REVIEW ARTICLE ON DEPRESSION AND ANTI-DEPRESSANT ACTIVITY OF VARIOUS MEDICINAL PLANTS

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ABSTRACT

Depression, a rising concern in this current world is one of the most common psychological disorders that people regardless of age, gender, occupation experience. It has an impact on the mental as well as physical stability, personal and social relations. Although a wide variety of the synthetic drugs available in the market are used to treat depression, they however are associated with more side effects than they are efficacious. It has been found that only about 30% of patients reacted to the available medications and the remaining did not achieve complete recovery. Hence, many clinical investigations have been conducted to broaden approaches in order to develop an effective antidepressant without side effects. Plants have been used as medicines to treat various ailments since ancient days. Nowadays people prefer herbal medicinal therapies as alternatives to chemical and synthetic drugs to treat various diseases because they believe that natural products are more safe and cause fewer side effects even when used for a long time. A database search was performed using the following terms: depression, major depressive disorder, alternatives treatments, clinical trials, antidepressants, medicinal plant and extracts. Thus, the aim of this review is to enlist some plants which have antidepressant property.

Keyword: - *Depression, Pathophysiology, Clinical trials, Antidepressants, Alternatives, Medicinal Plants*

1. INTRODUCTION

Depression, also referred to as major depressive disorder (MDD), is a common psychological condition that affects many people. It is characterized by a pervading and sustained low mood, lack of interest in activities inflicting vital disability in daily life [1]. A decline in the quality of life is seen in many people around the world with MDD [2,3]. According to the Global Burden of Disease Study 2010, MDD was classified as the second leading cause of disorder worldwide and was thought to play a significant role in the development of ischemic heart disease and suicide [4] Depression not only affects a person's performance in a variety of circumstances including education, employment, and interpersonal relationships, but it also contributes to higher rates of misdemeanor and substance abuse. Furthermore, the risk of suicide among patients with depression appears to be more than other mental disorders [5]. People of all genders, ages and backgrounds suffers from depression. According to WHO predictions, depression shall become the second largest sickness in terms of morbidity by another decade within the world. Currently, 1 in 5 women worldwide suffers from depression as well as 2 % of college students, and 5 % of teenagers also experience depression, which goes largely underdiagnosed.

1.1 Types of depression

Depressive disorder comes in various forms, even as several different illnesses:

- **Major depression** is exhibited by a combination of symptoms that interfere with one's ability to work, sleep, eat and enjoy once pleasant activities. These disabling occurrences of depression might occur once, double or many times in a short period of time.

-**Dysthymia**, a less severe form of depression is characterized by long, chronic symptoms that don't completely disable, but prevent you from being active, working hard or from feeling responsible. In general, individuals with dysthymic depression jointly experience major depressive episodes.

-**Manic-depressive** or **bipolar** is not nearly as current as different varieties of depressive illnesses. It involves sequences of depression and elation or mania. The mood swings are typically dramatic and abrupt, though most frequently they are moderate.

Once within the depressed cycle, one will have any or all different the symptoms of a depressive disorders. Any or all of the symptoms described underneath mania could become fully fledged once a person is in the wild cycle. Mania commonly affects thinking, judgment, and social behaviour in ways which could cause serious issues and embarrassment.[6]

1.2 Pathophysiology of Depression

The characteristics symptoms of MDD that cause complexity in the treatment of the disorder lies within the domain of cognitive, emotional and physiological effects [7]. Depression is a heterogenous syndrome and a variety of biological mechanism may be involved, which makes it challenging to pinpoint the pathophysiology at play and thus complicating the diagnosis and treatment of depression and related mood disorders [8].

