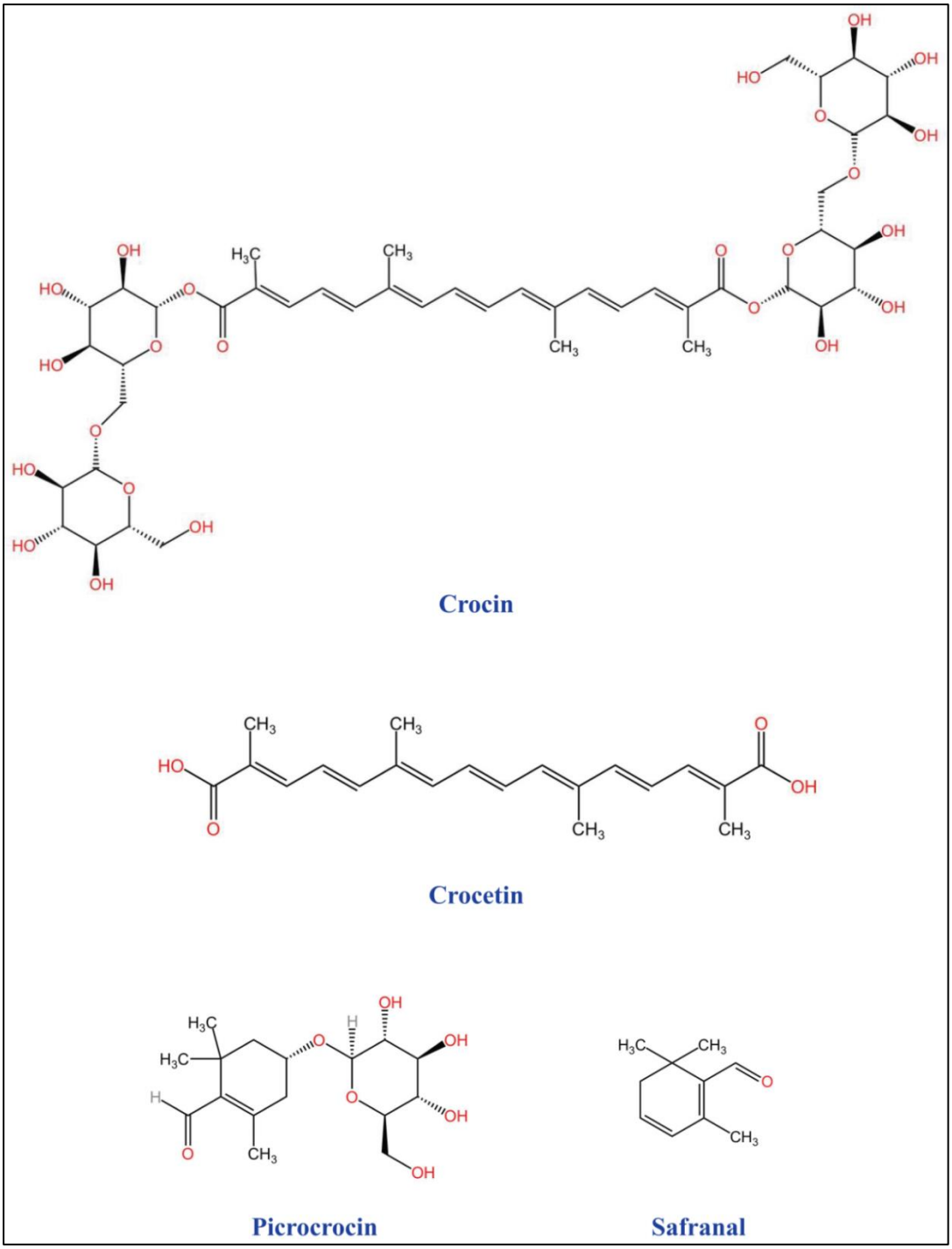

Figure 6: Chemical Structures of Crocin, Crocetin, Picrocrocin & Safranal

1.2.3 Medicinal Uses of Saffron

Antioxidant: Carotenoids including crocin and crocetin work synergestically with safranal, dimethylcrocetin and flavonoids to protect tissues from the harmful effects of free radicals and reactive oxygen species (ROS) (Mzabri et al., 2019).

