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Ganoderma lucidum: An Emerging Nutritional Approach to Manage Depression

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ABSTRACT

Depression is a highly prevalent neuropsychiatric illness that significantly reduces the quality of life of the patients. While psychotherapy and pharmacotherapy remain the most common treatments, their limitations, including treatment resistance and adverse side effects, have driven interest in alternative therapies to complement conventional antidepressant therapies. *Ganoderma lucidum* (*G. lucidum*), a medicinal mushroom, is gaining attention for its potential in managing depression symptoms, largely attributed to its bioactive compounds, polysaccharides, and triterpenoids. These compounds collectively exhibit antidepressant-like effects in animal models of depression, mainly acting through mechanisms such as modulating the monoamine neurotransmission system, enhancing BDNF expression, and balancing pro- and anti-inflammatory cytokines in depressive animals. Furthermore, clinical studies suggest that *G. lucidum* may alleviate depression-like symptom in humans. This review explores the antidepressant potential of *G. lucidum* and the mechanisms by which its primary bioactive compounds exert their effects.

KEYWORDS

Ganoderma lucidum; major depressive disorder; alternative medicine; neurotransmission; neuroinflammation

Introduction

Major depressive disorder (MDD) is a prevalent and debilitating mental health condition, characterized by persistent sadness, loss of pleasure or loss of interest in activities, changes in appetite or weight, disrupted or altered sleep behavior, feeling tired or fatigue, feelings of low self-esteem, guilt or pessimism, inability to concentrate, and having suicidal thoughts.[1] Depression is both emotionally and physically harmful, and adversely affecting the patient's daily living.[2] In the worst scenario, it can lead to suicide. As depression continually contributes to the growing number of suicides, it has become the fourth major cause of death in young people, with approximately 700,000 cases annually.[3] Pharmacological antidepressants are the most commonly used treatment for depression, aiming to treat depression by attempting to reverse the underlying pathophysiological mechanisms of

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depression. For example, the first two antidepressants – iproniazid, a monoamine oxidase (MAO) inhibitor, and imipramine, a tricyclic antidepressant (TCA) – were introduced alongside the monoamine depletion hypothesis. MAO inhibitors increase monoamine concentrations by preventing their breakdown, while TCAs inhibit serotonin and norepinephrine reuptake, raising their levels in the synaptic cleft.[4–8] Currently, selective serotonin reuptake inhibitors (SSRI), selective serotonin noradrenaline reuptake inhibitors (SNRI), norepinephrine and specific serotonin antidepressant (NaSSA), and norepinephrine and dopamine reuptake inhibitors (NDRI) are the prevalently prescribed antidepressants (Table 1).[7–10]

Despite the development of different types of antidepressants, their overall efficacy is still a concern. A meta-analysis conducted in 2008 reported that the benefits gained from antidepressants were relatively small, even for patients with severe depression.[11] There is often a 4- to 12-week delay before antidepressants begin to alleviate symptoms following the start of treatment.[12] Moreover, antidepressants are often associated with side effects including nausea, dry mouth, insomnia, somnolence, dizziness, and sexual dysfunction, while severe side effects include memory impairment, increased heart rate, hypertension, and hypersensitivity reactions.[5,6,13,14] Additionally, antidepressants may lead to side effects such as emotional detachment, mood instability, and a sense of emotional

Table 1. Comprehensive overview of various classes of antidepressants, summarizing their development periods and mechanisms of action with representative examples.

Types of Antidepressants	Time of Development	Mechanism of Action	Side Effects
Monoamine oxidase inhibitors[4,6]	1950s	• Inhibiting monoamine oxidase (MAO) • Inhibiting MAO-A or both MAO-A and MAO-B • Increasing the availability of monoamine neurotransmitters	Hypotension, weight gain, sexual dysfunction, insomnia, gastrointestinal symptoms
Tricyclic antidepressants[7,8]	1950s	• Inhibiting serotonin and norepinephrine reuptake • Inhibiting serotonin and norepinephrine transporter proteins • Increasing the availability of serotonin and norepinephrine	Sedation, dry mouth, blurred vision, constipation, weight gain, sexual side effects
Selective serotonin reuptake inhibitors[4,6]	1970s	• Inhibiting serotonin reuptake • Inhibiting serotonin transporter protein • Increasing the availability of serotonin neurotransmitter • Little effect on other neurotransmitters or receptors	Diarrhoea, constipation, sexual dysfunction, insomnia, weight changes
Serotonin-noradrenaline reuptake inhibitors[7,8]	1980s	• Inhibiting of serotonin and norepinephrine reuptake • inhibiting serotonin and norepinephrine transporter proteins • Minimal effect on other postsynaptic serotonin receptor • Better tolerated than tricyclic antidepressants	Nausea, headache, sexual dysfunction, sweating
Noradrenaline and specific serotonergic antidepressants[10]	1980s	• Antagonizing noradrenaline, serotonin, histamine receptors	Sedation, drowsiness, weight gain, blurred vision, nausea
Norepinephrine-dopamine reuptake Inhibitors[10]	2000s	• Inhibiting reuptake of dopamine and norepinephrine • Minimal effect on other monoamine receptors	Insomnia, headache, dizziness, sweating, dry mouth

blunting.[13] Treatment-resistant depression (TRD) presents another significant challenge, characterized by a lack of response to antidepressants. Current solutions for TRD are limited and often insufficient, and even when remission is achieved, TRD patients face a substantially higher risk of relapse, underscoring the need for innovative approaches to manage depression.[15,16]