It is well acknowledged that the pathophysiology of MDD is complex involving interaction between several biological systems, environmental influences and genetic predispositions. Over time, hypotheses about the pathophysiology of depression have emerged. First, the traditional monoamine hypothesis postulated that alteration in levels of one of the monoamines: serotonin, norepinephrine, and dopamine cause depression. Amidst those, we can also include the inhibition of neurogenesis, oxidative and nitrative stress, disruption of the neurodegenerative processes particularly through hypothalamic–pituitary–adrenal (HPA) changes or inflammatory processes [9]. Abnormalities in the hypothalamic-pituitary-adrenal axis (HPA axis) have been associated with a hyperactive response to stress in depressed patients (the diathesis-stress model). Anti-inflammatory drugs are being researched as antidepressants because it has been discovered that people with depression have higher levels of inflammatory markers in their bodies. been found in patients with depression. These pathophysiological mechanisms are reciprocally connected with one another. The mechanism of action of ketamine, an N-methyl-D-aspartic acid (NMDA) receptor antagonist has recently sparked a lot of interest in studies on the glutamatergic system. In addition, stressful life events can give rise to depressive episodes in vulnerable individuals [10].

2. ANTIDEPRESSANTS

Antidepressants are medications that are effective in treating depression as well as anxieties, eating disorders, chronic- neuropathic pain, dysmenorrhea, migraines, attention-deficit hyperactivity disorder (ADHD) and neurotic compelling disorder [11].

Numerous antidepressants have been discovered on the basis of their mechanism and functional activity [12,13,14,15] they are:

- the selective serotonin reuptake inhibitors (SSRIs)
- serotonin–norepinephrine reuptake inhibitors (SNRIs) including include buprenorphine, tryptophan
- norepinephrine reuptake inhibitors (NRIs)
- norepinephrine-dopamine reuptake inhibitors (NDRIs)
- norepinephrine-dopamine releasing agents (NDRAs)
- tricyclic antidepressants (TCAs)
- tetracyclic antidepressants (TeCAs)
- monoamine oxidase inhibitors (MAOIs) and low-dose antipsychotics

3. MEDICINAL PLANTS AS ANTIDEPRESSANTS

It is a fact that conventional antidepressants are now considered the main treatment for this health problem, but they exhibit relevant side effects, notably those of the anticholinergic type, which are responsible for changes in psychic functions, and drug interactions. The adverse side effects of these drugs involve anxiety, diaphoresis, tachycardia, tremor, sedation, insomnia, serotonin syndrome, parkinsonism, postural hypotension, blurred vision, tolerance (with long time use) among other aggravating factors [16]. Therefore, it is preferable to search for antidepressants that are fast acting, better-tolerated, more effective and have less side effects. Numerous studies have shown that psychiatric problems, particularly depression and anxiety, frequently involve the use of complementary and alternative medicine (CAM) [17,18,19]. In addition, the use of medicinal plants and herbal medicines, compared to traditional ones, are necessary alternatives, since the absence or reduction of adverse effects through this is considerable (Subramaniyan V, et al., 2019). Herbal remedies and medicinal plants have been used by humans for a long time. Despite the fact that they may have some toxic effects, about 70% of the population now consumes these plants for disease treatment due to low toxicity [20]. While the quantities of specific elements can be quite high due to environmental contamination, herbal plants are not always toxic. A significant issue is fungal infection of plants that are preserved as these may degrade the overall quality as well as alter the chemical constituents of the plants. [21]

Plants that have shown considerable activities in animal studies and are used in clinical trials are presented as follows:

3.1 Saffron (*Crocus sativus L*)

Saffron or *Crocus sativus L*., of family Iridaceae, is one of the most expensive spices in the world having a number of therapeutic effects besides its traditional use as a food additive. In traditional medicines, saffron, its extracts and tinctures have been used as antispasmodic, analgesic, anti-inflammatory, sedative, carminative, sweat enhancer, expectorant, stimulant, gastric strengthener, aphrodisiac and as an agent to promote early menstruation. Animal studies have shown that aqueous and hydroalcoholic extracts of saffron have antidepressant properties [22,23]. In a randomized, double-blind clinical trial, patients with mild to moderate depression were treated with hydroalcoholic extract of saffron at a dose of 30 mg/d or fluoxetine at a dose of 20 mg/d to study the plant's antidepressant effects. An increased risk of bleeding is one of the negative effects of saffron that has been noted; but in this investigation, saffron did not cause an abnormal bleeding [24]. According to a clinical investigation, saffron capsule shows antidepressant benefits similar to imipramine in patients with mild to severe depression. The imipramine group experienced anticholinergic effects such as dry mouth and sedation which were significantly higher than those in the saffron group [25]. Another study on women with premenstrual syndrome found that daily consumption of saffron capsules at a dose of 30 mg/kg considerably reduced the symptoms of the disease as well as the depression. Saffron was found to have side effects which were higher than the placebo, though their difference was not significant [26]. It is proposed that the active compounds of saffron - safranal, crocetin and crocin, impede the reuptake of dopamine, norepinephrine, and serotonin as the basis for their antidepressant activity [27]. Experimental animal models have shown that saffron and its compound have antioxidant and anti-inflammatory capabilities that can lower oxidative stress [28–31]. When administered in combination with pharmacological antidepressants, it is shown that saffron extracts also alleviate depression, even in subjects who had been using the antidepressants with no improvement [32].