Antidepressant: Saffron helps in alleviating the symptoms of mild to moderate depression disorder by regulating the levels of 5-HT, NE, DA in different brain parts (Mzabri et al., 2019; Ghorbani et al., 2019).

In the Treatment of Sexual Disorder: Saffron efficaciously helps in combating women's sexual disorders induced by taking fluoxetine antidepressant and also improves sexual function in men with erectile dysfunction within 10 days of the treatment (Mzabri et al., 2019).

Antihypertensive: Saffron's petals can play a vital role in the reduction of blood pressure which is due to the effect on the peripheral resistance (Srivastava et al., 2010).

Anticarcinogenic: A study found that saffron synergistically work with sodium selenite or sodium arsenitein the prevention of cancer chemo (Abdullaev, 2006) and another study demonstrated that saffron can dose dependently inhibit various malignant cells (Mzabri et al., 2019). Moreover, pretreating with saffron for five consecutive days before administering anti-tumor drugs such as cisplatin can have inhibitory effect against cellular DNA injury induced by anti-tumor drugs (Mzabri et al., 2019).

In the Reduction of Blood Cholesterol: crocetin and crocin contribute in lowering blood cholesterol levels by restricting the fat and cholesterol absorption through the inhibition of pancreatic lipase and thereby reduce the severity of atherosclerosis (Mzabri et al., 2019).

Anti-Inflammatory and Analgesic: The antinociceptive and anti-inflammatory properties of saffron makes it useful in the alleviation of some acute and chronic pain and can also treat wounds, gingivitis, abscesses and fever (Mzabri et al., 2019).

Ocular Activity: Saffron extract can be used in the treatment of cataracts like eye disease and light-mediated photoreceptor cell death (Mzabri et al., 2019). Moreover, it can effectively improve blood flow in the retina and choroid, improve retinal function and can treat retinal degeneration (Srivastava et al., 2010).

Activity in Gastrointestinal and Genital System: Safranal helps in the reduction of the gastric ulcer surface and exert gastric protection by normalizing gastric volume and pH. Moreover, saffron also helps in the treatment of hemorrhoids, anus prolapse, amenorrhea, restricts intestinal fermentations and stimulate menstruation (Mzabri et al., 2019).

Effect on Cognitive Behavior: Crocin and crocetin can help in boosting memory and learning skills (Srivastava et al., 2010).

Different phytochemicals are responsible for exerting the therapeutic attributes of saffron (Figure 7).