To address these issues, researchers have turned to nutraceuticals and complementary medicines, with herbal medicines gaining particular attention due to their high medicinal value, patient tolerability, and various bioactivities.[3,17] *Ganoderma lucidum* is a medicinal mushroom with a long history of use for thousands of years in enhancing longevity. Native to Asia, *G. lucidum* has high nutritional and medicinal values and was first recorded in the traditional Chinese medicine encyclopaedia, "Shen Nong's Ben Cao Jing" (Shennong's Classic of Materia Medica).[18] Approximately 400 bioactive compounds have been extracted from its fruiting bodies, mycelia, and spores. Studies have shown these compounds possess immunomodulatory, antitumor,[19] radioprotective,[20] antidiabetic,[21] hepatoprotective,[22] anti-inflammatory,[23] anti-allergic,[24] anti-oxidative,[25] and antimicrobial effects.[26] Furthermore, studies have found that *G. lucidum* confers neuroprotective and neurogenesis-enhancing effects, with potential applications in treating various neurological disorders, particularly neurodegenerative diseases.[27,28] Recently, researchers have begun to probe the potential of *G. lucidum* in managing depression and mood disorders.[29,30] Studies have found that the two major bioactive compounds of *G. lucidum*, polysaccharides and triterpenoids, possess antidepressant-like and anxiolytic-like effects in various animal models. For instance, in a mouse model of depression, *G. lucidum* polysaccharides were found to reduce depression-like behaviors via regulating Dectin-1 dependent pathways.[30] Similarly, *G. lucidum* triterpenoids demonstrated the ability to reduce both depression- and anxiety-like behaviors through modulating both the central and peripheral inflammation.[31] As the number of studies investigating the antidepressant-like effects of *G. lucidum* polysaccharides and triterpenoids continues to grow, we aim to conduct a comprehensive review, encompassing both preclinical and clinical studies. Given that depression is a multifactorial disorder, our review focuses on *G.* lucidum as a promising antidepressant candidate by examining how it exerts its antidepressant-like effects through addressing each of the key underlying pathophysiology. Furthermore, we propose future directions for research to advance the understanding of the potential of *G. lucidum* for depression management.

Taxonomy and bioactive compounds of G. *lucidum*

Taxonomy of *G. lucidum*

Despite *G. lucidum* being well renowned for its medicinal value, the taxonomy of the *Ganoderma* genus, to which it belongs, remains highly complex and chaotic. *G. lucidum*, also referred to as *G. lucidum* (Curtis) P. Karst., was first described by Karsten in 1881 in Peckham, London, UK. Since then, this taxon name has been widely applied to most morphologically similar laccate species within the *Ganoderma* genus, which led to significant taxonomic confusion.[32–34] This is partially because early classifications relied heavily on morphological traits such as fruiting body characteristics and spore shape. The advent of molecular techniques, particularly DNA sequencing, allowed researchers to analyze genetic differences among speciesm and molecular works revealed that many species previously classified as *G. lucidum* were, in fact, distinct taxa.[32] For example, the traditional medicinal fungus Lingzhi has long been considered synonymous with *G. lucidum*, and many commercial products or scientific studies used *G. lucidum* as the scientific binomial of Lingzhi.[34,35] However, based on the morphology and molecular analysis of the rDNA nuc-ITS sequences, and additional gene fragments of mt-SSU, RPB1, RPB2, and TEF1-α of Lingzhi, Cao et al., 2012[34] proposed a new species *G. lingzhi* to differentiate Lingzhi from *G. lucidum*. Hennicke et al.[36] discovered that two commercially sold strains labeled as *G. lucidum* are actually distinct species. This distinction is based on differences in their basidiocarp morphology, ITS and beta-tubulin sequences, and triterpenic acid profiles, which reveal that they correspond to *G. lucidum* and

G. lingzhi, respectively. Similarly, Smith & Sivasithamparam[37] proposed *G. steyaertanum* as the correct name for a species in Australia and Indonesia that had been mistakenly labeled as *G. lucidum*. Additionally, Wang et al.[33] demonstrated that *G. multipileum* Hou is the accurate name for the *Ganoderma* species commonly referred to as *G. lucidum* in tropical Asia. With advancements in molecular techniques, more species misidentified as *G. lucidum* will become distinct. Therefore, in certain literature, *G. lucidum* sensu lato refers to all laccate species within the *Ganoderma* genus historically identified as *G. lucidum*, while *G. lucidum* sensu stricto specifically denotes *G. lucidum* (Curtis) P. Karst., the species originally discovered by Karsten. In this article, all the preclinical and clinical studies reviewed claim to use bioactive compounds or products derived from *G. lucidum* for treatments.

Bioactive compounds of *G. lucidum*

G. lucidum is renowned for its diverse bioactive compounds which have demonstrated a broad spectrum of pharmacological activities, with polysaccharides and triterpenes being the primary and most important components that have been extensively studied.[38,39] Triterpene are highly prevalent naturally occurring compounds. Squalene, a linear hydrocarbon molecule made up of 30 carbon atoms, serves as a precursor in the biosynthesis of triterpene. Cyclization of squalene forms lanosterol, which is the first cyclic intermediate and the starting point for lanostane-based triterpenes synthesis. Through a series of chemical modifications, lanosterol is converted into lanostane, which is the structural backbone for triterpenes, providing a fundamental tetracyclic hydrocarbon framework upon which various functional groups and side chains are added to form diverse triterpene compounds.[40] Triterpenoids are highly oxidized triterpenes extracted from the fruit body and mycelium of *G. lucidum*.[41] Ganoderic acids, triterpenoids containing a carboxyl group, are the primary triterpenoids in *G. lucidum* with over 150 derivatives identified across *G. lucidum* and other *Ganoderma* species (Fig. 1).[42,43] These compounds exhibit antihypertensive and antitumor activities and are capable of regulating histamine release and cholesterol synthesis.[44,45] Additionally, studies showed that they target NF-κB, RAS-MAPK, and PI3K/Akt/mTOR, leading to cell cycle arrest and the induction of apoptosis.[46,47] "Together, these findings highlight the multifaceted bioactivities of ganoderic acids, particularly their anti-tumor potential, as they modulate key signaling pathways to inhibit cancer progression and promote apoptosis. Beyond triterpenoids, polysaccharides represent another major class of bioactive compounds in *G. lucidum*. Several polysaccharides have been extracted from the fruit body, spores, mycelia, and cultivation broth.[48,49] *G. lucidum* polysaccharides are heteropolymers, while glucose is a major sugar component, and other components including xylose, mannose, galactose, and fucose in different conformations including 1–3, 1–4, and 1–6-linked β and α-D (or L)-substitutions were also reported.[50–53] These macromolecules range greatly in their structures, molecular weights, and biological activities such as anti-inflammatory, hypoglycemic, and immunomodulatory activities.[54–57] Notably, their anticancer properties vary depending on branching conformations and solubility.[50,58] In addition to polysaccharides and triterpenoids, *G. lucidum* also contains other bioactive components, such as steroids, sterols, nucleotides, fatty acids, and