3.2 Lavender (*Lavandula angustifolia*)

The lavender plant, *Lavandula angustifolia*, from the Lamiaceae family has long played a role in traditional medicines due to its properties such as gastrotonic, diuretic, analgesic, anti-spasmodic, carminative, nerve tonic, insomnia treating, anti-anxiety, sedative and also in Alzheimer's disease (Harati et al., 2014). Clinical studies have demonstrated that using lavender essential oil in aromatherapy can lessen pain, anxiety, depression, and stress [33]. Patients with mild to moderate depression were divided into two group in a double-clinical trial: the case group receiving 20 mg/d of citalopram plus 5 mg of lavender twice daily and the other group (control group) receiving 20 mg citalopram twice daily. 4 weeks and 8 weeks following treatment the case group's depressive symptoms were dramatically reduced. Both groups complained of dizziness and dry mouth, while no significant difference was found between them [34]. In another double-blind clinical trial, the study conducted shows that lavender caused lower antidepressant effect compared to imipramine in patients with mild to moderate depression. The combination of imipramine with lavender had a much greater antidepressants effect than just imipramine alone. Complaints about the anticholinergic side effects such as dry mouth and urinary retention were reported in the imipramine group, whereas the lavender group complained of headache [35].

3.3 Curcumin

Turmeric (*Curcuma longa Linn*) is a spice which contains the natural chemical component curcumin. Multiple animal models of depression have revealed considerable antidepressant benefits of curcumin. However, because of its poor absorption rate hence the poor bioavailability, its efficacy in clinical trials is lower [36]. An experimental study demonstrated antidepressant effect of curcumin in patients with major depression. The experiment shows that the combination of fluoxetine and curcumin resulted in a reduction of 77.8% of the symptoms, which was higher than the individual effects of fluoxetine (64.7%) and curcumin (62.4%). In this study, curcumin was well tolerated by the patients and caused lesser side effects compared to fluoxetine [37]. The effect of daily curcumin intake was studied on patients with major depressive disorder was investigated in a double-blind clinical experiment (Lopresti et al,). Patients were randomly allotted to curcumin (500 mg twice daily) or placebo groups. After 4 weeks of therapy, there was no discernible difference in the remission of depression symptoms between the two groups. However, the curcumin group's depressed symptoms markedly improved after 8 weeks. Furthermore, the subgroup of atypical major depression experienced better results with curcumin [38]. In another clinical trial, the subjects received antidepressants (escitalopram or venlafaxine) with either 500-mg/d of curcumin or a placebo. The symptoms significantly decreased, according to the results. No complaints about the side effects of the medications were reported [39]. According to studies, curcumin improves the symptoms of depression by affecting the biological mechanisms involved in depression, including monoaminergic activity, inflammatory process, oxidative and nitrative pathways and activity of the HPA axis. In mice exposed to depression curcumin also boosts neurogenesis in the frontal cortex and hippocampus [40].