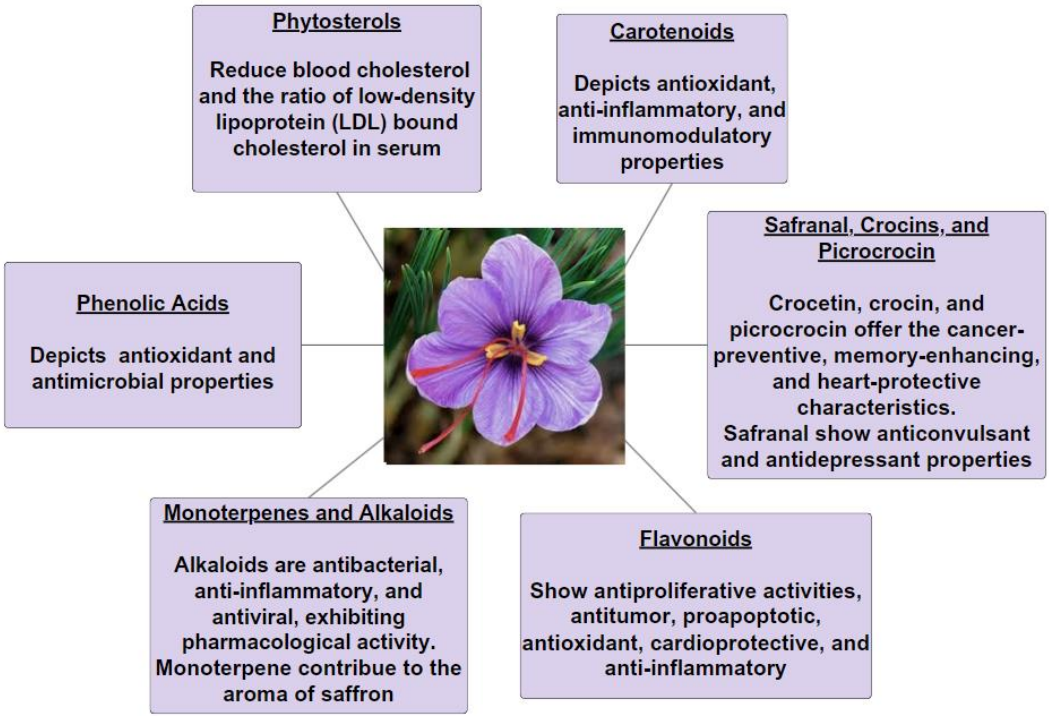

Figure 7: Therapeutic Attributes of Different Phytochemicals of Saffron (Maqbool et al., 2022).

1.2.4 Saffron as an Alternative to Depression Therapy

In spite of being as the primary treatment options, the efficacy of synthetic antidepressants reduce because of insufficiency in executing high response rate, faster therapeutic effects, high remission rates and prolonged use of such antidepressants results in drug tolerance development (Tian et al., 2022; Yang et al., 2018; Hausenblas et al., 2013). Moreover, the associated adverse effects results in deterioration of patient's condition (Dai et al., 2020; Yang et al., 2018). Various clinical trials reported that saffron is a safer potential medicinal plant for alleviating depression which can work in effective way without exerting any adverse side effects (Dai et al., 2020). Upon the examination of the saffron's pharmacological effects, the role of crocin in the inhibition of the reuptake of DA and NE and the role of safranal in the inhibition of 5-HT reuptake was found which result in exerting the overall antidepressant activity (Ghorbani et al., 2019).

1.2.5 Proposed Mechanism of Action of Saffron in Depression

Saffron's Role in Neurotransmitters: Crocin plays role in the inhibition of the reuptake of DA and NE and safranal plays role in the inhibition of 5-HT reuptake allowing their longer exposure in the brain to exert their antidepressant activity (Ghorbani et al., 2019; Dai et al., 2020; Siddiqui et al., 2022). Besides, the components of saffron work as NMDA receptor antagonist and GABA-α agonists (Pazoki et al., 2022).