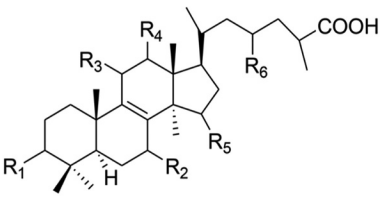

Figure 1. General structure of ganoderic acids. For the extensively studied ganoderic acid A, R^1= R^3= R^6= O, R^2= R^5= β-oh, R^4= H; ganoderic acid B, R^1= R^2= β-oh, R^3= R^5=R^6= O, R^4= H; ganoderic acid C1, R^1= R^3= R^5= R^6= O, R^2= β-oh, R^4= H; ganoderic acid C2, R^1= R^2= R^5= β-oh, R^3= R^6= O, R^4= H.

minerals, though these have been studied to a lesser extent.[59–61] However, the quantity and composition of bioactive compounds in both natural and commercially cultivated *G. lucidum* vary significantly, influenced by factors such as cultivation conditions, extraction methods, and strains used.[62–64] In this article, most studies investigating the antidepressant-like effects of *G. lucidum* focus on polysaccharide or triterpenoid extracts, with the exception of Zhao et al.[65] who investigated the effects of a polysaccharide-peptide.

Ganoderma *lucidum* demonstrates antidepressant-like effects

Pre-clinical studies

Although multiple biological activities of *G. lucidum* have been investigated in several diseases, its effects on depression have not been well studied (Table 2). Polysaccharide extracts are an important bioactive constituent of *G. lucidum*. Li et al.[30] reported that *G. lucidum* polysaccharides (GLP) had antidepressant-like effects in a mouse model of chronic social defeat stress (CSDS)-induced depression. Mice first received a single dose of GLP at 1, 5, and 12.5 mg/kg through intraperitoneal (i.p.) injection 60 minute prior to the tail suspension test (TST). The injections were continued for 5 more days before subjecting the mice to a forced swim test (FST) 60 minute after the last injection.[30] Overall, GLP had a dosage-dependent, acute, and robust antidepressant-like effect by significantly reducing immobility time in the TST and depressive-like behavior in the FST in GLP-injected non-stressed mice. Further studying antidepressant-like effects of daily GLP in mice subjected to CSDS revealed similar amelioration of depressive-like behaviors in the TST and FST compared to GLP-treated animals.[30] Albeit showing antidepressant-like effects of *G. lucidum* in the CSDS model, one limitation is that the stress period lasted only 10 days. Considering patients with MDD usually suffer from long-term stress and require long-term medications,[66] it is necessary to investigate whether physiological changes differ during short-term stress and long-term stress, and whether the antidepressant-like effects of *G. lucidum* would still be present in the animals after prolonged periods of stress.

Testing antidepressant-like effects of triterpenoid extracts of *G. lucidum* was also performed in a maternal separation (MS) plus adulthood sub-stress mouse model of depression in both male and female animals.[31] Maternally separated animals pretreated with *G. lucidum* triterpenoids (GLT) at 10, 20, and 40 mg/kg through i.p. injections over 3 weeks performed various behavioral tests, including the sucrose preference test (SPT), FST, TST, splash test, and nest-building test to assess the antidepressant-like effects of GLT. Treatments with GLT exerted positive effects, alleviating anxiety- and depression-like behaviors in all behavior tests.[31] In the open field test (OFT), GLT-treated MS mice showed increased distance moved and time spent in the central zone, suggesting an anti-anxiety effect.[31] However, one limitation of this study is that preemptive and prophylactic treatments were administered before the adulthood sub-stress. Although preventive treatment is available for post-stroke depression,[67] post-partum depression,[68] and depression relapse,[69] it is not commonly provided in early life stress-related adulthood depression.[70] This study could be improved by administering the GLT treatments after subjecting to adulthood stress. Another limitation is that all the experimental groups were subjected to adulthood stress; hence, whether depression-like behaviors were induced by maternal separation or adulthood stress could not be distinguished.

Another study investigated the antidepressant-like effects using polysaccharide-peptide (PGL) extract from the spores of *G. lucidum* in mice subjected to chronic unpredictable mild stress (CUMS).[65] The PGL extract consisted of 67.68% polysaccharides and 8.41% peptides. Animals were subjected to CUMS for 4 weeks or 8 weeks followed by oral administration of PGL at 100, 200, and 400 mg/kg for 4 weeks before behavior testing, including TST, FST, and OFT. All PGL treatment concentrations exhibited antidepressant-like effects in the SPT and FST.[65] Similar to the observation of Li et al.,[30] this study also tested the antidepressant-like effects of *G. lucidum* in non-stressed mice with oral administration of 100, 200, and 400 mg/kg PGL 60 minute prior to the various behavioral

Table 2. Summary of preclinical and clinical studies on the therapeutic effects of *Ganoderma lucidum*, highlighting its antidepressant-like properties and the mechanisms underlying these effects.

Types of Study	Authors	Bioactive Compound Studied	Dose and Dosage	Animal Model/ Patients	Antidepressant therapeutic effect	Methods for Molecular Assessment
Bioactive compound studies	Matsuzaki et al., 2013[38]	Water-soluble extract from *Ganoderma lucidum* mycelia (MAK) (triterpenes, and polysaccharides)	300 or 1000 mg/kg MAK, administrated 60 minutes prior to behaviour tests; p.o.	Male Sprague-Dawley rats	MAK acts as a 5-HT_{2A} antagonist to achieve antidepressant-like effects	Head-twitch test
	Li et al., 2021[30]	*Ganoderma lucidum* polysaccharides (GLP)	1, 5, or 12.5 mg/kg GLP, administrated daily for 5 days; i.p.	Male C57BL/6 mice subjected to chronic social defeat stress (CSDS)	GLP treatment has the following effects in stressed animals: • Reduce the brain IL-1β and TNF-α level • Elevate the brain IL-10 and BDNF level • Inhibit the activation of microglia and astrocytes induced by CSDS • Upregulate the AMPA receptor expression • Upregulate Detin-1 expression	Western blot Immunofluorescent staining
	Zhao et al., 2021[37]	*Ganoderma lucidum* polysaccharide-peptide (PGL) (polysaccharides and peptides)	100, 200 or 400 mg/kg PGL, administrated daily for 4 weeks; p.o.	Male C57BL/6 mice subjected to chronic unpredictable mild stress (CUMS)	PGL treatment has the following effects in stressed animals: • Elevate the brain serotonin and norepinephrine level • Reduce the peripheral corticosterone level • Elevate the peripheral BDNF level • Upregulate the brain expression of Synapsin I and PSD95 • Induce the BDNF/TrkB pathway	Immunoassay Real-time RT-PCR High-performance liquid chromatography (HPLC) Western blot
	Mi et al., 2022[31]	*Ganoderma lucidum* triterpenoids (GLT)	10, 20, 40 mg/kg for three weeks GLT, administrated daily for 3 weeks; i.p.	Male and female C57BL/6J mice subjected to maternal separation (MS)	GLT treatment has the following effects in stressed animals: • Reduce the peripheral and brain IL-1β, IL-6 and TNF-α level • Elevate the peripheral and brain IL-10 level • Inhibit the activation of microglia induced by MS	Enzyme-linked immunosorbent assay (ELISA) Quantitative real-time PCR (qPCR) Western blot Immunofluorescence
	Huang et al., 2017[28]	GLP	30 mg/kg GLP, administrated daily for 90 days; P.O.	APP/PS1 transgenic mice and C57BL/6 mice	GLP treatment has the following effects APP/PS1 animals: • Enhance the neurogenesis • Induce FGFR1/ERK/AKT pathway	Western blot Immunofluorescent staining

