A Review on Saffron in the Treatment of Depression in Women

By

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements
for the degree of
Bachelor of Pharmacy (Hons.)

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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.
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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.
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Approval

The thesis titled “A Review on Saffron in the Treatment of Depression in Women” submitted by Farhana Akter Shifa (20146088) 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 serious mental disability that is more prone to occur in women than men. The objective of this study was to assess the effect of saffron on depression in women with specific diseases such as postmenopause, perimenopause, overweight, and breast cancer. Especially whether it can be used as a safer treatment than the standard treatments, can reduce the symptoms of depression, and improve quality of life. The method of this study was conducting a strategic search in PubMed and Google Scholar to collect relevant articles published between 2004 and 2024. After the total screening process, 4 clinical trial articles related to women in depression with specific diseases were selected. The results showed that saffron significantly reduced symptoms of depression and improved quality of life among postmenopausal women, perimenopausal women, overweight women, and women with breast cancer. However, more studies including long-term investigations are needed to prove firmly the efficacy of saffron on depression in women.

Keywords: Saffron; Depression; Women; Menopause; Overweight; Breast Cancer

Dedication

To my father whose dedication is the foundation upon which my life is built and my mother for her companionship in every part of my journey.

Acknowledgment

I would like to express my profound gratitude to the Almighty Allah, the Most Gracious and the Most Merciful, for keeping me healthy mentally and physically during this journey. Thanks to Him for the strength He gave me each day.

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List of Acronyms

5-HT	5-hydroxytryptamine
ANOVA	Analysis of Variance
BDNF	Brain-derived neurotrophic factor
CBT	Cognitive-behavioral therapy
CNS	Central Nervous System
CRP	C-reactive protein
DA	Dopamine
DMDD	Disruptive Mood Dysregulation Disorder
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
GABA	Gamma-aminobutyric acid
GCS	Greene Climacteric Scale
HDL	High-density lipoprotein
HPA	Hypothalamic-Pituitary-Adrenal
IDO	Indoleamine 2,3-Dioxygenase
IFN-γ	Interferron-gamma
IL	Interleukins
IPT	Interpersonal psychotherapy
KYN	Kynurenic Acid

LDL	Low-density lipoprotein
MAO	Monoamine oxidase
MAOIs	Monoamine oxidase inhibitors
MDD	Major Depressive Disorder
Mets	Metabolic disorders
NDRI	Norepinephrine–dopamine reuptake inhibitor
NE	Norepinephrine
NET	Norepinephrine transporter
NMDA	N-methyl-D-aspartate
PANAS	Postive and Negative Affect Schedule
PDD	Persistent Depressive Disorder
PMDD	Premenstrual Dysphoric Disorder
PMS	Premenstrual Syndrome
PST	Problem-solving therapy
QUIN	Quinolinic Acid
SERT	Serotonin transporter
SF-36	Short Form-36 Health Survey
SIRTs	Sirtuins
SNRIs	Serotonin and Norepinephrine Reuptake Inhibitors

SPSS	Statistical Package for the Social Sciences
SSRIs	Selective Serotonin Reuptake Inhibitors (SSRIs)
TCAs	Tricyclic antidepressants
TNF-α	Tumour Necrosis Factor-alpha
TRP	Tryptophan
USA	United States of America
WHO	World Health Organization

Chapter 1

Introduction

1.1 Depression Overview

Depressive disorders are mental illnesses that are among the most common disorders and can affect an individual's thoughts, moods, physical health, and overall life negatively (Gökdağ & Kızıltepe, 2023; Cui, 2015).

1.1.1 Symptoms & Classification

An individual may have psychological symptoms such as stress, low self-esteem, sadness, low mood, hopelessness, intolerance and irritability, difficulty in making decisions, absence of motivation or not feeling interested in anything, a sense of guilt, and thoughts of self-harm or even suicide. In addition, some examples of physical symptoms are- fatigue, sleep pattern alteration, weight gain or weight loss, shifting appetite, loss of libido and unexplained aches and pains. An individual may also exhibit reduced productivity at work, difficulty with home and family life, and avoidance of social activities and friends as examples of social symptoms (Sassarini, 2016).

People suffering from depression experience higher functional disability than those with chronic diseases like high blood pressure, diabetes, heart disease, and arthritis. Compared to patients with chronic illness, depressed patients spend more time in bed, lose more work days, and experience more physical discomfort (Rakel, 1999).

In accordance to the Fifth edition of The Diagnostic and Statistical Manual of Mental Disorders (DSM-5), depressive disorders are mainly classified as follows (Maina et al., 2016):

- Major Depressive Disorder (MDD)

- Disruptive Mood Dysregulation Disorder (DMDD)
- Persistent Depressive Disorder (PDD)
- Premenstrual Dysphoric Disorder (PMDD)
- Depressive disorder induced by substances/drugs
- Depressive disorders from other medical conditions

1.1.2 Prevalence

According to an estimation by The World Health Organization (WHO) (2023), there are 280 million people worldwide with depression. Also, in another study, around 10% experienced depression in 2018 (Saeed et al., 2019). Between 1990 and 2017, incident cases of depression in number increased by 49.86% worldwide (Liu et al., 2020). Moreover, severe depression among adolescents is a matter of great concern because it increases their tendency to commit suicide 30 times (Liu et al., 2020). Among 20 to 39-year-old adults in the United States of America (USA), depression prevalence is much higher in women (10.1%) than men (5.5%) (Rome et al., 2022).

1.1.3 Etiology

Genetic factor:

It is found that first-degree relatives of depressed persons have almost a 3-fold increase in their risk of developing an MDD than the relatives of the general population (Lesch, 2004). Also, according to earlier twin and adoption studies, the likelihood of MDD being heritable is approximately 31–42% (Tian et al., 2022).

Neurotransmitters:

In the genesis of depression, neurotransmitters are assumed to have a significant role. Throughout the nervous system, 4, 24 Serotonin which is also called 5-hydroxytryptamine (5-HT) is broadly distributed and lack of it can lead to mental health

disorders such as depression, anxiety, phobias, etc. (Tian et al., 2022). Dysregulation of other neurotransmitters such as norepinephrine (NE), dopamine (DA, a contraction of 3,4-dihydroxyphenethylamine), glutamate and gamma-aminobutyric acid (GABA) are also involved in developing depressive disorders (Hasler, 2010).

Hypothalamic–Pituitary–Adrenal (HPA) axis:

The activation of the HPA axis can be triggered by chronic stress (Lang & Borgwardt, 2013). Hyperactivation of this HPA axis is considered to be one other factor in MDD which is presumed to be generated from glucocorticoid receptor malfunction. This malfunctioning impairs the HPA axis negative feedback circuit and might cause depression through reduction of hippocampus volumes and neurogenesis impairment. As a result, cortisol level in the depressed person works as an important determinant of the risk and recurrence time of an MDD episode (Verduijn et al., 2015).