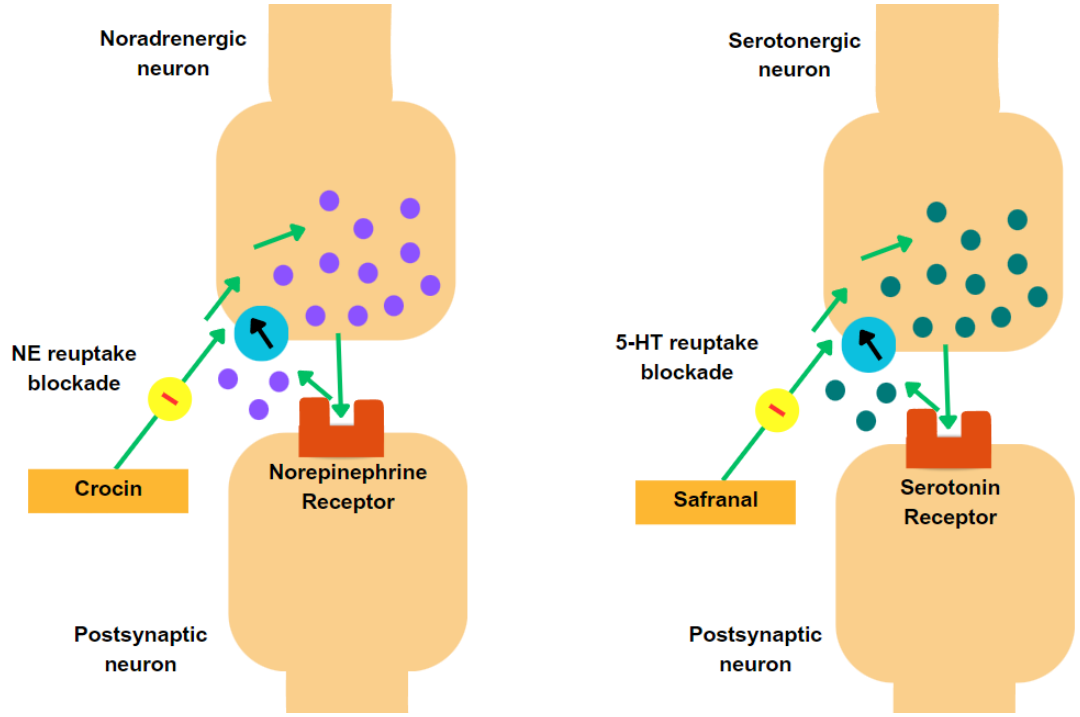

Figure 8: Inhibition of NE Reuptake by Crocin and 5-HT Reuptake by Safranal (Siddiqui et al., 2022).

Saffron's Role in Inflammation: Crocin which is one of the main constituents of saffron helps in the impediment of the activation of nuclear factor-kappa B (NF-κB) pathway that get initiated by the trigger of interleukin 1 beta (IL-1β) (Shafiee et al., 2017). Additionally, crocin exert anti-inflammatory response through the messenger ribonucleic acid (mRNA) expression decrement of some proinflammatory cytokines, cyclooxygenase-2 (COX-2) enzyme and inducible nitric oxide synthase (iNOS) (Kawabata et al., 2012).

Saffron's Role in Neuroplasticity: Saffron by elevating the hippocampus region's BDNF concentration improves the neuroplasticity to exert the antidepressant effect (Philpotts et al., 2023; Lin et al., 2021; Sangiovanni et al., 2017).

Saffron's Role in Stress: Stress induces the pituitary adenylate cyclase-activating polypeptide (PACAP) inhibition that can be blocked by crocin through upregulation of the endogenous PACAP leading to the activation of extracellular regulated protein

kinases (ERK) – cyclic AMP response element binding (CREB) signaling pathway which help in the improvement of synaptic plasticity and enhancement of neuronal survival as depicted in figure 9 (Lu et al., 2020; Siddiqui et al., 2022).