3.4 Chamomile

Ancient Rome, Greece and Egypt were all familiar with the use of chamomile dried flowers as a natural remedy. Chamomile has been used in these countries to treat digestive problems, lessen pain and heal wounds and injuries. There are different species of chamomile, but the two most widely used variants worldwide are German chamomile (*Matricaria recutita*) and Roman chamomile (*Chamaemelum nobile*). German chamomile has been found to alleviate the symptoms of depression in both animal human models [41]. According to a double-blind clinical trial conducted (Amsterdam et al.,) chamomile had a stronger antidepressant effect than placebo in patients with mixed anxiety and depressive disorder (MADD). In addition, patients with MADD responded more significantly to chamomile compared to other patients. It is also proposed that chamomile extract and its active compounds such as apigenin and quercetin, modulate norepinephrine, dopamine, serotonin, and GABA messaging, regulate the activity of hypothalamic-pituitary-adrenal axis, and inhibit monoamine oxidase enzyme activity as the mechanism underlying the antidepressant effects of chamomile [41]. In another controlled trial, it is found that drinking of chamomile tea significantly improved the quality of sleep and depression in women during the postpartum period [42]. Chamomile essential oil is commonly used for aromatherapy in people with insomnia, anxiety and one of its most popular products which have sedative effects is tea [43]. The ethanolic extract of chamomile, which has been shown in recent studies on rats to have a restorative effect on memory deficits and motor-coordination problems may be useful in patients with behavioral problems. The cleansing properties of free radicals, which can be produced by the active compounds present in the chamomile's extract may be the cause of the its ability to improve memory [44].

3.5 Maidenhair tree or Ginkgo (*Ginkgo biloba*)

Ginkgo, from the Ginkgoceae family, is a large and deciduous tree with fan-shaped leaves. It is an indigenous tree of China, Japan and Korea, but is now grown in many parts of the world. Various parts of the plant such as seeds and leaves widely used in traditional Chinese medicine for the treating many diseases. Pharmacologically, the pure extract of the plant leaves has the potential to open arterial arteries and activate the blood circulation in the arteries, which itself provides more perfusion to the tissues. The leaf extract of the herb increases the blood flow to the brain, and thus, improves memory and intellectual ability [45]. Ginkgo tablets are marketed in Iran as a memory enhancer and booster. In numerous clinical investigations, the antidepressant properties of ginkgo herb have been investigated. In a double-blind clinical trial, 81 patients with major depressive disorder were randomly assigned into two groups of routine electroconvulsive therapy with ginkgo pills (40 mg/8 h), the control group received placebo treatment (2 weeks). After intervention, the extract group had a better cognitive status and less depression compared with the placebo group [46]. In a different double-blind clinical trial, 27 patients with seasonal mood disorder were given either ginkgo biloba or a placebo for 10 weeks. Based on the study results, no significant difference was found between the two groups in terms of depression score, which might be related to the small size of the samples [47].

Additionally, clinical trials have shown that treating individuals with serious depression concurrently with trimipramine (200 mg) and ginkgo extract (240 mg/d) significantly reduced the sleep disturbances that trimipramine-induced [48]. The ginkgo extract also improves sexual dysfunctions caused by antidepressants in patients with major depression [49].

3.6 St John's wort (*Hypericum perforatum L.*)

Hypericum perforatum L. which is the scientific name for common Saint John's wort is native to Western Europe, Asia, and North Africa [50]. To dates several studies have been made on antidepressants effect of this plant as an herbal remedy in animal models as well as humane studies [51]. The St John's wort extract was more effective than placebo in double-blind randomised clinical trials on patients with mild to moderate depression, with effects comparable to fluoxetine, imipramine, and sertraline. Furthermore, its side effects were significantly lower when compared to the previously mentioned drugs [50,52,53,54,55]. The antidepressant effects of the plant is attributed to main effective compounds of the herb, hyperforin and hypericin, and studies have shown that hyperforin is a superior option to hypericin in terms of anti-depressant activity [56]. Biochemical investigation have demonstrated that the plant extract is a weak inhibitor of monoamine oxidase enzyme but inhibits synaptosomal resorption of serotonin, dopamine, and norepinephrine. The plant extract exerts a down regulative effect on beta adrenergic receptors and an up regulative effect on serotonin receptors [51]. It has been stated that the methanolic plant extract adjusts the expression of the genes that control the hypothalamic–pituitary– adrenal axis and reduces the elevated levels of serum adrenocorticotropin and corticosterone (Butterweck et al., 2001). The antidepressant effect of *H.perforatum* compound, hypericin have been demonstrated in a study , whereby its consumption has shown the significant increased of 3-methoxy-4-hydroxyphenylglycol level [57].