(*Continued*)

Table 2. (Continued).

Types of Study	Authors	Bioactive Compound Studied	Dose and Dosage	Animal Model/ Patients	Antidepressant therapeutic effect	Methods for Molecular Assessment
Clinical studies	Tang et al., 2005[46]	*Ganoderma lucidum* polysaccharides (Ganopoly)	5400 mg Ganopoly, administrated daily for 8 weeks; p.o.	123 neurasthenia patients, 50 males and 73 females	Ganopoly treatment has the following effects in patients: • Reduce the sense of fatigue • Increase the sense of well-being	N.A.
	Zhao et al., 2012[47]	Spore powder of *Ganoderma lucidum* (polysaccharides and triterpenoids)	1000 mg spore powder, administrated 3 times daily for 4 weeks; p.o.	48 breast cancer patients with cancer-related fatigue undergoing endocrine therapy	Spore powder treatment has the following effects in patients: • Reduce anxiety and depression level • Reduce peripheral IL-6 and TNF-α level • Reduce the sense of fatigue	ELISA
	Pazzi et al., 2020[29]	Micromilled carpophores of *Ganoderma lucidum*	6 g micromilled carpophores, administrated daily for 6 weeks; p.o.	64 women with fibromyalgia syndrome (FMS)	Carpophores treatment has the following effect in patients: • Elevate level of happiness • Decrease depression level	N.A.

tests. The PGL treatments significantly ameliorated depression- and anxiety-like behaviors, indicating robust and acute antidepressant-like effects.[30,65] A study conducted by Matsuzaki et al.[71] investigated the antidepressant-like effects of a water-soluble extract from the culture media of *G. lucidum* mycelia (MAK). The MAK extract contained mainly polysaccharides, triterpenes, and lignin. Animals were orally administered MAK at 300 and 1000 mg/kg 60 minute prior to FST, OFT, elevated plus-maze (EPM), or contextual fear-conditioning test. Animals treated with 1000 mg/kg MAK displayed decreased immobility in the FST and decreased freezing rate in the contextual fear-conditioning test. These results indicate that MAK possesses both antidepressant- and anxiolytic-like effects.[71]

Overall, these preclinical studies showed that polysaccharides and triterpenes of *G. lucidum*, especially triterpenoids, have antidepressant- and anxiolytic-like effects in various animal models. However, it is important to note that some studies used only male animals,[30,65,71] whereas prevalence of clinical depression is higher among women than men.[72] Hence, future studies should include female animals in each group to investigate sex differences in the response to *G. lucidum*. Notably, some studies consistently reported acute and robust antidepressant-like effects after administration of a single dose of *G. lucidum* in non-stressed animals.[30,65,71] Rapid-acting antidepressants are relatively rare, as most antidepressants usually take about 2–3 weeks to show any beneficial effects in MDD patients after starting the treatment.[73] One rapid-acting antidepressant is ketamine, which targets N-methyl-D-aspartate receptor (NMDAR) and GABAergic interneurons.[74] A single dose of ketamine was found to have rapid-acting and long-lasting effects in MDD patients.[75,76] The above preclinical studies suggest that *G. lucidum* could have acute antidepressant-like effects, which would be highly promising clinically. However, it is important to note that the above findings were based on behavior results from non-stressed animals rather than animals pre-exposed to stress, and no underlying mechanism of the acute effects was reported in these studies.[30,65,71] Moreover, the antidepressant-like actions of *G. lucidum* in native and stressed animals can vary because of their different behaviors and physiological characteristics.[77,78] In addition, no acute antidepressant effects of *G. lucidum* have been observed in clinical human studies (discussed in the next section). Although the acute antidepressant-like effects reported in preclinical studies are reminiscent of ketamine, the findings may be less convincing, as *G. lucidum* and ketamine may not have similar mechanisms of action. Hence, whether *G. lucidum* indeed possesses acute antidepressant-like effects in humans should be the focus of future research.

Clinical studies

To the best of our knowledge, several clinical studies have demonstrated the potential of *G. lucidum* in ameliorating depression- and anxiety-related behaviors such as fatigue in breast cancer, neurasthenia, and fibromyalgia symptoms. Although these findings are indirectly related to major depression, they still provide valuable insights into the potential use of *G. lucidum* for managing depression and opening new windows of opportunities for mood and anxiety disorders.

Tang *et al.*[79] conducted a randomized double-blind, placebo-controlled trial with 123 Chinese neurasthenia patients (50 males and 73 females) randomly received either Ganopoly, a polysaccharide extract of *G. lucidum*, or placebo at a dosage of 1800 mg three times a day for a duration of 8 weeks. Patients with neurasthenia are often affected by anxiety or depressive symptoms, and it is often regarded as a Chinese form of depression.[80,81] This clinical trial provided valuable insights into the potential application of *G. lucidum* for managing MDD. The study used the clinical global impression (CGI) scale to assess treatment efficacy on improving neurasthenia and the visual analogue scale (VAS) to assess the patient's sense of well-being and sense of fatigue.[79] The 8-week Ganopoly regimen was found to significantly alleviate neurasthenia symptoms by 15.5% and reduce sense of fatigue by 28.3% compared to baseline, whereas the placebo group showed reductions of only 4.9% and 20.1%, respectively.[79] These results suggest that *G. lucidum* may be effective in alleviating symptoms

associated with MDD, as demonstrated by the significant improvements in neurasthenia symptoms and fatigue reduction compared with the placebo group.