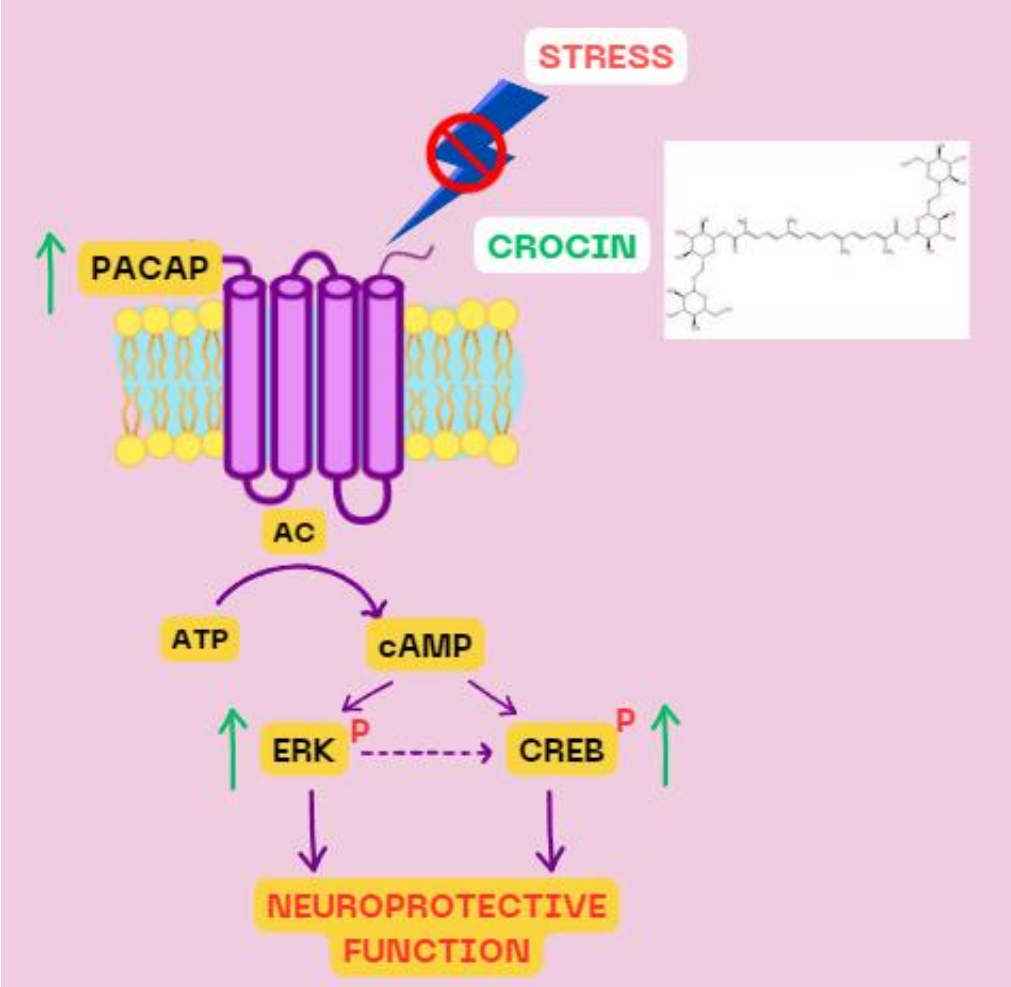

Figure 9: Neuroprotective Function of Crocinin in Stress Induced Depression (Lu et al., 2020).

1.3 Aim of the Study

The study aims to assess the effect of saffron in women suffering from depression associated with postpartum period, premenstrual syndrome and menopause by evaluating the clinical trials data.

Chapter 2

Methodology

A literature search on PubMed and Google Scholar was conducted for the identification of relevant articles published from the year 2004 to 2024 by using Medical Subject Headings (MeSH) terms and keywords related to depression, depressive disorder in women, medicinal plants, saffron, proposed mechanism of saffron in depression and depression associated with other clinical complications/ disease. The search was ended on 10 March 2024. Inclusion criteria were as follows: (i) clinical trials on depression; (ii) articles published from 2004 to 2024. Exclusion criteria: (i) preclinical studies; (ii) published in language other than English; (iii) studies with insufficient data on plant's role in depression. 2 persons individually conducted the search and verified to ensure that there was no error.

The search resulted in 234 records which came down to 120 through initial screening and duplications removal. Through further screening 4 articles relating to saffron in the treatment of women's depression with specific diseases published between 2008 and 2018 were selected eventually. The overall screening procedure is depicted in Figure 10.