Neuroinflammation:

Inflammation is associated with the pathogenesis and pathophysiology of depression which is hypothesized by the studies over the previous 20 years. Multiple studies found that for patients who had autoimmune or infectious diseases, depression was more common among them than in general people (Tian et al., 2022). In a study, significantly increased levels of the acute phase C-reactive protein (CRP), and pro-inflammatory cytokine interleukin (IL)-6 were found in depressed people compared to the people in the control group (Verduijn et al., 2015). Another study hypothesized that pro-inflammatory cytokines such as TNF-α, IFN-γ, IL-1β, IL-2, and IL-6 reduce serotonin synthesis and induce Indoleamine 2,3-Dioxygenase (IDO) activity in the time of inflammation. IDO catalyzes the breakdown of tryptophan (TRP) into quinolinic acid (QUIN) and kynurenic acid (KYN) (Figure 1). QUIN functions as a pro-inflammatory

mediator, gliotoxin, and neurotoxin. Overall, reduction of serotonin synthesis and neurodegeneration through IDO activity leads to the genesis of MDD (Feltes et al., 2017).

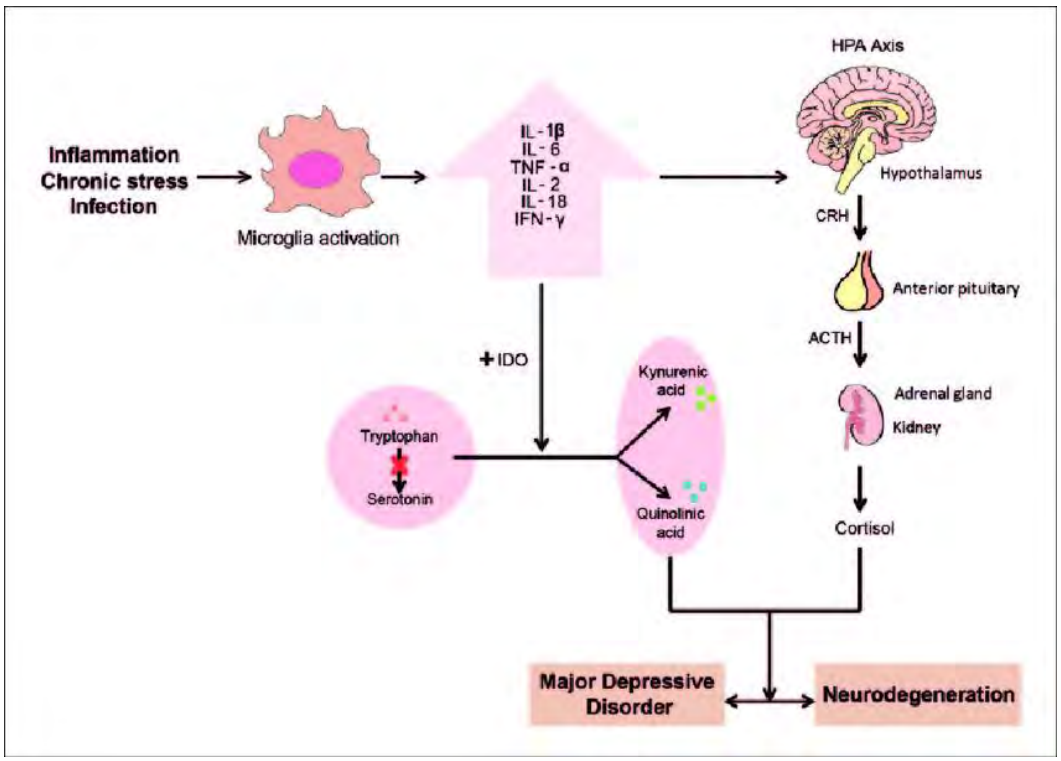

Figure 1: Hypothesis of How Neuroinflammation is Involved in MDD (Feltes Et Al., 2017).

Neurotrophic factors:

Another important pathological mechanism in MDD is neurotropic growth which is reduced by low levels of BDNF which means brain-derived neurotrophic factor (Verduijn et al., 2015; Maletic et al., 2007). BDNF plays an important role in synaptic plasticity (Yang et al., 2020). Decreased plasticity of the synapse leads to decreased glutamate which reduces the synaptic transmission and induces neuronal degeneration resulting in depression (see Figure 2).

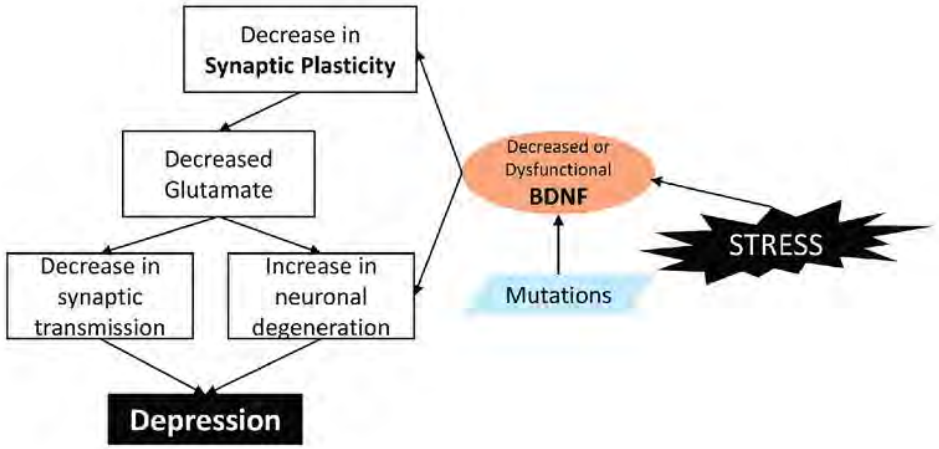

Figure 2: How Changes in BDNF Can Lead to Depression (Yang Et Al., 2020).

Endogenous Metabolites:

Depression is more common in patients with metabolic disorders (Mets) than in the general population (Song & Kim, 2016). It is found that endogenous metabolites are linked with genesis of depression (Tian et al., 2022). An important metabolism regulator is Sirtuins (SIRTs). Sirtuins have been shown to impact a wide range of biological mechanisms such as oxidative stress, protein aggregation, and inflammatory responses, which are related to the diseases of the central nervous system (CNS). They also have protective roles in neuropathological conditions. Due to the association of with inflammation, improper neurotransmitter secretion, and synaptic dysfunction, SIRTs play an important role in developing depression (Figure 3) (Song & Kim, 2016).