In 2012, Zhao *et al.*[82] conducted a randomized controlled trial with 48 female breast cancer patients undergoing endocrine therapy who experienced cancer-related fatigue and mood disorder. Patients were divided into two groups: an experimental group receiving 1000 mg *G. lucidum* spore powder for 4 weeks, and a control group receiving a placebo for the same duration.[82] This study is highly valuable, as the patients were affected by 1) cancer-related fatigue, 2) breast cancer, 3) endocrine therapy, and all of which were strongly associated with the development of MDD or the occurrence of depressive episodes. Several studies have investigated on how each of these factors contributes to depressive symptoms. For example, in the systematic review of Brown & Kroenke[83] confirmed a significant correlation between cancer-related fatigue and depression, as well as anxiety. Furthermore, multiple studies have also shown the high prevalence of depression among breast cancer patients. In the cross-sectional study of Purkayastha *et al.*,[84] 22% of the 270 exhibited moderately severe to severe depression. Similarly, Tsaras *et al.*[85] reported that 38.2% of 152 breast cancer patients in their study were classified as depressed. These findings strongly demonstrated that depression is a common comorbidity in breast cancer patients.[84,85] Additionally, the side effects of endocrine therapy are also associated with depression.[86,87] Crucially, when Zhao *et al.*[82] assessed the levels of anxiety and depression of the patients using the hospital anxiety and depression scale (HADS),[82] the mean scores of patients from the experimental (10.9 ± 4.1) and control (10.8 ± 3.9) group were approximately 11, indicating minor to moderate levels of depression and anxiety.[88] Although this study was conducted in breast cancer patients, it provided critical insights into the potential of *G. lucidum* in alleviating MDD. In the study, 4-week *G. lucidum* spore powder treatment significantly decreased the levels of depression and anxiety levels. The cognitive functions together with the physical and emotional well-being of patients were also remarkably improved. In addition, there were reductions in the serum concentrations of TNF-α and IL-6,[82] which is consistent with the findings from animal studies. These findings highlight the potential of *G. lucidum* in alleviating MDD symptoms, particularly through its modulatory effects on serum TNF-α and IL-6 levels.

Additionally, a recent double-blind randomized, placebo-controlled pilot clinical trial conducted by Pazzi *et al.*[29] examined the potential application of micromilled *G. lucidum* carpophores in 64 female fibromyalgia patients experiencing physiological distress.[29] Participants were randomly assigned to either the *G. lucidum* group or the placebo group. During the 6-week treatment, patients received 6 g of micromilled *G. lucidum* carpophores per day, while the control received 6 g placebo composed of Ceratonia siliqua flour. Geriatric Depression Scale (GDS) was used to assess the level of depression in patients.[29] The secondary symptoms of fibromyalgia, such as fatigue, sleep impairment, pain catastrophizing, and fear of movement, are significantly associated with high depression.[89] Although no statistically significant differences between groups were found, the study showed that after 6-week treatment with *G. lucidum*, there were improvements in the GDS scores from 7.6 to 5.36, Satisfaction with Life Questionnaire, as well as happiness and satisfaction with life and reduced depression, demonstrating the beneficial effects of *G. lucidum* in reducing depression.[29]

Taken together, although no clinical trials have been conducted specifically on MDD patients, the participants in existing studies experienced depression-related symptoms, and treatment with *G. lucidum* demonstrated significant alleviation of depression and anxiety. These findings support the potential use of *G. lucidum* in ameliorating MDD symptoms. However, further clinical studies are essential to evaluate the antidepressant effects of *G. lucidum* in MDD patients across both genders. Future research should also explore its impact on other depression-related biomarkers, such as hippocampal volume, to deepen our understanding of the underlying mechanisms.[90] Since herbal medicines are often used as complementary treatments, so it is critical to investigate whether combining *G. lucidum* with conventional antidepressants could enhance patient outcomes.