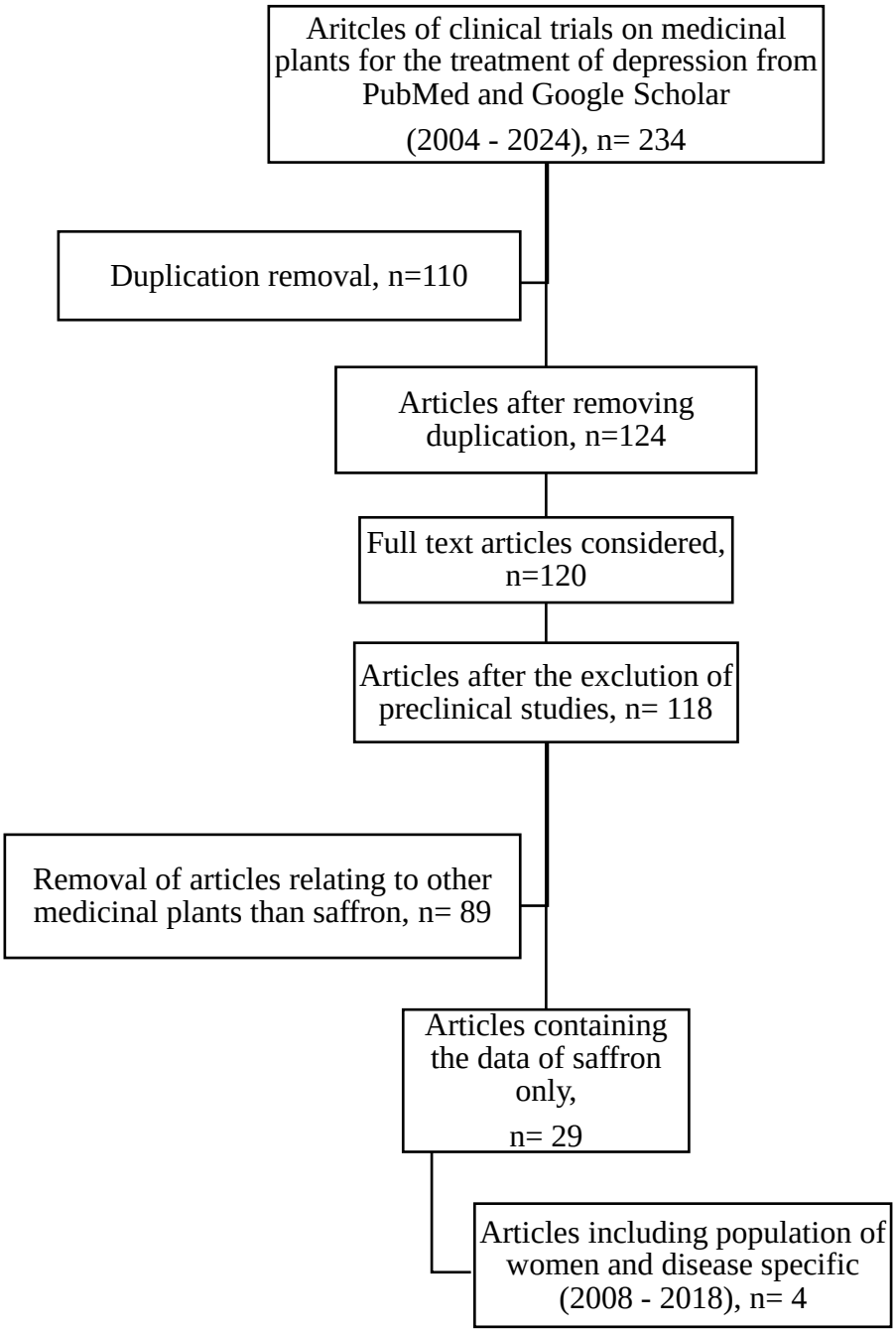

Figure 10: Screening Procedure for Finding Relevant Articles

Chapter 3

Result and Discussion

3.1 Saffron on Depression in Women with Premenstrual Syndrome

Agha-Hosseini et al. (2008) carried out a double-blind, randomised and placebo-controlled trial between December 2005 and April 2007 involving women aged 20 to 45 who reported having normal menstrual cycles regularly and had experienced the symptoms of premenstrual syndrome for a minimum of six months, to find the efficacy of saffron in treating premenstrual syndrome associated with depression. Women who completed the clinical trial (N = 47) were allocated at random to the treatment group (N = 24) receiving a 15 mg capsule of saffron two times a day and to the control group (N = 23) receiving an equivalent dose of placebo capsule two times a day during their menstrual cycle 3 and cycle 4. As per the Total Premenstrual Daily Symptoms score which was regarded as the primary outcome measure, 19 women (76%) from the saffron group a showed response compared to 2 women (8%) from the placebo group. A significant difference ($p < 0.001$) was observed in saffron group between cycle 3 and cycle 4 and the significant difference was found between the two protocols in cycle 4 ($t = 5.92$, $df = 48$, $p < 0.001$). On the other hand, according to the Hamilton Depression Rating Scale (HDRS) which was regarded as the secondary outcome measure, 15 women (60%) from the saffron group showed response compared to 1 woman (4%) from the placebo group. A significant difference ($p < 0.001$) was observed in saffron group between cycle 3 and cycle 4 and the significant difference was found between the two protocols in cycle 4 ($t = 8.99$, $df = 48$, $p < 0.001$). Moreover, no significant difference of adverse effect frequency was obtained between the saffron and placebo group. Thus, such improvements in both of the measuring parameters with a significant difference between cycle 3 and cycle 4

suggest that saffron could effectively alleviate the symptoms of premenstrual syndrome and depression.