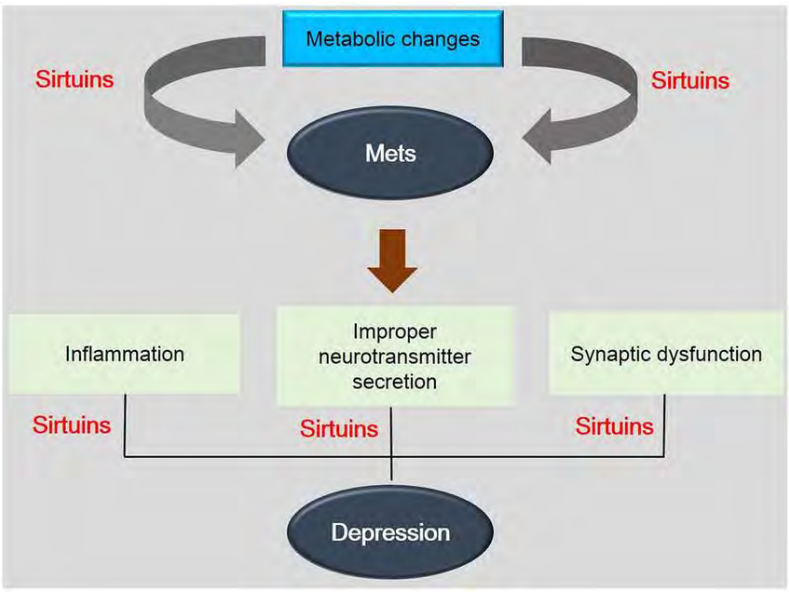

Figure 3: Role of Sirtuins in the Relation Between Depression and Metabolic Disorders (Mets) (Song & Kim, 2016).

Microbiome–gut-brain axis:

Multiple studies have already proved that the axis of the microbiome–gut–brain is critical for controlling the brain's neurotransmission, mood, and behavior. Furthermore, some animal studies have shown that stress can bring changes in the composition and variety of the gut microbiota which is associated with depressive behavior. Recent research has shown that specific neurotransmitter levels in the gut and brain can be affected by the gut microbiota. The neurotransmitters are- serotonin (5-HT), dopamine, noradrenaline, glutamate, and GABA. Additionally, it is also found from recent studies that gut microbial alterations might disrupt the barrier of the gut and elevate inflammatory cytokines in the periphery (Tian et al., 2022).

Overall, the mechanisms involved in the pathophysiology of depression are illustrated in Figure 4.

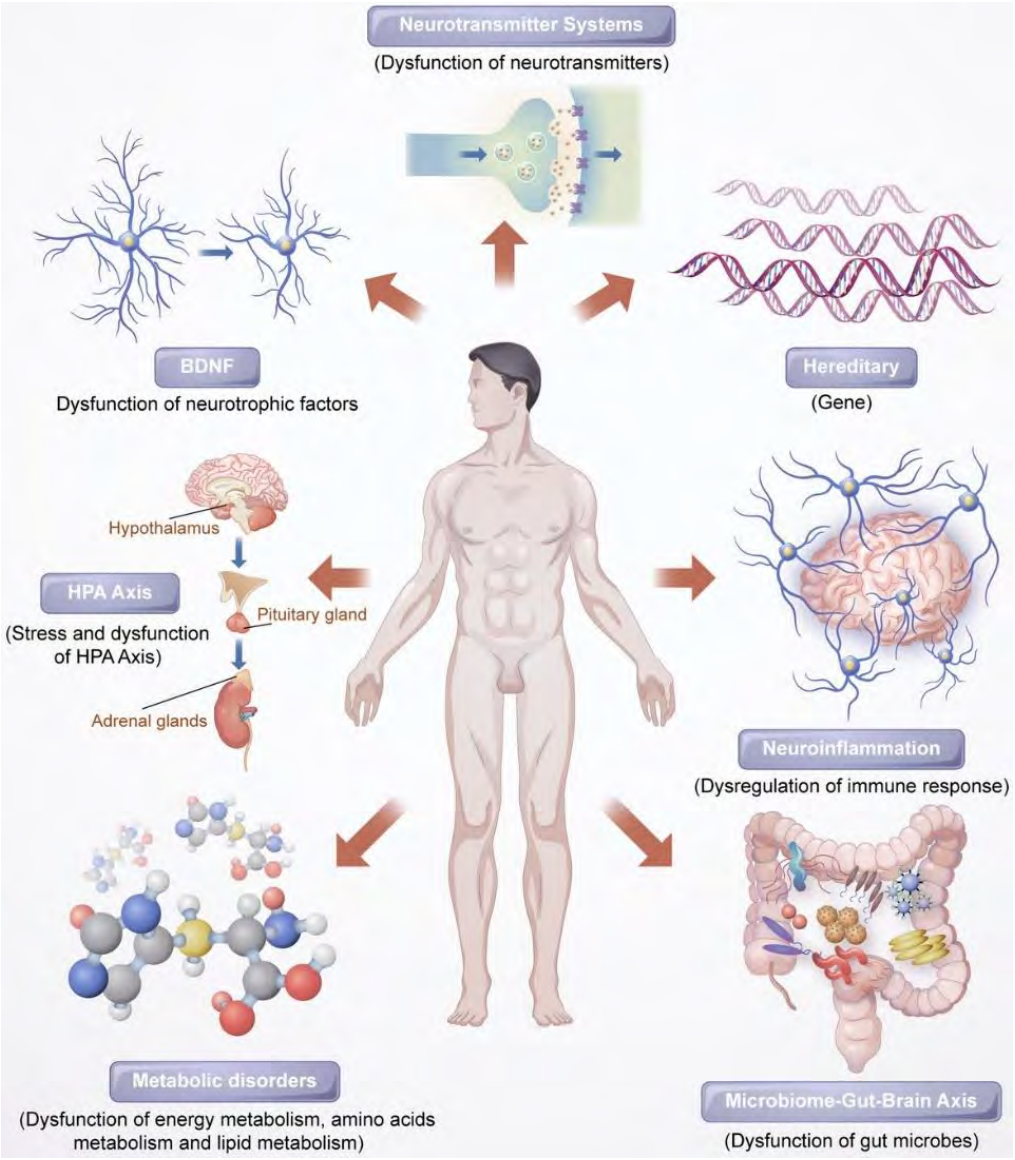

Figure 4: Pathological Mechanisms of Depression (Tian et al., 2022).

1.1.4 Risk Factors

Other than genetic and biological factors, there are some risk factors associated with depression. They are- temperament, traumatic events during childhood, relationships with family and peers, and some factors regarding mentality and emotion (Gökdağ & Kızıltepe, 2023).

