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Research Progress on Ganoderma lucidum Polysaccharides in Ameliorating Depression in Mice

Hexin Chang[1, *]

[1]Department of Biopharmaceutical, Zhejiang A&F University, Zhejiang, China
*Corresponding author: hexinchang84@gmail.com

Abstract:

Depression is a psychiatric disorder with a complex pathogenesis. It involves multiple factors such as neuroinflammation, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, neurotrophic factor deficiency, and gut microbiota dysbiosis. Currently, clinically used drugs for depression typically have a single target and can cause severe adverse reactions. However, natural polysaccharides exhibit diverse pharmacological activities and can act on multiple targets. This indicates natural polysaccharides have the potential of being a promising source for the development of new antidepressant drugs. As the main active component of Ganoderma lucidum, Ganoderma lucidum polysaccharides (GLP) have attracted significant attention due to their prominent immunomodulatory and neuroprotective effects. GLP exerts antidepressant effects through a multi-target and multi-pathway mechanism. This prompt GLP can be a natural antidepressant candidate with great development potential. This study aims to systematically elaborate on the potential molecular mechanisms by which GLP improve behavioral performance in mouse models of depression, thereby providing a theoretical basis for its subsequent in-depth research and clinical application.

Keywords: Major Depressive Disorder; Ganoderma Lucidum Polysaccharides; Natural Polysaccharides.

1. Introduction

Severe and persistent negative emotions, accompanied by physical fatigue, weakness, sleep disorders, etc, are common manifestations of depression [1]. It is a prevalent mental health disorder that can also trigger major illnesses such as neurodegenerative abnormalities, cardiovascular diseases, and diabetes. Theories suggest that the onset of depression and related high-risk mental illnesses is associated with neural signal damage, inflammation, metabolic disorders, etc [1, 2]. The primary ones include the monoamine theory, inflammatory response, and the hypothalamic-pituitary-adrenal axis (HPA axis) [2].

At present, depression treatment is mainly conducted from three aspects: pharmacotherapy, psychotherapy, and physical therapy. Clinically, depression is treated with a combination of psychotherapy and pharmacotherapy [2]. However, the efficacy of this combined treatment model is generally at a moderate level, and there exists significant inter-individual heterogeneity in treatment response [2]. Among them, selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and norepinephrine reuptake inhibitors (NRIs) are commonly used antidepressant drugs [3]. However, they have drawbacks such as significant adverse reactions, slow onset of action, and single targets, making it difficult to meet clinical needs.

Natural polysaccharides are biological macromolecules widely distributed in nature, possessing a variety of pharmacological activities (and promising applications) such as antioxidation, anticoagulation, antithrombosis, anti-apoptosis, anti-neuroinflammation, regulation of intestinal flora to improve the gut-brain axis, and anticancer effects [4]. With abundant pharmacological activities, multiple action targets and low toxicity, natural polysaccharides are ideal substances for the development of new antidepressant drugs. Current studies have shown that natural polysaccharides can effectively prevent and alleviate depressive symptoms through multi-target mechanisms such as regulating intestinal microbiota, anti-inflammation and antioxidation, which can be seen in Table 1 [5].

Table 1. Natural polysaccharides and chemical drugs in antidepressant therapy [5]

Projects	Source	Mechanism of Action	Multi-system Synergistic Effect	Adverse reaction
Chemical Drugs	Chemical Synthesis or Semi-synthesis	Primarily Single-target	Mainly acts on the central nervous system, with limited effects on other systems	Long-term use may cause nausea, insomnia, sexual dysfunction, and potentially lead to metabolic syndrome.
Natural Polysaccharides	Natural products from plants, fungi, animals, etc.	Multi-target	Integrate the gut-brain axis, immune and metabolic systems to improve systemic inflammation and oxidative stress	Mild

In recent years, with the in-depth research on the Gut-Brain Axis (GBA), studies have found that it is closely related to depression. The gut microbiota is the key factor affecting the gut-brain interaction, and a large number of studies have now confirmed that depression is closely associated with the gut microbiota [6].

Due to their chemical structure, polysaccharides are usually difficult to be degraded by human digestive enzymes [5]. Short-chain fatty acids (SCFAs), the key metabolites produced during the fermentation process, can cross the blood-brain barrier, regulate neuroinflammation, neuroendocrinology, neurotransmitter metabolism, and the levels of brain-derived neurotrophic factor (BDNF), as well as repair the damaged intestinal barrier function. By regulating the gut-brain axis, SCFAs further improve brain function and ultimately exert an antidepressant effect [5].

Researchers have conducted experimental studies on the effect and mechanism of Ganoderma lucidum spore polysaccharides in the adjuvant treatment of depression. The experimental results show that the injection of GLP at high dose (1.68 mL per mouse), medium dose (0.42 mL per mouse), and low dose (0.21 mL per mouse) could effectively improve symptoms in depressed mice induced by chronic stress stimulation [1]. This effect is achieved by increasing the contents of monoamine neurotransmitters (dopamine, norepinephrine, and serotonin) in the rat brain, indicating that GLP has a role in the adjuvant treatment of depression [1].