3.2 Saffron in the Treatment of Hot Flashes Associated Depression in Post-Menopausal Women

Kashani et al. (2018) conducted a multicenter, randomized, double-blind, parallel group clinical trial for 6 weeks where post-menopausal women having at least moderate hot flashes participated and the study was conducted to find the saffron's potency in the alleviation of the symptoms of hot flashes associated depressive disorder in such women. Women who completed the trial (N = 56) were allocated at random to the treatment group (N = 28) receiving a 15 mg saffron capsule two times a day and to the control group (N = 28) receiving an equivalent dose of placebo capsule two times a day. Differences in the score change of Hot Flash-Related Daily Interference Scale (HFRDIS) and HDRS from baseline to the trial's end between the saffron group and placebo group was used as the primary outcome measure. Comparison of the changes in HFRDIS and HDRS scores from baseline to each time point between the saffron group and placebo group, partial response rates (25–50% reduction in the HDRS score) and complete response rates (≥ 50% reduction in HRDS score) and remission rates (HRDS score ≤ 7) were regarded as the secondary outcome measure. The study depicted that saffron group demonstrated significant reduction in both HDRS score and HFRDIS score at week 2, 4 and 6 which was greater than those of the placebo group. Moreover, between the two groups no significant difference was observed in the adverse events frequency. Such changes in the measuring parameters suggest that, in post-menopausal women saffron can safely and efficaciously alleviate the symptoms of hot flashes along with the associated depressive disorder.

3.3 Saffron on Postpartum Depression in Women

Tabeshpour et al. (2017) carried out a double-blind, randomized, and placebo-controlled trial for two months on breastfeeding mothers to find the saffron's potency in the alleviation of the postpartum depression symptoms. Women who completed the trial (N = 60) were allocated at random to the treatment group (N = 30) receiving saffron in the dose of 30 mg/day and to the control group (N = 30) receiving an equivalent dose of placebo. The difference in the Beck Depression Inventory-Second Edition (BDI-II) scores from baseline to week 8 was considered as the primary outcome measure. In addition, secondary outcome measure were clinical treatment response rate which is regarded as increment in mean BDI score of $\geq 50\%$ from the baseline and remission rate which is regarded as BDI score of ≤ 13 points. The mean BDI-II scores of saffron group at the baseline was 20.3 ± 5.7 that got reduced to 8.4 ± 3.7 at week 8 ($p < 0.0001$) whereas, placebo group experienced the reduction from 19.8 ± 3.2 to 15.1 ± 5.4 ($p < 0.01$). Moreover, the final assessment depicted that in saffron group around 96% of the people were in remission whereas, in placebo group 43% of the people were in remission ($p < 0.01$). Furthermore, saffron group experienced 66% complete response rate compared to 6% of placebo group. So, the study depicted that saffron is a safer and effective option in treating women's postpartum depression.

3.4 Saffron in Treating Postpartum Depression as Fluoxetine in Women

Kashani et al. (2016) carried out a double-blind, randomized clinical trial for 6 weeks involving women aged 18 to 45 who were diagnosed with postpartum depression to compare the saffron's potency with fluoxetine antidepressant in improving the condition. Women who completed the trial (N = 64) were allocated at random to the

treatment group (N = 32) receiving a 15 mg saffron capsule two times a day and to the control group (N = 32) receiving a 20 mg fluoxetine capsule two times a day. In this study, general linear model repeated measures evaluated the comparison of saffron's potency with fluoxetine in the alleviation of the postpartum depression symptoms which was used as primary outcome measures. Along with that, both saffron group and placebo group were compared on the basis of the HDRS scores improvement from baseline at each time point, partial responders (HDRS score reduction of 25–50 %), responders (HDRS score reduction of ≥ 50 %), remitters (≤ 7 HDRS score) and the time requiredfor responding to the treatment. No significant difference was found for time × treatment interaction on HDRS score between the saffron group and fluoxetine group [F (4.90, 292.50) = 1.04, p = 0.37]. In saffron group, 6 patients (18.8 %) and in fluoxetine group, 7 patients (21.9 %) experienced remission showing no significant difference between them (p = 1.00). Furthermore, in saffron group, 13 (40.60 %) patients and in fluoxetine group, 16 (50%) patient experienced complete response showing no significant difference (p = 0.61). Moreover, by week 6, 32 patients in the both of the groups experienced partial response showing no significant difference (p = 1.00). Additionally, adverse events frequencies experienced by saffron group and fluoxetine group were not significantly different. So it is depicted that for alleviating the symptoms of postpartum depression, saffron is a safer substitute that function as effectivelyas fluoxetine.