Some medical conditions that can develop depressive disorders are- Hypothyroidism, Stroke, Huntington's disease, Parkinson's disease, Head injuries, Cushing's disease, and Multiple sclerosis (Maina et al., 2016).

In addition, light deprivation induces depression-like behavior (Lang & Borgwardt, 2013). In a meta-analysis, low levels of vitamin D are also found to be associated with depression (Verduijn et al., 2015; Anglin et al., 2013).

1.2 Women and Depression

In women, one of the main causes of disease-related disability is depression. Women experience an episode of depression approximately two times as frequently as men do. The reason may be partially explained by the sex differences in brain neuroanatomy and neurophysiology (Sassarini, 2016). Also, some other theories highlight the differences in biological vulnerability, thought patterns, need for affiliation, and emotion reactivity and regulation across the sexes. (Derry et al., 2015).

Depression in women is connected with the reproductive cycle. During the luteal phase of every menstrual cycle, premenstrual syndrome (PMS) with associated mood disturbances occurs regularly (Sassarini, 2016). Hormonal changes, especially low levels of estrogen during the lifecycle are found to be linked with an increased rate of depression among them. Since estrogen tends to have anti-inflammatory effects on microglia, low estrogen periods may increase neuroinflammation (Peirce & Alviña, 2019). Also, it is found that depression in post-menopausal women is correlated with estrogen receptor polymorphisms (Sassarini, 2016). According to a study, women without a history of depression during the premenopausal state experienced a three-fold increase in depression throughout the menopausal transition (Alblooshi et al., 2023).

Moreover, sex and disease (neural or somatic) interact to cause depression (Nemeth et al., 2013). Breast cancer and obesity are two somatic disorders that can lead women to depression.

Women's experience in having breast cancer or undergoing treatment is traumatic because it affects their self-image and sexual relationships negatively. Moreover, it may result in psychological responses during their disease and treatment process, such as denial, anger, or intense fear. Additionally, many breast cancer patients have depression and anxiety as common psychological comorbidities (Tsaras et al., 2018). According to an analysis, 30.2% of women with breast cancer experienced depression. The prevalence of depression was the highest in Pakistan (83%) and the lowest in Taiwan (8.3%) (Biparva et al., 2023).

In the population, obesity and depression are highly comorbid. The prevalence of MDD in obese samples was found within the range of 18.6 to 24.1% in nationally representative samples. Many symptoms of MDD such as fatigue, weight gain, increased appetite, and sleep disturbance are found in the reports of obese adults with higher rates (Schneider et al., 2013). According to a study, women who are in middle age, have high neural fat in serum, high cholesterol, and elevated low-density lipoprotein (LDL) but lower high-density lipoprotein (HDL). As a result, they have negative impacts on physical and mental health by causing hyperlipidemia and hypertension which may result in depression (Park & An, 2006). The correlation between obesity and depression in women is now widely accepted. Despite having studies indicating no correlation or bi-directional association, numerous studies, including longitudinal studies have found a correlation between obesity and depression (Hicken et al., 2013).

1.3 Depression Treatment Strategies

1.3.1 Pharmacotherapy

Currently, there are numerous classes of drugs accessible for treating depressive disorders (see Table 1).

Table 1: *List of Antidepressants with their mechanism of actions (Fajemiroye et al., 2016; Ostuzzi et al., 2018).*

Classes	Drugs	Mechanism of Action
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine Paroxetine Sertraline Citalopram Fluvoxamine	Selective inhibition of 5-HT reuptake and thus increase the concentration of 5-HT
Serotonin and norepinephrine reuptake inhibitors (SNRIs)	Venlafaxine Duloxetine	Inhibition of reuptake of 5-HT and NE
Tricyclic antidepressants (TCAs)	Desipramine Imipramine Clomipramine Nortriptyline Amitriptyline	Block the Serotonin transporter (SERT) and Norepinephrine transporter (NET) and inhibit reuptake of 5-HT and NE
Non-selective Monoamine oxidase inhibitors (MAOIs)	Phenelzine Iproniazid Tranylcypromine Isocarboxazid	Block the Monoamine oxidase (MAO) enzyme and prevent the breakdown of 5-HT and NE
Monoamine oxidase A inhibitors	Toloxatone Moclobemide	Block the Monoamine oxidase A enzyme
Antagonist /reuptake inhibitor	Nefazodone	Block 5-HT2 receptors and prevents reuptake of 5-HT and NE to increase their availability in the synaptic cleft
α2-antagonist	Mirtazapine	Block presynaptic a2-receptor and block disinhibition 5-HT and NE release.
Norepinephrine–dopamine reuptake inhibitor (NDRI)/Atypical	Bupropion Amineptine	Inhibit reuptake of DA and NE

1.3.2 Psychotherapy

Psychotherapy combined with pharmacotherapy works most effectively against mild to moderate depression (Rakel, 1999).

Various psychotherapies are being implemented nowadays, especially cognitive-behavioral therapy (CBT), interpersonal psychotherapy (IPT), and problem-solving therapy (PST) (Weitz et al., 2018).

One effective type of psychotherapy is cognitive behavioral therapy which tries to improve an individual's self-esteem through encouragement. In this therapy, the negative thoughts associated with depression are replaced with a more positive and realistic perspective on daily life (Rakel, 1999).

1.3.3 Exercise and Diet

It has been shown that running has similar efficacy as psychotherapy in treating mild to moderate depression (Rakel, 1999). Physical activity can decrease symptoms of depression since it has been shown to improve psychological well-being, physical health, cognitive functioning, and life satisfaction (Carek et al., 2011).

Additionally, dietary interventions can be a promising novel intervention in the field against depression (Firth et al., 2019).

1.3.4 Electroconvulsive Therapy

High efficacy of electroconvulsive therapy has achieved remission within just one to two weeks over 90% of patients. It is often reserved for patients who don't respond to medication, have symptoms of psychotic or catatonic, and are suicidal. The frequency of the treatment is three times per week and will be continued until there is an improvement in the patient (Rakel, 1999).

1.3.5 Bright Light Therapy

Bright light treatment increases the melatonin level gradient, elevates mood, and boosts sleep efficiency (Lang & Borgwardt, 2013). Patients who have seasonal affective disorder can be highly benefitted by this therapy. In combination with pharmacotherapy, bright light therapy works the best.

1.3.6 Phytotherapy

Though there are many chemical and synthetic drugs available for treating depression, different species of plants worldwide are getting scientifically invested and tested in animal models and human models to present safer and more effective novel medicines to anxiety and depressive disorder patients (see Table 2).

Table 2: Medicinal Plants Used in Depressive Disorders (Fajemiroye et al., 2016; Bakhshaei, 2017; Saki et al., 2014).