To summarize, current clinical drugs for depression have drawbacks such as slow onset of action, single target, low cure rate, and high recurrence rate. In contrast, natural polysaccharides have multiple action targets. By regulating targets such as the gut microbiota, anti-inflammation and antioxidation, the physiological regulation of the human body can be achieved [5]. Therefore, the development of antidepressant drugs derived from natural sources is imminent. Moreover, GLP possesses extensive pharmacological activities; meanwhile, animal experiments have confirmed their effect in improving depressive symptoms. Thus, they are suitable candidates for new antidepressant drugs and hold significant research and application value.

2. Natural Polysaccharides

Natural medicines possess certain biological activities and are classified into carbohydrates, glycosides, phenylpropanoids, quinones, flavonoids, steroids, alkaloids, terpenoids, and other categories [6]. Biological macromol-

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ecules composed of more than 10 monosaccharides linked by glycosidic bonds are called polysaccharides [8]. Many polysaccharides, which are active ingredients of traditional Chinese medicines, exhibit strong biological activities, including anti-oxidative stress activity, anti-apoptotic effect, anti-neuroinflammatory effect, and anti-excitatory amino acid toxicity effect [4]. Some polysaccharides can also affect the intestinal flora and regulate neural development through three pathways-immune pathways, neuronal pathways, and endocrine system pathways-to exert neuroprotective effects [7].

Depression is a neuropsychiatric disorder with complex etiology, involving numerous human regulatory pathways; thus, treating depression with traditional single-target drugs is challenging. Natural polysaccharides exhibit diverse biological activities, regulate multiple pathways in the human body, possess multi-target regulatory capabilities and good safety, and reduce metabolic complications and organ toxicity caused by long-term use of synthetic antidepressants in patients [5].

2.1 Ganoderma Lucidum Polysaccharides

Ganoderma lucidum belongs to the fungi of the genus Ganoderma, family Polyporaceae, class Hymenochaetomycetes, and subphylum Basidiomycota [9]. As a traditional Chinese medicinal material with the property of "both food and medicine" in China, it has received extensive attention and research. Ganoderma lucidum contains a variety of active components, including polysaccharides, triterpenoids, proteins, and sterols, and exhibit multiple biological activities such as anti-tumor, hypoglycemic, immunomodulatory, antioxidant, and antidepressant effects [10]. Studies have shown that Ganoderma lucidum has unique advantages in regulating immune system function: it exerts different regulatory effects on different immune cells, and can regulate innate immunity and adaptive immunity by activating immune cells in the body and stimulating the secretion of cytokines [9].

GLP are heteropolysaccharides mainly composed of glucose, galactose, mannose, fucose, xylose, and arabinose linked via different proportions and types of glycosidic bonds, and exhibit multiple biological activities such as anti-inflammatory, antioxidant, anti-tumor, and neuroprotective effects [11].

3. GLP in Ameliorating Depression

3.1 Experimental Investigation of GLP in Animal Models

Li et al. from Yunnan University conducted an experimental investigation on the mechanism by which GLP improve depressive-like behaviors in mice. In this study, the researchers administered GLP to mice via intraperitoneal injection, and evaluated the antidepressant effects of GLP through behavioral tests (such as the tail suspension test, forced swimming test, open field test, etc.) and the chronic social defeat stress (CSDS) model [12]. Researchers showed rapid and significant antidepressant effects in tail suspension experiments 60 minutes after intraperitoneal injection of GLP in mice; the effects still persisted in the forced swimming test 5 days later, and no hyperactivity (a common side effect of psychostimulant drugs) was observed [11]. In the CSDS model of mice, GLP significantly improved the depressive-like behaviors of the mice.

3.2 Mechanisms of Action of GLP in Ameliorating Depression

3.2.1 Immunomodulatory Function of GLP

Researchers from Yunnan University concluded through experiments that GLP possess immunomodulatory functions. Specifically, GLP can significantly inhibit the expression of cytokines IL-1β(Interleukin-1β) and TNF-α(Tumor Necrosis Factor-α), and promote the expression of cytokines IL-10(Interleukin-10) and BDNF by regulating Dectin-1-mediated immune responses, thereby exerting neuroprotective and antidepressant effects.

At the molecular level, molecular biology detection (Western Blot protein assay) was used to detect the expression of proteins such as Dectin-1 (Dendritic Cell-Associated C-Type Lectin 1), IL-1β, TNF-α, IL-10, BDNF, GluA1 (Glutamate Receptor A1 Subunit), GluA2 (Glutamate Receptor A2 Subunit), and p-GluA1 (Phosphorylated Glutamate Receptor A1 Subunit) in mice after intervention with GLP injection. The experimental results showed that after GLP treatment, the levels of IL-1β and TNF-α in mice significantly decreased to near normal levels; the expression of IL-10 and BDNF significantly increased; the protein levels of p-GluA1, GluA1, and GluA2 were restored; and the expression of Dectin-1 was upregulated [12].