Saffron has demonstrated its efficacy in treating depression in women with premenstrual syndrome, depression associated with post-menopausal hot flashes, postpartum depression and also has depicted its efficaciousness as fluoxetine in the alleviation of postpartum depression symptoms (See table 2).

Table 2: Summary of Clinical Trials Examining Effects of Saffron on Women Suffering from Depression

Author (year)	Design	Population	Treatment Group	Control Group	Result
Agha-Hosseini et al. (2008)	A double-blind, randomized and placebo-controlled trial between December 2005 and April 2007	Women between the age of 20–45 years experiencing premenstrual syndrome for at least 6 months (N = 47)	A 15 mg saffron capsule two times a day during cycles 3 and 4 (N = 24)	Equivalent dose of capsule placebo twice a day during cycles 3 and 4 (N = 23)	In saffron group, both Total Premenstrual Daily Symptoms and HDRS showed a significant difference ($p < 0.001$) between cycles 3 and 4 indicating that saffron effectively alleviated symptoms of premenstrual syndromes (PMS) and depression.
Kashani et al. (2018)	A 6-week, multicenter, randomized, double-blind, parallel group clinical trial	Post-menopausal women with at least moderate hot flashes (N = 56)	A 15 mg saffron capsule two times a day (N = 28)	Equivalent dose of Placebo twice a day (N = 28)	Saffron groups's significant reduction in both HDRS score and HFRDIS score at week 2, 4 and 6 which was greater than those of the placebo group, depicted that in post-menopausal women saffron can safely and efficaciously alleviate the symptoms of hot flashes along with the associated depressive disorder.
Tabeshpour et al. (2017)	A 8 week double-blind, randomized, and placebo-controlled trial	Breastfeeding mothers (N = 60)	A 15 mg saffron capsule two times a day (N = 30)	Equivalent dose of placebo two times a day (N = 30)	Mean BDI-II scores of saffron group at the baseline was 20.3 ± 5.7 that got reduced to 8.4 ± 3.7 at week 8 ($p < 0.0001$) whereas, placebo group experienced the reduction from 19.8 ± 3.2 to 15.1 ± 5.4 ($p < 0.01$) with significant difference in remission rate ($p < 0.01$) and complete response rate between the 2 groups depicting that saffron is safer and effective option in treating women's postpartum depression
Kashani et al. (2016)	A 6-week, double-blind, randomized clinical trial	Breastfeeding women aged 18 to 45 with postpartum depression (N = 64)	A 15 mg saffron capsule two times a day (N = 32)	A 20 mg fluoxetine capsule two times a day (N = 32)	No significant difference was found for time × treatment interaction on HDRS score between the saffron group and

					fluoxetine group [F (4.90, 292.50) = 1.04, p = 0.37] along with no significant difference between the 2 groups in remission rate (p = 1.00), complete response rate (p = 0.61) and partial response rate (p = 1.00) which depicted that saffron is a safer substitute functioning as effectively as fluoxetine to alleviate postpartum depression symptoms.

Chapter 4

Conclusion and Future Anticipation

As women are more prone to depression and the depression may also associate with other detrimental clinical conditions, it is necessary to find safer and effective management strategy for the alleviation of depression. The result of the clinical trials depicted that saffron can effectively alleviated depression in women including postpartum depression, depression associated with premenstrual syndrome and depression with post-menopausal hot flashes, and saffron also work as efficaciously as fluoxetine in treating postpartum depression. Besides, the studies also reported that saffron when used at therapeutic doses, shows no significant adverse effects. Hence, as the prevailing treatment options for depression are synthetic antidepressants with various adverse reactions and slower response rate, saffron can be used as safer alternative medication. However, as depression is chronic in nature, extended studies are needed to validate the effectiveness of saffron in depression so that saffron extract or supplement can be used and prescribed worldwide other than the usually prescribed synthetic antidepressant for treating depression in both men and women of all ages.

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