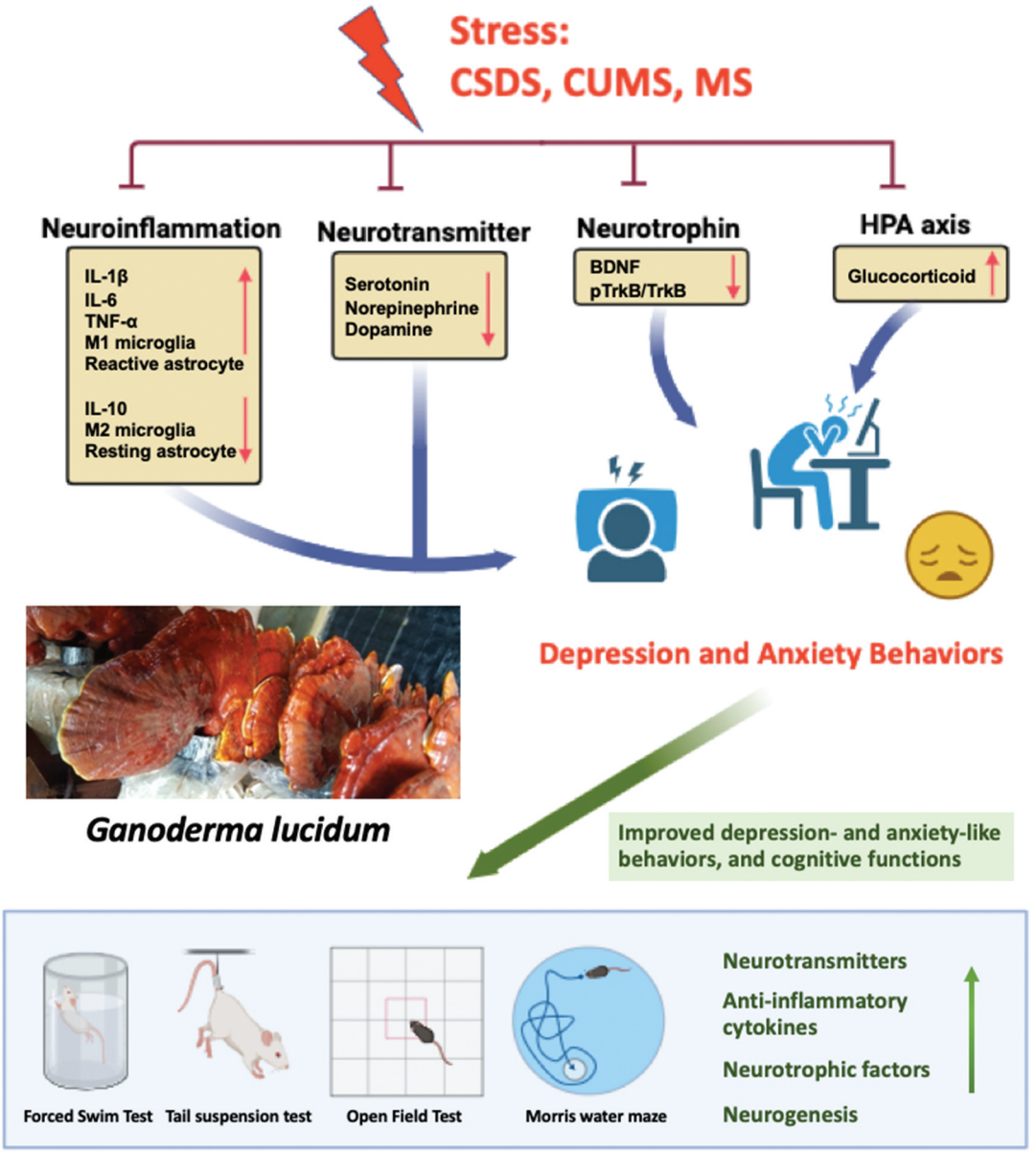

Figure 2. Overview of stress-induced physiological changes and the therapeutic effects of *Ganoderma lucidum* in animal models of depression. Chronic stress disrupts neurotransmitter balance, promotes neuroinflammation, reduces neurotrophin levels, and dysregulates the HPA axis, collectively contributing to depression and anxiety-like behaviors. *Ganoderma lucidum* counteracts these effects by modulating neurotransmitter levels, reducing inflammation, enhancing neurotrophic factors, and promoting neurogenesis, leading to improved emotional and cognitive outcomes. Behavioral improvements are assessed through tests such as the forced swim test, tail suspension test, open field test, and Morris water maze.

Underlying mechanism of the antidepressant-like effects of G. *lucidum*

Depression is a highly complex and multifaceted neuropsychiatric disorder. Various biological, psychological, and social factors can contribute to its development. The pathophysiology of depression is believed to be associated with changes in brain structures, neurotransmitter systems, and immune systems. Other factors that can play a role in depression include genetics, dysregulated hypothalamic–

pituitary–adrenal (HPA) axis, and disrupted endocrine hormone synthesis. Indeed, the development of depression is likely a consequence of the interplay between all of these factors.[91] Therefore, the antidepressant would presumably be more beneficial and effective for the patients, if it could target multiple aspects of the pathophysiology of MDD (Fig. 2).

Monoamine regulation

The monoamine hypothesis proposes that depression is caused by a deficiency in monoamine neurotransmitters including norepinephrine, serotonin, and dopamine.[92,93] This hypothesis is based on the observation that reserpine, a hypertension drug that was found to deplete monoamine neurotransmitters, caused depression-like behaviors in hypertensive patients.[94,95] This hypothesis was further supported by the development and success of antidepressants such as MAO inhibitors, TCA, and SSRIs that either target MAO or serotonin and norepinephrine transporters to increase the concentration of monoamine neurotransmitters.[6]

The effects of *G. lucidum* (MAK) on central serotonergic (5-HT) activity were investigated by Matsuzaki et al.[71] using the head-twitch test. All animals were administered 2,5-Dimethoxy-4-iodoamphetamine hydrochloride, a 5-$HT_{2A/2B/2C}$ receptor antagonist that induces a head-twitch response. Treatment with MAK significantly decreased head-twitching, indicating it has inhibitory effects against 5-HT_{2A} receptor.[71] The 5-HT_{2A} receptor plays an important role in the action of antidepressant drugs that regulate serotonin levels. Moreover, the inhibition of 5-HT_{2A} receptors by atypical antipsychotics can be used to augment the antidepressant effects of SSRI.[96,97] Therefore, *G. lucidum* may achieve its antidepressant-like effects by inhibiting 5-HT_{2A} receptors in the brain. The action of *G. lucidum* on serotonergic pathways was further supported by a study investigating the sleep-promoting effects of a triterpene-enriched ethanol extract. Chronic administration of the ethanol extract in mice markedly increased hypothalamic serotonin levels and significantly elevated mRNA levels of several genes involved in the serotonergic synapse pathway including Tph2, Itpr2, and Gng13,[98] indicating its role in regulating the serotonin pathway. A recent molecular study also suggested that *G. lucidum* can regulate norepinephrine concentration, using high-performance liquid chromatography to measure monoamine concentrations in the brains of CUMS mice. They found the levels of serotonin and norepinephrine were significantly reduced in the prefrontal cortex (PFC) of CUMS mice, which were reversed by chronic PGL treatment in a dose-dependent manner.[65] Interestingly, the level of dopamine in the PFC was not significantly decreased by CUMS or increased by the PGL treatment.

Neurogenesis enhancement

Although the role of neurogenesis in the pathology of depression is still controversial, some studies have observed increased neurogenesis in depressed subjects after antidepressant treatments, indicating that increased neurogenesis is part of the action of antidepressants.[99–101] Although no direct evidence shows that the antidepressant-like effects of *Ganoderma lucidum* are mediated through enhancing neurogenesis, a few studies have suggested that *Ganoderma lucidum* can enhance neurogenesis.