Medicinal plant	Active principles	Mechanism of Action
Albizia julibrissin (mimosa)	Julibroside	Affinities for 5-HT1a and 5-HT2c receptor binding. Anxiolytic and antidepressant properties lengthen sleep duration and reduce sleep latency.
Annona cherimola (Custard Apple)	Liriodenine, anonaine and nornuciferine	Through an increase in monoaminergic neurotransmission, it gives antidepressant-like action
Cimicifuga racemosa (black cohosh)	Triterpenes and derivatives of flavones	Acts in the vasomotor center of the hypothalamus. Additionally, in vitro and in vivo research points to have a dopaminergic impact.
Crocus sativus (saffron)	Safranal	Acting by dopamine, norepinephrine, serotonin reuptake inhibition, GABA agonist, and N-methyl-D-aspartate (NMDA) receptor antagonist
Echium amoenum (borage)	Rosmarinic acid, Thesinine	Antidepressant, anxiolytic effects (unknown mechanism)
Hypericum perforatum (St. John's wort)	Hyperforin, Hypericin	Antagonist of NMDA receptors; selective inhibitor of MAO-A and MAO-B; inhibition of 5-HT, NE, and DA uptake; mild interactions with the GABA-A receptor; suppression of interleukin 6 release
Lavandula angustifolia (Lavender)	Linalool and linalyl acetate	Effect similar to anxiolytics probably via 5-HT1A receptors. Reduce sadness and anxiety by modulating GABA
Litsea glaucescens (Mexican Bay Leaf)	Linalool and b-pinene	Relationships with dopaminergic receptors, a2- and b-adrenoceptors, and serotonergic 5-HT1A receptors D1
Melissa officinalis (Lemon Balm)	Rosmarinic acid, oleanolic acid, and ursolic acid	Inhibitor of rat brain GABA transaminase
Mimosa pudica (Shameplant)	Norepinephrine, mimosine, d-pinitol, and b-sitosterol	By mediating the serotonergic system, gives an antidepressant-like effect
Panax ginseng (Korean ginseng)	Ginsenoside rb1 ginsenoside rg1	Modification of the HPA axis, modulation of dopamine, norepinephrine and serotonin; antioxidant and anti-inflammatory properties; inhibition of the production of nitric oxide
Passiflora incarnata (Maypop)	Orientin, vitexin, isovitexin, isoorientin, and chrysin	Agonist of the GABA-A and GABA-B receptors
Piper methysticum (kava kava)	Kawain, methysticin, dihydromethysticin, dihydrokavain, and yangonine	Kavalactones inhibit MAO-B and prevent noradrenaline from being uptake
Rhodiola rosea (roseroot)	Rosavin	Inhibition of MAO-A, and inhibition of Monoamine modulation (5-HT)

Tagetes lucida (Sweetscented Marigold)	Quercetin, gallic acid, caffeic acid	Regulates 5-HT1A and 5-HT2A receptors
Valeriana officinalis (garden heliotrope)	Valerenic acid and valerenol	Induce the response to different GABA-A receptors
Viola odorata (sweet violet)	Venlafaxine Duloxetine	Inhibit reuptake of 5-HT and NE
Withania somnifera (ashwagandha)	Bupropion amineptine	Inhibit reuptake of DA and NE

1.4 Saffron (*Crocus sativus* L.)

Saffron is collected from stigmas of a mythical aromatic medicinal plant Crocus sativus L. (Midaoui et al., 2022). There are three red stigmas present in each flower of this plant (see Figure 5). The weight of one stigma of saffron is approximately 2mg. It takes 150,000 carefully picked flowers to get about 1 kg of this precious spice (Siddiqui et al., 2018). That is why, it is also called 'red gold' (Midaoui et al., 2022). It is known to be among the most expensive spices worldwide (Maggi et al., 2020).

Figure 5: Red Stigmas of Saffron Flower (Nyeem & Amin, 2018).

1.4.1 Taxonomy

The taxonomy is as follows (Srivastava et al., 2010):

- Kingdom: Plantae
- Division: Magnoliophyta

- Class: Liliopsida
- Order: Asparagales
- Family: Iridaceae
- Genus: *Crocus*
- Species: *C. sativus*

1.4.2 Structure

The primary parts of a saffron plant are- corm, stem, leaves, and flowers. In each flower, there are 6 petals, 3 stamens (male part of the flower), and 3 prolonged styles with a reddish-orange stigma (female part of the flower) on top of each. The corm of the saffron is coated with a membrane of thin, brown color. From the center of the corm, multiple long, thin leaves grow. Amid the leaves, a stem grows with one to three flowers (see Figure 6) (Salehi et al., 2022).

Figure 6: Main Parts of Saffron Plant (Salehi et al., 2022).

1.4.3 Cultivation Regions

In the world, the main regions of cultivation of saffron are Iran, India, Greece, Italy, Spain, and Morocco. There are other cultivation areas such as France, Switzerland, Japan, Australia, Egypt, Israel, New Zealand, and Azerbaijan (Salehi et al., 2022).

Almost 90% of the world's total production of saffron happens in Iran alone, making Iran one of the greatest producers of saffron (Moghaddasi, 2010). India produces 5% of the total production (Kumar et al., 2022).

1.4.4 Phytochemistry

In saffron, more than 150 volatile and non-volatile elements are found to be present. This includes carotenoids, polyphenols, flavonoids and terpenes (Midaoui et al., 2022). Among them, carotenoids are the most important constituents (Maggi et al., 2020).

Saffron is valuable due to its four major and biologically active compounds. They are- crocin and crocetin (carotenoids deriving from zeaxanthin, which are responsible for the yellow color) and two oxidation products of carotenoids- picrocrocin (provides the bitter flavor), and safranal (provides the specific odor and aroma) (see Figure 7) (Maggi et al., 2020; Midaoui et al., 2022; Shafiee et al., 2018).

