

Analysis of the Antidepressant Effects and Mechanisms of Icariin II Based on The GABAergic Nervous System

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Abstract: This article summarized the research progress on the antidepressant mechanism of icariin II, mainly elaborating on its mechanism from five aspects: GABAergic nervous system, inflammatory response, oxidative stress, neurotrophic factors, and neurotransmitters in the brain. Its clinical application value was further explored to provide a theoretical basis for the development and utilization of icariin II in treating depression.

Keywords: GABA; Icariin II; Depression; Inflammatory response

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1. Introduction

Depression is a common mental illness with a global prevalence of approximately 9% to 13%. Its main symptoms include low mood, loss of interest, and low energy levels. It is estimated that more than 100 million people worldwide suffer from depression, accounting for approximately 10% to 20% of the global population. The treatment method for depression is mainly through antidepressant drugs or antidepressant therapy. However, these methods are associated with side effects and adverse reactions, such as headaches and insomnia. Traditional Chinese medicine (TCM) is beneficial for improving depression symptoms. Therefore, it is urgent to develop a safe and effective antidepressant drug with no obvious side effects. Icariin II is one of the main active ingredients in the barrenwort plant. It is commonly used in TCM to nourish the kidneys, replenish essence, promote blood circulation, and relieve pain. It also has a strong regulatory effect on the central nervous system. Wen *et al.* have shown that icariin II significantly improved spontaneous movement defects, behavioral indicators from elevated plus maze tests, serum biochemical indicators, and the levels of 5-Hydroxytryptamine (5-HT) and norepinephrine (NE) in the hypothalamic tissue of mice ^[1]. At the same time, icariin II exhibits certain neuroprotective effects on brain GABAergic neurons ^[2,3]. The main active ingredient, icariin II, has been found to have significant antidepressant effects. More studies have shown that icariin II plays an important role in the GABAergic nervous system and its relationship with depression has gradually gained attention.

2. GABAergic nervous system

Gamma-aminobutyric acid (GABA) is an important inhibitory neurotransmitter that regulates the normal function of the central nervous system. It can inhibit excitatory nerve conduction and increase inhibitory nerve conduction. In the cerebral cortex, GABA is widely distributed in brain areas such as the cortex and hippocampus and exerts various biological effects through different receptors. Among them, GABA receptors have 2 subtypes: gamma (γ) and delta (δ). Alpha (α)-, beta (β)-, and γ -3 β -receptors are mainly distributed in the cerebral cortex and hippocampus, while β -receptors are mainly distributed in the thalamus and striatum. The pathogenesis of depression is highly complex and is currently believed to be caused by the combined action of multiple factors, among which neurotransmitter imbalance is an important basis for the onset of depression. Zhang *et al.*, Wang *et al.*, and Hou *et al.* showed that monoamine neurotransmitters such as dopamine, 5-HT, NE, and glutamate are the main neurotransmitters that mediate the development of depression [4-6]. Recently, studies have found that icariin II affects the pathogenesis of depression by regulating multiple neurotransmitters. Ming found that icariin II exerted antidepressant effects by promoting GABA synthesis and inhibiting GABA degradation [7]. Wang also found that icariin II exerted antidepressant effects by upregulating the glutamate receptor signaling pathway [8]. Based on previous research, it was indicated that the GABAergic nervous system plays an important role in maintaining normal brain function and abnormalities in the GABAergic nervous system can lead to depression and other mental diseases.

3. Inflammatory response

The inflammatory response plays an important role in the development of depression. Research by Kokkosis *et al.* showed that inflammatory response can lead to neuronal damage and changes in synaptic plasticity, which is one of the important causes of depression [9]. Icariin II can reduce the neuroinflammatory response by inhibiting microglia activation, thereby improving depressive symptoms. Zheng *et al.* injected mice intraperitoneally with icariin II (30 mg/kg) for 4 consecutive weeks and found that intraperitoneal injection of icariin II inhibited microglial activation and significantly reduced the mice's spontaneous activity rate and body weight [10]. Zhou found that intraperitoneal injection of icariin II significantly reduced the deterioration of behavioral and biochemical indicators in mice induced by chronic restraint stress [11]. Zeng *et al.* also found that intraperitoneal injection of icariin II significantly reduced chronic stress-induced plasma tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β), and interleukin-6 (IL-6) levels [12]. Therefore, icariin II exerts antidepressant effects by inhibiting the inflammatory response. Sun used a mouse tail suspension test and a forced swimming test to examine the effect of icariin II on oxidative stress-induced neuroinflammation in mice [13]. The results showed that when compared with the control group, the superoxide dismutase (SOD) activity and malondialdehyde (MDA) content in the serum and hippocampus of mice in the observation group were significantly increased ($P < 0.05$). Icariin II can reduce the SOD, MDA contents, and p-p65 protein expression levels ($P < 0.05$). Results also showed that the reduction of SOD activity can activate reactive oxygen species (ROS) and activate the nuclear factor κ B (NF- κ B)-p65 signaling pathway in mouse hippocampus tissue. The above results indicated that icariin II improved depressive-like behavior by inhibiting the oxidative stress response. However, its specific mechanism requires further study.