Huang et al.[28] studied the potential effects of chronic oral administration of GLP in a transgenic mouse model of Alzheimer's disease (AD). The GLP treatments significantly increased the number of BrdU/NeuN double-positive cells in the hippocampus of transgenic AD mice, indicating enhanced neurogenesis. To further understand how GLP enhances neurogenesis, Ki67 and SOX2 (markers used to evaluate NSC proliferation status and the size of stem cell populations, respectively) were assessed. The Ki67 protein is expressed during active cell division, whereas SOX2 is expressed in NPCs to maintain cell pluripotency.[102,103] GLP-treated transgenic AD mice and non-transgenic C57BL/6 mice showed significantly increased numbers of Ki67 and SOX2 double-positive neural progenitor cells (NPCs) in the subgranular zone (SGZ), but the number of SOX2-positive cells remained unchanged, suggesting that the enhanced

neurogenesis by GLP was mediated through increased NPC proliferation without increasing the size of the NPC pool.[28] The findings are consistent with a study investigating the changes in SOX2-positive NSCs during running-induced enhanced neurogenesis in transgenic SOX2-GFP mice, which found that the size of the NSC pool remained constant.[104] Furthermore, *in vitro* studies on NPC cell cultures derived from adult mouse hippocampus, embryonic mouse cortex, and induced pluripotent human stem cells showed increased EdU incorporation after treatment with GLP,[28] further supporting that GLP can enhance NPC proliferation. In addition, GLP-treated NPCs formed more neurospheres than vehicle-treated NPCs in the sphere-formation assay, indicating that GLP also increased the self-renewal ability of NPCs.[28] This study also investigated the changes in gene expression underlying the enhanced neurogenesis in NPC cell cultures, focusing on two growth factor receptors involved in NPC proliferation, fibroblast growth factor receptor 1 (FGFR1) and epidermal growth factor receptor (EGFR). Overall, GLP treatment increased the level of FGFR1 phosphorylation with no effects on EGFR phosphorylation.[28] Two pathways downstream of FGFR1 activation are involved in cell proliferation, the Raf/MEK/ERK and PI3K/AKT/mTOR pathways. After 5–10 minute of GLP treatment, increased ERK and AKT phosphorylation was observed, whereas adding FGFR1 inhibitor PD173074 to the cell culture blocked the neurogenesis-enhancing effects of GLP, as demonstrated by decreased levels of FPFR1, ERK, and AKT phosphorylation, and EdU incorporation.[28] Overall, these *in vitro* studies and *in vivo* animal studies in AD mice showed that *G. lucidum* can increase neurogenesis by enhancing NPC proliferation. However, whether these effects are observed in animal models of depression and whether neurogenesis is involved in the antidepressant-like effects of *G. lucidum* require further investigation.

BDNF elevation

Neurotrophins are a family of proteins that play crucial roles in neuron development, survival, and function. Some studies have proposed that changes in the levels of neurotrophin-3 (NT-3) and brain-derived neurotrophic factor (BDNF) in the brain are linked to depression.[105] The role of BDNF in depression was further confirmed by the finding that BDNF infusion in the midbrain resulted in antidepressant-like effects in a learned helplessness animal model of depression,[106] and other animal studies also showed that chronic treatment with antidepressant drugs increased mRNA levels of *Bdnf* and tropomyosin receptor kinase B (TrkB), the BDNF receptor in the hippocampus.[107] This hypothesis was further reinforced by a postmortem study in MDD patients treated with antidepressants, which found increased *Bdnf* expression in various brain regions.[108]

Moreover, AMPA receptor augmentation and upregulation are believed to be a mechanism of conventional antidepressants. Studies have found that the AMPA potentiator could increase BDNF levels in the brain by a calcium-independent mitogen-activated protein kinase (MAPK) pathway or a calcium-dependent pathway.[109–111] Given the strong interplay between the AMPA receptors and the BDNF pathway, in the study of Li et al.,[30] GLP treatment significantly increased the expression levels of three AMPA receptors P-GluA1(s845), GluA1, and GluA2 in the hippocampus of CSDS mice, indicating that the antidepressant-like effects of GLP are probably mediated through increasing BDNF via an AMPA potentiation effect. Consistent with this finding, GLP-treated CSDS mice showed increased BDNF expression level in the hippocampus.[30] Chronic treatment with PGL also significantly increased the mRNA and protein levels of BDNF in the prefrontal cortex in CUMS animals.[65] In contrast, TrkB receptor antagonist K252a blocked the increase in BDNF levels, the activation of TrkB pathway, and the behavior changes by PGL in CUMS animals, indicating that the antidepressant-like effects of PGL are dependent on the activation and potentiation of the BDNF/TrkB pathway. In addition, in PGL-treated CUMS animals, increasing BDNF levels resulted in increased levels of postsynaptic density-95 (PSD-95), which is vital for regulating AMPA receptors at synapses.[112] The relationships between BDNF, PSD-95, and AMPA receptor further support that the antidepressant-like effect of *G. lucidum* is dependent on the BDNF pathway.

Regulation of inflammation, microglia, and glucocorticoid

Both peripheral and central inflammations have been closely linked to depression.[113] An imbalance between pro- and anti-inflammatory cytokines is believed to be one of the pathophysiology of depression, with several studies reporting that MDD patients have compromised immune systems. Increased concentrations of interleukin 1 (IL-1) and interleukin 2 (IL-2) were reported in an unpredictable chronic mild stress (UCMS) rat model of depression.[114] A meta-analysis reviewed 107 studies on 5166 depression patients and 5083 controls found elevated levels of pro-inflammatory cytokines IL-1, IL-2, and tumor necrosis factor-alpha (TNF-α).[115] The anti-inflammatory effects of some antidepressants further support this relationship. Antidepressants desipramine and fluoxetine have been shown to reduce the concentration of circulating TNF-α in an animal model of inflammation.[116] In human participants challenged by phytohemagglutinin and lipopolysaccharide, treatment with antidepressants significantly decreased the production of pro-inflammatory cytokine interferon-γ (IFN-γ) and increased the production of anti-inflammatory cytokine interleukin 10 (IL-10).[117]

Whether the immunomodulatory properties of *G. lucidum* are linked to its antidepressant-like effects has been widely investigated. Some studies have shown that *G. lucidum* treatments can affect the levels of pro- and anti-inflammatory cytokines. Studies by Mi et al.[31] and Li et al.[30] found that *G. lucidum* treatments could reverse the inflammatory cytokine imbalance in the brains of stressed animals.[30,31] Despite using different animal models and detection methods (Mi et al.[31] used qPCR in MS mice, and Li et al.[30] used Western blotting in CSDS mice), both studies found that *G. lucidum* treatments normalized the expression levels of pro- and anti-inflammatory cytokines in the hippocampus of stressed animals back to the levels of the control animals. Such effects were also observed in the PFC of MS mice. Moreover, GLT reduced the peripheral serum levels of pro-inflammatory cytokines IL-1β, IL-6, and TNF-α and increased the levels of anti-inflammatory cytokines IL-10.[31] In a clinical study of cancer-related fatigue in breast cancer patients with mood disorders, Zhao et al.[82] found that *G. lucidum* spore powder treatments significantly reduced serum concentrations of IL-6 and TNF-α. These studies suggest that the antidepressant-like effects of *G. lucidum* are mediated partly by normalizing the abnormal expression of pro- and anti-inflammatory cytokines.