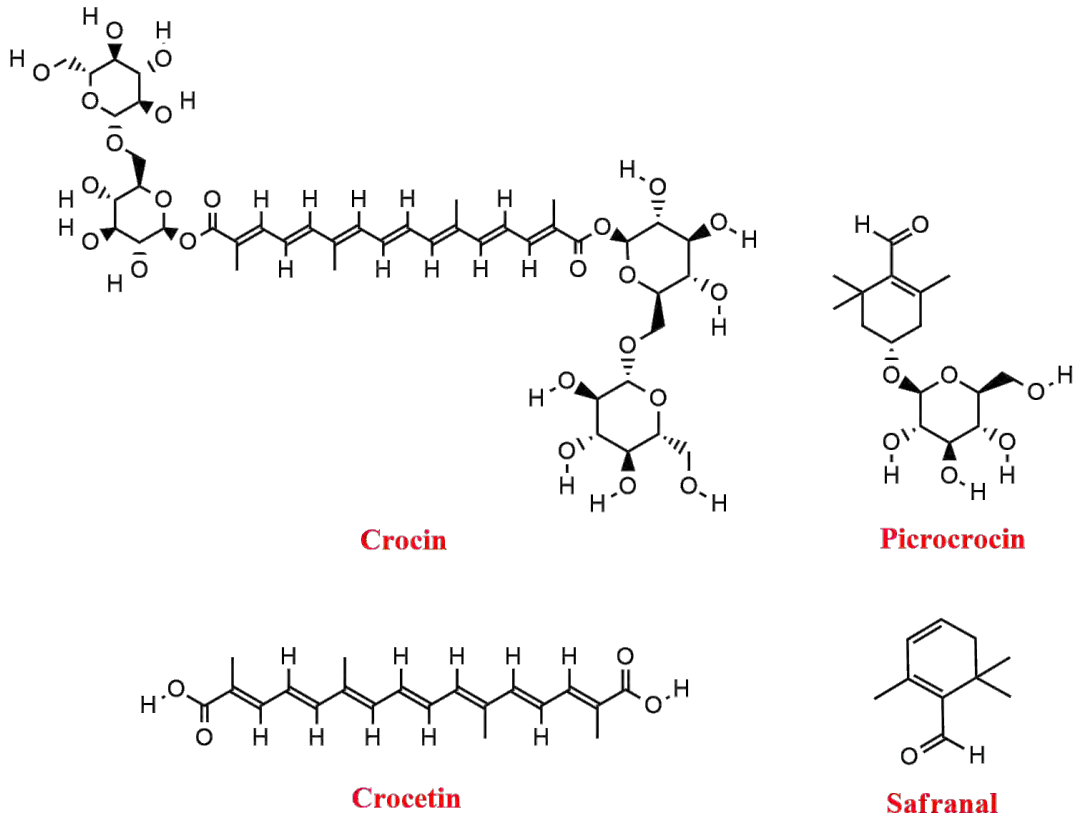

Figure 7: Chemical Structures of Crocin, Crocetin, Picrocrocin and Safranal.

1.4.5 Medicinal Uses

Traditionally, saffron has been used as an expectorant, digestion stimulant, relaxant and exhilarating agent. In addition, it is used in menstruation, and fetus abortion. Due to the relaxant effect of its essential oil, it could also be useful for treating insomnia which originates from the nervous system. Saffron strengthens memory power, improves concentration, improves sexual desire and is spasm calmative. It is used against depression, Alzheimer's, and Parkinson's diseases. Also, saffron was used in treating other diseases such as dermal diseases, cholera, bloody diarrhea, urine infection, fever, measles, liver and spleen syrose, hepatitis, and diabetes. Moreover, it reduces the chances of heart disease. Many researchers have reported that saffron has anticancer and antitumor effects also (Moghaddasi, 2010).

1.4.6 Saffron in Depression

Saffron extracts and their constituents, safranal and crocins have been reported to activate the serotonergic, noradrenergic, and dopaminergic systems, hence exerting antidepressant effects in mice given the forced swim test (Midaoui et al., 2022). According to another study of animal models, saffron also prevented the reuptake of serotonin, dopamine, and norepinephrine in the synapse resulting in prolonged antidepressant action (Dai et al., 2020) (see Figure 8). It was also found that crocetin effectively treated depression in mice (Midaoui et al., 2022).

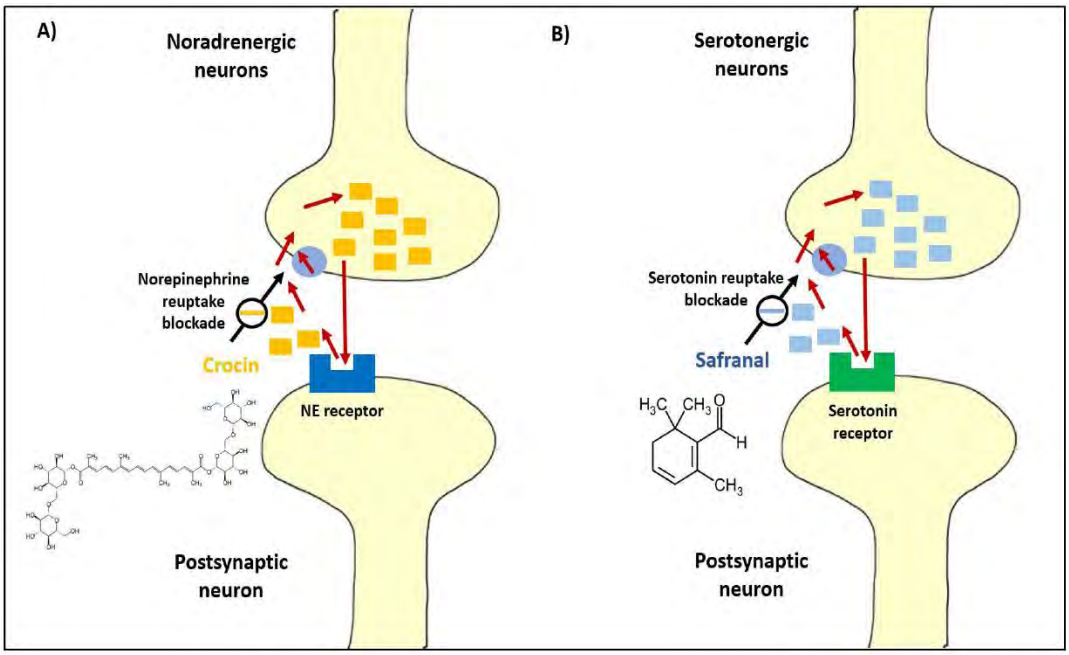

Figure 8: Saffron in Inhibiting Reuptake of Monoamines (Norepinephirine, Serotonin) (S. A. Siddiqui et al., 2022).

1.5 Objective of the Study

To assess the effect of saffron on depression in postmenopausal women, perimenopausal women, overweight women, and women with breast cancer. Especially whether it can reduce the symptoms of depression, improve quality of life, and be safer than the standard treatments.

Chapter 2

Methodology

A search was conducted strategically using PubMed and Google Scholar to find relevant articles related to clinical trials on medicinal plants in treating depression published between 2004 and 2024 using MeSH terms and combinations of relevant keywords- “depression” OR “depressive disorder” AND “medicinal plants”, “saffron” AND “depression OR depressive disorder”, The end search date was 10 March 2024. Inclusion criteria were as follows: (i) clinical studies on depression. (ii) published between 2004 and 2024. Exclusion criteria: (i) non-human studies; (ii) published in a language other than English. 2 individuals independently completed the search and were cross-checked to eliminate any errors.