3.7 *Rhodiola rosea L*

Rhodiola rosea L., a member of the Crassulaceae family, is found in Europe, Asia, and North America. In traditional medicine, this herb has been used for a very long time to cure a variety of ailments, including anxiety and sadness. R. rosea is currently recognised as an adaptogen plant, increasing stress resistance and promoting physical vigour [58]. According to studies, individuals with depression who receive cotherapy with R. rosea and tricyclic antidepressants have a greater antidepressant response than those who receive standard antid epressant medications alone [59]. The antidepressant effects of R. rosea were studied in patients with mild to chronic depression in a randomised double-blind clinical trial (Darbinyan et al.,). Patients (90 subjects) were divided into two intervention groups (extract at 340 and 640 mg/d) and a placebo group. The extract significantly improved general depression, insomnia, and emotional instability at both doses, while the placebo had no effect. None of the groups complained about the medication's side effects [60]. In a double-blind clinical trial study conducted by Mao et al, the antidepressant efficacy of *R. rosea* was compared to sertraline. A total of 57 patients with major depression were randomly assigned to one of three groups: extract, sertraline, or placebo. Although the extract's activity was lower than that of sertraline, it resulted in fewer adverse reactions (30% versus 63%) [61]. This plant extract has antidepressant properties by increasing the levels of serotonin, dopamine, and norepinephrine in various parts of the brain [58,62].

3.8 Ginseng

Ginseng has been used medicinally for centuries in Korea, Japan, China, and the United States [63,64]. Ginseng contains natural antioxidant compounds, which explains why it has been used for so long. These ginsenosides, derived from ginseng roots, leaves, stems, and fruit, have a variety of pharmacological effects. They are divided into approximately 100 different categories [65]. Ginsenosides have been proposed as an effective treatment for organ damage and cell death, as well as immunological and metabolic diseases, in numerous studies [66,67,68]. Furthermore, these pharmacologically active constituents have been shown to support neurogenesis, synaptogenesis, neuronal growth, and neurotransmission, thereby protecting the central nervous system from unexpected events; ginseng is also said to be excellent for memory improvement [69,70]. Ginseng, as a potent natural antioxidant, modulates apoptosis by reducing the excessive inflammatory response in acute or chronic inflammation [71]. Apoptosis that is abnormal can impair organ function. Many different protein types exist in the human body, and their interactions maintain the balance of mechanisms related to proliferation, differentiation, and apoptosis. When this homeostasis is disrupted, it can harm the immune system and lead to a variety of deadly diseases [72,73]. Ginseng effectively reduces stress, a major cause of depression. This activity has been demonstrated in animal models of depression. Ginseng showed comparable efficacy to the commercially available antidepressant, fluoxetine [74]. Furthermore, depression has been linked to memory loss. This is due to the fact that depression causes

progressive nerve cell damage [75]. Memory loss was reduced in elderly patients treated with anxiolytics, according to clinical studies. These clinical studies suggest that ginseng has the potential to reduce anxiety [76].

4. CONCLUSION

In general, pre-clinical and clinical evaluations of medicinal plants are difficult and complex. One of the major problems in this regard is the production of standard herbal medicines with a specific and constant combination with the potential for reproduction. There are several herbal medicinal products in forms of capsules, pills, and drops on the market that are prescribed for relaxation, anti-anxiety, anti-depression uses and improving the sleep problems. Before presenting the herbs in the form of drugs on the market, their safety has to be determined in numerous studies and legal approvals should be obtained from the Food and Drug Administration or similar organizations for them. Some medicinal herbs have shown antidepressant effects similar to those of the conventional antidepressants in the treatment of patients with mild to moderate depression as well as the major depression. Medicinal plants do not have significant side effects in patients and the reported side effects for them are not significantly different from placebo. However, additional studies with a larger sample size are needed to confirm their antidepressant effects, adverse effects and toxicity in different individuals.

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