In addition, frozen sections of mouse brain tissue were prepared to detect the number of microglia and astrocytes. In chronic CSDS model mice, the number of Iba1+ (microglia) and GFAP+ (astrocytes) in the hippocampus increased significantly, while that in mice treated with GLP injection decreased significantly. Meanwhile, in this study, 2 hours before each GLP injection, the researchers first administered an intraperitoneal injection of Laminarin (a specific antagonist of Dectin-1). After conducting the forced swimming test on the mice, the levels of IL-1β and TNF-α proteins were detected. The results showed that when Dectin-1 bound to Laminarin, the inhibitory effect of GLP on IL-1β and TNF-α almost completely disappeared; at the same time, the behavioral performance of the mice was consistent with that of mice not treated with

GLP [12].

These experimental results indicate that GLP can improve depressive-like behaviors in mice by activating Dectin-1 receptors, regulating the neuroimmune system, and enhancing AMPA receptor function [12].

3.2.2 Regulation of GLP on Monoaminergic Neurotransmitters

Foreign researchers consider that the relative or absolute deficiency of monoaminergic neurotransmitter concentrations in the brain is one of the important mechanisms underlying the development of depression [3]. In depressed rat models induced by chronic stress, the contents of monoaminergic neurotransmitters (serotonin, norepinephrine, dopamine) and tyrosine hydroxylase which serves as the rate-limiting enzyme for the synthesis of catecholamine neurotransmitters in the brain are significantly lower than those in normal rats. Liu et al. confirmed through animal experiments that Ganoderma lucidum spore polysaccharides can improve depressive symptoms and achieve the effect of adjuvant treatment for depression by increasing the contents of monoaminergic neurotransmitters (dopamine, norepinephrine, serotonin) in the rat brain [1].

3.2.3 Antidepressant Function of GLP via Modulating Gut Microbiota

The gut microbiota can synthesize neuroactive metabolites that directly mediate neurotransmission [2]. It can regulate the expression of BDNF and the profile of neurotransmitter receptors [2]. Polysaccharides can selectively modulate the gut microbiota and exert prebiotic effects [2]. Through metabolism by the gut microbiota, polysaccharides produce SCFAs, which can compensate for the reduced production of SCFAs in patients with depression [2]. SCFAs can exert neuroprotective effects via the vagus nerve and circulatory pathways [2]. The gut-liver-brain neural axis is a bidirectional reflex arc [7]. The sensory afferent fibers of the hepatic branch of the vagus nerve can indirectly sense the gut microenvironment and transmit this sensory information to the solitary nucleus in the brainstem. Subsequently, the signals are transmitted to the vagal parasympathetic nerves and enteric neurons. By regulating the number of peripheral regulatory T (p-Treg) cells, it maintains gut homeostasis, which is crucial for the prevention and treatment of gut immune-mediated diseases. Inflammatory bowel disease (IBD) is an autoimmune gastrointestinal disorder triggered by chronic psychological stress. It is characterized by chronic inflammation and recurrence. IBD can exacerbate the inflammatory response in the central nervous system, leading to symptoms such as anxiety and depression.

Ganoderma lucidum extract containing GLP can significantly increase the abundance of Bifidobacterium and reduce the number of potentially pathogenic bacteria in mouse models [7]. It can improve the overall composition of the gut microbiota. GLP can maintain the integrity of the gut mucosa and enhance immune function by upregulating the expression of tight junction proteins in gut mucosal cells [7]. Additionally, GLP can regulate the composition of the gut microbiota through the NLRP3/NF - κB signaling pathway and inhibit the activation of inflammasomes [13]. GLP alleviates neuroinflammation and thereby exerts an antidepressant effect.

3.2.4 GLP Promote Neurotrophy and Synaptic Plasticity

BDNF is a key protein that maintains neuronal survival, differentiation, and synaptic plasticity. It serves as an important biomarker for the pathogenesis of depression [3]. The expression level of BDNF in the serum or plasma of depressed patients is abnormally low; however, it returns to the baseline level after successful treatment with antidepressants or electroconvulsive therapy. Experiments conducted by Li et al. confirmed that injecting GLP into mice can increase the expression of BDNF, thereby rapidly alleviating depressive symptoms in mice [12].

4. Conclusion

Results from animal experiments show that the injection of GLP exerts a rapid antidepressant effect. GLP can exert antidepressant effects through two pathways. Firstly, they are fermented by intestinal flora to produce SCFAs that can cross the blood-brain barrier. Then the SCFAs regulate the metabolism of neurotransmitters and neurotrophic factors. Secondly, GLP exerts neuroprotective and antidepressant effects via immunomodulatory function. GLP can regulate Dectin-1-mediated immune responses, balancing the neuroimmune system, and enhancing the function of AMPA receptors. Based on these two pathways, neuro-related pathways such as the gut-liver-brain axis and the NLRP3/NF-κB signaling pathway play a regulatory role. In conclusion, GLP is a natural antidepressant substance worthy of attention and research. It can regulate human physiological functions through multiple targets, achieving antidepressant effects while exhibiting low toxicity. Further in-depth studies on GLP are needed to refine the mechanisms underlying their antidepressant actions, thereby providing insights for the development of novel antidepressant drugs.

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