From the search, 234 records were found. After performing initial screening and removing duplications, the number of records came down to 120. At the end of the total process, 4 clinical trials related to saffron in depression in women with specific diseases published between 2019 and 2023 were selected to work on. The total screening process is demonstrated in Figure 9.

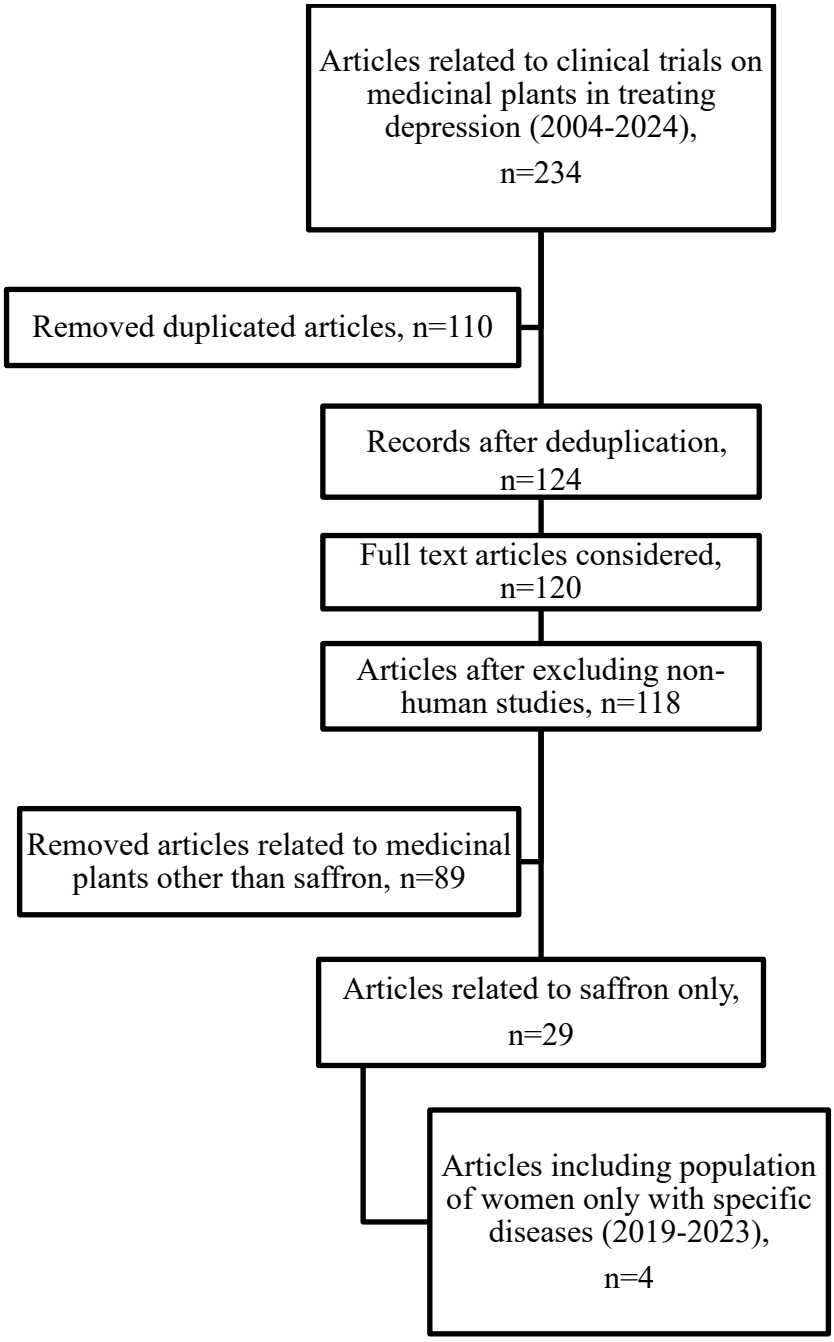

Figure 9: Screening Process in Finding Articles

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Chapter 3

Results & Discussion

3.1 Saffron on Depression in Postmenopausal Women

Delam et al. (2023) showed that saffron tea has the potential as a complementary treatment for depression in postmenopausal women. This research aimed to determine whether herbal tea of saffron impacts happiness among postmenopausal women. A randomized clinical trial was conducted on postmenopausal women for 6 weeks in Iran in 2021. The sample size was 72. In the intervention group, 36 samples were given a cup of tea daily with 30 mg of saffron with white rock candy and lukewarm water. The other 36 samples in the control group were given white rock candy and lukewarm water only. For randomization, the randomized blocks method was used. 70 patients finished the study (Intervention group: 34, Placebo group: 36). For assessment, a demographic information questionnaire (including age, menopausal age, marital status, and education level) and the Oxford Happiness Questionnaire (29 items with minimum happiness score of 29 and maximum happiness score of 116) were used. Then the data were entered and analyzed by using SPSS software. Fisher's exact test and t-test of an independent sample were used for statistical analysis. A significant increase ($p<0.001$) was found in the mean happiness score among the saffron tea group (from 42.93±8.54 to 61.58±8.24) than the control group (from 43.11±6.81 to 42.75±10.23).

3.2 Saffron on Depression in Perimenopausal Women

Lopresti and Smith (2021) reported that saffron brought greater improvements in symptoms of depression among perimenopausal women. The purpose of this research was to determine the efficacy and tolerability of a saffron extract, affron on menopausal symptoms in perimenopausal women. A double-blind, two-arm, parallel-group

randomized controlled trial was conducted on perimenopausal women who were having problems related to menopause for 12 weeks in Australia in 2020. The sample size was 86. In the intervention group, 43 samples were given 28 mg saffron extract (affron) per day in tablets with excipients (calcium hydrogen phosphate and microcrystalline cellulose). In the control group, the other 43 samples were given placebo tablets having the same excipients. For randomization, the randomized blocks method was used by using a randomization calculator. 76 patients finished the study (Intervention group: 39, Placebo group: 37). For assessment, the Short Form-36 Health Survey (SF-36), the Greene Climacteric Scale (GCS), and also positive and Negative Affect Schedule (PANAS) were used. For statistical analysis, different tests such as the t-test of an independent sample, chi-square, ANOVA, Cohen's d, and Shapiro–Wilk normality test were used. All of these data were analyzed. Results showed that the reduction in GCS psychological score was significantly greater ($p<0.001$ & between group p-value 0.032) with a reduction in depression scores of 32% from baseline to week 12. Again, compared to placebo, the reduction in the PANAS negative affect score was significantly greater ($p<0.001$ & between group p-value 0.043) and the increase in the PANAS positive affect score was also significantly greater ($p<0.001$ & between group p-value 0.169) among the control group. However, it did not show greater improvement in somatic symptoms, vasomotor symptoms, or any other quality of life compared to placebo. The tolerability of saffron was well and there was not any significant adverse report noted.

