



A Review On Herbal Medicines For The Treatment Of Depression

Mr. Vikas B. Kakde -1, Mr. Hansraj B. Teple-2, Mr. Abhijit V. Joshi -3, Mr. Rajesh B. Jadhav-4.

^{1/2/3} -Student , 3- Assistant Professor.

^{1/2/3/4} -(Raosaheb Patil Danve College Of Pharmacy , Badnapur)

Abstract :

Depression, a mental illness that is receiving increasing attention, is caused by multiple factors and genes and adversely affects social life and health. Several hypotheses have been proposed to clarify the pathogenesis of depression, and various synthetic antidepressants have been introduced to treat patients with depression. However, these drugs are effective only in a proportion of patients and fail to achieve complete remission. Recently, herbal medicines have received much attention as alternative treatments for depression because of their fewer side effects and lower costs. In this review, we have mainly focused on the herbal medicines that have been proven in clinical studies (especially randomized controlled trials and preclinical studies) to have antidepressant effects; we also describe the potential mechanisms of the antidepressant effects of those herbal medicines; the cellular and animal model of depression; and the development of novel drug delivery systems for herbal antidepressants. Finally, we objectively elaborate on the challenges of using herbal medicines as antidepressants and describe the benefits, adverse effects, and toxicity of this medicine.

keywords – Antidepressants, Herbal Medicine As Antidepressants, The Benefits And Risks Of Herbal Medicines , Novel Drug Discovery Systems, Future Strategies For The Treatment Of Depression.

I. INTRODUCTION :

Depression is a mental illness that adversely affects people's feelings, thoughts, and behaviors, as well as their physical health. The main symptoms of depression include anhedonia, sadness, depressed mood, and slow movements.¹ Depression is mainly caused by the interaction of genetic and environmental factors; however, the exact etiology and pathological mechanisms of depression remain unclear.^{2,3} Currently, several hypotheses regarding depression are discussed, and the widely accepted potential mechanisms are listed below: The monoamine hypothesis: The insufficient activity of monoamine neurotransmitters has been observed in the central and peripheral nervous systems of patients with depression. Some antidepressants increase the concentration of monoamine neurotransmitters in the synaptic cleft of neurons via several pathways, including the inhibition of serotonin reuptake, norepinephrine reuptake, and serotonin and norepinephrine reuptake, to regulate mood.⁴⁻⁶ The hypothalamic–pituitary–adrenal (HPA) axis: Patients with depression were found to have aberrant HPA axis stimulation. The long-term activation of the HPA axis by emotional stress leads to a chronic increase in glucocorticoid levels in the brain, leading to the onset of depression.^{7,8} HPA axis imbalance is associated with decreased glucocorticoid receptor (GR) function, ultimately leading to central nervous system dysfunction.^{9,10} Antidepressants have been shown to increase the expression and biological functions of GRs in patients with depression as well as in animal and cellular models. ^{8,11} The neuroinflammation hypothesis: Stress may increase the release of neurotransmitters and pro-inflammatory cytokines (including tumor necrosis factor- α , interleukin (IL) 1β , and IL6), which are directly involved in the development of depression.^{12,13} The neurotrophic theory: A reduction in brain-

derived neurotrophic factor (BDNF) levels was observed in the serum and postmortem brain tissue of patients with depression, and the increased levels of BDNF in the central nervous system are associated with the efficacy of antidepressants.^{14,15} In addition to the above hypotheses, the glutamate hypothesis, epigenetic theory, and circadian rhythm play important roles in depression and the effect of antidepressants.^{16- 19} Although there are many hypotheses regarding the pathogenicity of depression, the mechanism of action of antidepressants remains to be fully understood, and many challenges remain regarding clinical medication, including the choice of antidepressants and long term treatment. Therefore, optimizing the efficacy of antidepressants and minimizing their side effects remain a challenge

ANTIDEPRESSANT :