4. Oxidative stress

During the development of depression, the oxidative stress response in brain tissues such as the hippocampus and amygdala is significantly enhanced. At the same time, the antioxidant defense system is weakened, leading

to neuronal damage, axonal degeneration, and death. This may be an important mechanism in the pathogenesis of depression. When in a depressed state, ROS can induce neuroinflammation, cause irreversible damage to nerve cells, and also induce cell apoptosis. Hu's research showed that antioxidants can reduce oxidative stress in hippocampal neurons^[14]. Icariin II plays an anti-oxidative stress role in the treatment of depression by reducing the ROS content in the brain^[15]. Ma found that a high dose of icariin II can significantly reduce ROS content in the hippocampus tissue of mice with depression models and alleviate brain tissue damage^[16]. When compared with the control group, high-dose icariin II intervention significantly reduced ROS and nitric oxide (NO) levels in the hippocampus tissue of mice in the observation group ($P < 0.01$). Additionally, icariin II can effectively increase the expression levels of antioxidant enzymes, such as SOD, CAT, etc., thereby protecting brain cells from oxidative stress damage^[17]. Gao *et al.* found that icariin II reduced the expression levels of oxidative stress-related genes (SOD1, SOD2, and glutathione peroxidase (GSH-Px)) in a chronic stress model^[18]. Therefore, some scholars speculate that icariin II may reduce oxidative stress damage in brain tissue by enhancing the expression levels of antioxidant enzymes. In addition, some scholars have found that icariin II can effectively promote glutathione production^[19]. Oxidative stress mainly includes two forms: DNA damage and lipid peroxidation. DNA damage refers to the reduction or loss of various enzyme activities in cells, while lipid peroxidation refers to lipid peroxidation in the body. In animal models, icariin II was shown to effectively reduce the production of intracellular ROS. However, the antioxidant effect of icariin II is not limited to the protective effect of antioxidants. Studies have shown that icariin II can also improve depressive symptoms when used clinically to treat patients with depression.

5. Neurotrophic factors and neurotransmitters in the brain

Depression is a chronic disease with high clinical recurrence and suicide rates, which has a serious impact on the patient's physical and mental health. Therefore, it is necessary to conduct in-depth research on the mechanism of depression to develop effective treatment methods. Neurotrophic factors (NRFs) are an important type of cytokines in the central nervous system that can regulate neurogenesis and synaptic plasticity. NRFs are mediators that transmit information between neurons and glial cells. Current research has found that a variety of NRFs were involved in the occurrence and development of depression, such as nerve growth factor (NGF), neurotrophic factor receptor 1 (NRF-1), and vascular endothelial growth factor (VEGF). Icariin II improves depressive behavior by regulating the expression levels of these NRFs. Currently, its mechanism of action in the treatment of depression needs to be further studied.

Currently, the pathogenesis of depression has not been fully elucidated. It is believed to be caused by an imbalance of neurotransmitters due to the abnormal activity of brain neurons. Dopaminergic neurons play an important role in the occurrence and development of depression, where reduced levels of dopaminergic neurons may lead to an imbalance of neurotransmitter levels^[20]. Xin *et al.* showed that the reduced number and function of 5-HT neurons were the main mechanism of depression^[21]. Gao *et al.* used chronic unpredictable mobility stress (CUMS) to establish a rat depression model and found that icariin II significantly improved the depressive-like behavior of CUMS rats^[22]. Its mechanism may be related to the enhancement of GABAergic neuron activity. Icariin II can reduce the 5-HT level in mice, increase the 5-HT content in the serum, and at the same time improve the elevated plus maze behavioral indicators, 5-HT, and NE content in the hippocampus tissue of CUMS rats^[23]. Su has shown that the levels of neurotransmitters such as 5-HT and NE in the brains of depressed patients were significantly reduced after administration of icariin II. Icariin II can improve the decline in the levels of 5-HT and NE in the brains of mice. At the same time, icariin II can also reduce the expression

level of GABA receptors in mouse brain tissue. GABA receptors regulate downstream signaling pathways by mediating glutamate release, neurotransmitter release, and synaptic transmission. Therefore, icariin II has a protective effect on the GABAergic nervous system.

6. Conclusion

Icariin II exhibited significant antidepressant effects, where its mechanism may be related to increasing the content of GABAergic neurotransmitters and enhancing the activity of the GABAergic nervous system. This discovery provides the experimental basis for the further development of new antidepressant drugs. However, more in-depth studies are needed to clarify the mechanism of action and long-term efficacy of icariin II while paying attention to potential adverse reactions and drug interactions.

Disclosure statement

The authors declare no conflict of interest.

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