3.3 Saffron on Depression in Women with Breast Cancer

Salek et al. (2021) noted crocin use at the time of chemotherapy (doxorubicin-based) in patients diagnosed with breast cancer improved depression. Also, it may help in managing certain chemotherapy side effects, but it can increase the risk of leukopenia.

This research determined the effects of crocin administration at the time of chemotherapy (doxorubicin-based) in breast cancer patients on depression, anxiety, and toxicity profile of chemotherapy. A randomized clinical trial was conducted on women with non-metastatic Her2/neu positive or triple-negative breast cancer for 4 months in Iran in 2018. The sample size was 78. In the intervention group, 39 samples were given tablets of 30 mg of crocin per day during doxorubicin-based chemotherapy. In the control group, the other 39 samples were given tablets of cellulose as a placebo during doxorubicin-based chemotherapy. For randomization, the randomized blocks method was used. 72 patients finished the study (Intervention group: 36, Placebo group: 36). For assessment, Beck's Depression and Anxiety Inventories were used. Then the data were entered and analyzed by using SPSS software. For statistical analysis, the Shapiro–Wilk normality test, chi-square, and t-test were used. There was a significant reduction in the degrees of depression (from p=0.18 to p=0.001) in the crocin group. In contrast, there was a significant increase in the group with placebo (from p=0.18 to p = 0.036). Also, the crocin group showed a significant increase in leukopenia of grade II-IV (47.2% vs. 19.4% & p=0.012) and a significant decrease in hypersensitivity reactions (30.6% vs 5.6% & p=0.006), and neurological disorders (66.7% vs. 41.7% & p=0.03) than the placebo group.

3.4 Saffron on Depression in Overweight Women

Akhondzadeh et al. (2019) found that saffron has antidepressant properties among overweight women with depression at mild and moderate level. The research focused on determining the effects of saffron capsules on body weight, food craving, and depression among the population. A double-blind, randomized controlled trial was carried out on overweight women (Body Mass Index greater or equal to 25) with mild to moderate depression for 12 weeks in Iran in 2021. The sample size was 73. In the

intervention group, 36 samples were given a daily dose of 30 mg of saffron capsules. In the control group, the other 37 samples were given placebo capsules. For randomization, a computerized simple random allocation method was used. 52 patients finished the study (Intervention group: 27, Placebo group: 25). The data were entered and analyzed using SPSS software. For the assessment of depression, Beck's Depression and Anxiety Inventories were used. Also, body weight measurement, Appetite visual analogue scale, Food abstinence, and Food craving Questionnaire were used to assess food craving, appetite, and body weight. For statistical analysis, Shapiro–Wilk normality test, Greenhouse-Geisser correction, Mauchly's test of sphericity, independent samples t-test, chi-square and ANOVA were used. Result showed that mean depression score was reduced significantly ($p= 0.007$) in the saffron group (mean ± SD of changes −8.4 ±5.9) in comparison with the group of placebo (mean ± SD of changes −3.9 ± 5.5). In addition, there was not a significant effect of saffron on appetite ($p=0.83$), and body weight ($p=0.32$), and food craving ($p=0.54$). Also, side effects were reported less in the saffron group compared to the placebo group.

Overall, from the 4 randomized controlled trials (RCTs), a significant association between saffron and reducing depression in women is found (see Table 3).

Table 3: *Summarization of Studies*

Study	Study type	Duration	Population	Intervention	Comparison	Outcome
Delam et al. (2023)	RCT	6 weeks	Postmenopausal women (n=72)	A cup of tea daily with 30 mg of saffron, lukewarm water, and white rock candy (n=36)	Lukewarm water, and white rock candy only (n=36)	Increase in the mean happiness score significantly (p<0.001) (from 42.93±8.54 to 61.58±8.24) compared to the control group (from 43.11±6.81 to 42.75±10.23)
Lopresti and Smith (2021)	RCT	12 weeks	Perimenopausal women experiencing menopausal complaints (n=86)	A standardized saffron extract (affron) tablets with a daily dose of 28 mg (n=43)	Placebo tablets with the same excipients (n=43)	Improvements in psychological symptoms, specifically, significant reduction in GCS psychological score (p<0.001 & between group p-value 0.032) with a reduction in depression scores of 32%, significant reduction in the PANAS negative affect score (p<0.001 & between group p-value 0.043).and significant increase in the PANAS positive affect score (p<0.001 & between group p-value 0.169)
Salek et al. (2021)	RCT	4 months	Breast cancer patients (n=72)	Crocin in film-coated tablets (daily dose 30mg) (n=36)	Cellulose as placebo in film-coated tablets (daily dose 30mg) (n=36)	Depression decreased significantly in the crocin group (p=0.001 from p=0.18) compared to the control group (p=0.36 from p=0.18)
Akhondzadeh et al. (2019)	RCT	12 weeks	Overweight women with depression (n=73)	Crocus sativus capsules (daily dose 30mg) (n=36)	Placebo capsules (daily dose 30mg) (n=37)	Mean depression score was reduced significantly (p= 0.007) in the saffron group (mean ± SD of changes −8.4 ±5.9) in comparison with the group of placebo (mean ± SD of changes −3.9 ± 5.5).

Chapter 4

Conclusion

The findings suggest evidence that saffron has a significant association with reducing depression among postmenopausal women, perimenopausal women, overweight women, and women with breast cancer.

Herbal tea of saffron significantly raised the mean happiness score in the clinical trial among postmenopausal women. From the clinical trial of saffron in perimenopausal women, it was found that there was an improvement in mood and psychological symptoms, especially a significant reduction in depression score with reduced GCS scale and PANAS negative affect score. Moreover, any major adverse events were not found to be reported. Again, co-administration of crocin (one of the main constituents of saffron) in breast cancer patients during the chemotherapy with doxorubicin significantly decreased depression. Though crocin significantly increased the chemotherapy-induced leuokopenia, it significantly reduced other side effects such as hypersensitivity reactions, and neurological disorders. Additionally, another clinical trial reported that, saffron can be used as a safe supplement for reducing symptoms of depression in overweight women with depression at mild to moderate level. All these studies support that saffron may be used to reduce the symptoms of depression and improve quality of life.

A limitation of this study is that it included clinical trials which highlighted the results of short-term investigations. More studies including long-term investigations are needed to prove the efficacy of saffron on depression in women with specific diseases more accurately.

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