Antidepressants are a class of medication that can help relieve the symptoms of depression, such as low mood, anxiety, and worthlessness. They work by correcting chemical imbalances of neurotransmitters in the brain. There are at least seven types of antidepressants: Monoamine oxidase inhibitors (MAOIs), Norepinephrine and dopamine reuptake inhibitors (NDRIs), Selective serotonin reuptake inhibitors (SSRIs), Serotonin and norepinephrine reuptake inhibitors (SNRIs), Serotonin antagonist and reuptake inhibitors (SARIs), Tricyclic antidepressants (TCAs) and tetracyclic antidepressants (TeCAs). MAOIs and TCAs were among the first antidepressants developed. They have largely been superseded by newer antidepressants (such as SSRIs) that have fewer side effects, although these older antidepressants may still suit certain people or be effective when other antidepressants have been ineffective. Antidepressants generally provide some relief of symptoms within one to two weeks; however, it may take six to eight weeks of treatment before the full effects are seen. Common examples of antidepressants include selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine (Prozac), and serotonin and norepinephrine reuptake inhibitors (SNRIs), such as duloxetine (Cymbalta).² Different antidepressants cause different side effects, but common side effects include nausea, dizziness, weight gain, and sexual problems.

HERBAL MEDICINE AS ANTIDEPRESSANTS :

1) HYPERICUM PERFORATUM :



Fig1: Hypericum Perforatum Flower

Hypericum perforatum L., also known as St. John's wort (SJW), is a widely studied medicinal plant that is used to treat depressive symptoms; some of its important chemical components have been shown to exert antidepressant effects. The two main components, hypericin and hyperforin, together with polyphenols and flavonoids, are responsible for these antidepressant effects. In rats treated for depressive behavior, the natural products of SJW—rutin, hypericin, and pseudohypericin—have been shown to improve depressive behavior in the forced swimming test within a certain concentration threshold.¹²²⁻¹²⁴ STW3-VI, a standardized SJW

extract, significantly decreased plasma adrenocorticotrophic hormone (ACTH) and CORT levels induced by chronic stress in rats and mice. Moreover, STW3-VI increases the neutral growth of HT22 cells and inhibits the upregulation of inflammatory factors in lipopolysaccharide (LPS)-induced HT22 cells. From a clinical perspective, a meta-analysis of 29 RCTs (n= 5489) showed that hypericum preparations had better antidepressant properties than placebo (relative risk [RR] =1.28; 95% confidence interval and that its therapeutic efficacy was not worse than that of SSRIs and tricyclic antidepressants (RR=1.00; 95% CI: 0.90–1.11). A study by Kasper et al suggested that hypericum was effective for the long-term prevention of recurrent depression. The adverse effects of hypericum are low, and the number of subjects withdrawn from clinical trials ranged from 0% to 5.7%, which was not significantly different from placebo. Hypericum formulations are slightly better tolerated than serotonin reuptake inhibitors. 130 Remotiv, a SJW commercial product, has been shown to relieve stress, mild depression, and nervous tension and maintain emotional balance. Preclinical studies have shown that Remotiv modulates neurotransmitters, including presynaptic serotonin, norepinephrine, and dopamine membranes in the cleft and postsynaptic spaces. The long-term administration of Remotiv also reduces presynaptic neurotransmitter reuptake, increasing neurotransmitter concentrations in the synaptic cleft. Research has also shown that the depression-relieving effects of SJW extract are associated with an increase in gamma-aminobutyric acid (GABA) receptors and circulating GABA levels. In summary, as the most popular herbal medicine, SJW exerts the same effective antidepressant effect as various standard prescription antidepressants for mild-to-moderate major depression.

2) RHODIOLA ROSEA :



Fig -2 Rhodiola Rosea

Rhodiola rosea L. (RL), also called “golden root,” is used as an herbal plant in northern Europe and some countries in Asia, mainly to improve the symptoms of depression. RL extract elicited depression-like behaviors, such as a decreased sugar preference rate and exploration behavior in mice exposed to CUMS. The psychopharmacological mechanisms of RL in the depression-like behavior model were mainly related to the inhibition of monoamine oxidase A, the modulation of the content of 5-HT, and the cell proliferation and number of neurons in depressed rats and mice. Salidroside (SA), the primary bioactive compound in RL, exerts antidepressant activity in olfactory bulbectomized rats, which may be related to the regulation of the anti-inflammatory pathway and HPA axis activity. In mice with LPS-induced depression-like behavior, SA treatment significantly attenuated LPS-induced inflammation, reduced NE and 5-HT levels in the prefrontal cortex, and increased the expression levels of BDNF and TrkB within the BDNF/TrkB signaling pathway. A clinical trial of the standardized RL extract—SHR-5—was conducted in a randomized, double-blind, placebo-controlled study of patients with mild-to-moderate depression. Overall, depression and other emotional symptoms significantly improved, and no serious side effects were noted. Another randomized placebo-controlled trial in patients with mild-to-moderate depression found that RL had fewer adverse events and was better tolerated, although its antidepressant effect was less than that of sertraline.

THE BENEFITS AND RISKS OF HERBAL MEDICINES :

In general, herbal medicines consist of tissues and unpurified plant extracts and have some advantages, including low cost and fewer side effects.¹¹⁵ In addition, some herbal medicines are available without a prescription and are well tolerated and safe, making them suitable for treating patients for whom conventional treatments have failed or caused intolerable side effects.¹⁸⁵ Thus, natural remedies are a popular alternative or adjunct for people with mild mental illness, and if treatment fails, they do not have serious consequences.¹⁸⁶ Despite increasing evidence of the efficacy and safety of alternative therapies, along with the many Food and Drug Administration (FDA)-approved psychotropic drugs, clinicians need to be aware of the limitations and inadequacy of their clinical evidence. For limitations, herbal medicines lack the characteristics of the same concentration, active ingredients, and the same biological chemicals, unlike synthetic antidepressants. In addition, some herbal remedies are not tested with the scientific rigor that is required for conventional drugs, and are not tested for purity and potency. For example, SJW may have monoamine oxidase inhibitory effects or elevate serotonin, dopamine, and norepinephrine levels and should not be prescribed with other synthetic antidepressants. Ginkgo biloba extract may interact with anticoagulants and antiplatelet agents. Panax ginseng is widely used because it is well tolerated; however, it may be responsible for a decreased response to warfarin.

NOVEL DRUG DELIVERY SYSTEMS FOR HERBAL ANTIDEPRESSANTS :

Evidence from preclinical in vitro and in vivo experiments shows that some natural products and herbal medicines have strong antidepressant properties and few side effects, suggesting the need for the development of new drugs. However, only a few herbal medicines have passed the clinical phase and have been translated into clinical therapeutics. Compared with synthetic small compounds, herbal drugs are poorly soluble, permeable, and photodegradable, resulting in undesirable bioavailability through the blood–brain barrier (BBB). Several novel drug delivery systems (NDDS) have been developed to improve the efficacy of drug molecules.

FUTURE STRATEGIES FOR THE TREATMENT OF DEPRESSION :

For thousands of years, hundreds of herbal medicines have been used to treat patients with depression and have extensive clinical applications. These herbal medicines, including TCM, Ayurvedic medicine, and Western herbalism, exert therapeutic effects (clinically as monotherapy and complementary therapy) in patients with mild-to-moderate depression. The efficacy and safety of these herbal medicines have been demonstrated in relatively small groups of patients. Many preclinical studies have confirmed that similar to ketamine and synthetic antidepressants, herbal medicines alleviate depression-like behavior in animals and that the neurochemical changes in animals treated with herbal medicines are consistent with those in animals treated with these synthetic antidepressants. The main difference between herbal medicines and synthetic preparations as antidepressants to date is that all synthetic preparations have been approved by the FDA and have had their efficacy and safety demonstrated in clinical and preclinical trials. We have also evaluated the antidepressant effects of herbal medicines in placebo-controlled human trials. In conclusion, some natural medicines and their extracts have been used as antidepressants; however, the following efforts should be made to improve these herbal medicines: an effective and uniform standard should be established to control the quality of herbal medicines, effective biomarkers should be identified to evaluate the antidepressant effect of herbal medicines and better and more efficient delivery systems should be developed for herbal antidepressants.

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