Besides affecting the expression of cytokines, the antidepressant-like effects of *G. lucidum* could also act by inhibiting microglial proliferation and activation. Microglial cells are specialized macrophages in the central nervous system.[118] They have various phenotypes and functional states. In the resting state, the cells are ramified. Upon activation by injury, infection, or immune signals, microglia will polarize into the M1 state and become more amoeboid in shape. The M1 phenotype can secrete cytokines such as IL-1 and release reactive oxygen species (ROS). Hence, excessive M1 activation will damage tissues and contribute to the formation of a pro-inflammatory environment in the brain.[119] Furthermore, the pro-inflammatory cytokines secreted by M1 microglia could activate astrocytes. Under normal conditions, astrocytes are supportive cells promoting neuronal survival and synaptogenesis. However, activated astrocytes are pro-inflammatory and will cause astrocytic neurotoxicity and neuron cell death by secreting neurotoxins.[120] Li et al.[30] investigated the expression of microglial marker Iba1 and astrocyte marker GFAP in the hippocampus of CSDS mice. They found CSDS mice had significantly increased numbers of $Iba1^+$ and $GFAP^+$ cells, whereas GLP treatment reduced the number of $Iba1^+$ and $GFAP^+$ cells.[30] However, Iba1 and GFAP are not markers specific to activated microglia and astrocytes. To this end, Mi et al.[31] quantified the phenotype of the $Iba1^+$ and $GFAP^+$ cells, which showed that stress increased the number of $Iba1^+$ cells and transformed microglia into the M1 phenotype in the PFC and hippocampus of MS mice. Treatment with GLT for 3 weeks reduced the number of $Iba1^+$ cells and restored the activated microglia to their resting state with higher ramification.[31] These findings suggest that the antidepressant-like effects of *G. lucidum* are related to its ability to inhibit microglial activation and proliferation, and transform activated microglia back to their resting state. However, whether *G. lucidum* has the same effects on astrocytes requires further investigation.

Li et al.[30] revealed that the microglial inhibitory effect of GLP was mediated through Dectin-1 activation. Dectin-1 is a transmembrane receptor primarily expressed on the surface of immune cells, and its expression on microglial cells suggests it has the potential to regulate neuroinflammation.[121,122] As a pattern recognition receptor, Dectin-1 can recognize β-glucans, one of the major constituents of GLP. Li et al.[30] found that CSDS mice had significantly reduced protein levels of Dectin-1, which could be reversed by GLP treatment. Moreover, CSDS mice treated with Dectin-1 inhibitor laminarin (LAM) abolished the antidepressant-like effects of GLP in the TST, suggesting Dectin-1 activation and interaction as crucial for inhibiting microglial activation and for the antidepressant-like effect of GLP.[30] However, the role of Dectin-1 in neuroinflammation is controversial. A study of ischemic stroke and spinal cord injury in mice suggested that Dectin-1 activation promotes neuroinflammation[122] and even leads to demyelination and axonal injury.[123] However, some studies have found that Decin-1 activation in microglial cells does not lead to the significant production of cytokines and can enhance axonal regeneration.[121,124] The specific role of Dectin-1 activation is probably context-dependent, and whether Dectin-1 activation is involved in the antidepressant-like effects of *G. lucidum* requires further investigation.

Glucocorticoid is a type of steroid hormone with both pro- and anti-inflammatory properties. Glucocorticoid tends to demonstrate pro-inflammatory properties in animals under acute or chronic stress,[125] and chronic stress can lead to HPA axis hyperactivity and increase the level of glucocorticoids in MDD patients, subsequently increasing the level of pro-inflammatory cytokines.[126] Zhao et al.[82] found that CUMS mice had significantly elevated serum corticosterone levels, whereas chronic PGL treatment significantly decreased corticosterone levels compared to untreated CUMS mice.[65] The above findings indicate that the antidepressant-like effects of *Ganoderma lucidum* could be related to the regulation of the neuroendocrine system.

Future perspectives

Among the bioactive constituents of *G. lucidum*, polysaccharides and triterpenoids have been comprehensively investigated in various animal depression models, which showed their antidepressant-like effects are mediated through regulating monoamine, neuroendocrine, and immune systems, and increasing the BDNF expression in the brain.[30,31,65,71] Some studies on neurological disorders such as AD have shown that *G. lucidum* can enhance neurogenesis in specific brain regions. Considering the differences in the pathophysiology of AD and MDD, more studies are required to investigate whether the neurogenesis-enhancing effects are also observed in depressed animal models and whether neurogenesis contributes to the antidepressant-like effects. The study by Li et al.[30] suggested that Dectin-1 receptor, a direct molecular target of GLP, is involved in the antidepressant-like effects. Future studies could focus on the underlying molecular basis of the immunomodulatory effects of *G. lucidum*. For example, a study showed that GLP also interacted with Toll-like receptor 4 (TLR4),[127] Hence, whether TLR4 activation is also involved in the antidepressant-like activities of *G. lucidum* needs to be determined. Oxidative stress can also contribute to the development of depression. Excessive ROS secreted by activated microglia can disrupt the balance between the production of oxidants and antioxidant enzymes. Excessive ROS can also cause damage to the cell membrane, DNA, and mitochondria.[128] Polysaccharides and triterpenoids of *G. lucidum* have been shown to be excellent antioxidants. *In vitro* studies found that both GLP and GLT treatments protected cell cultures from ROS-induced apoptosis.[27,129] Future studies could focus on whether the antidepressant-like effects of *G. lucidum* are dependent on its antioxidant activities.

Furthermore, bioactive compounds of *G. lucidum* were found to promote neurite outgrowth via MEK/ERK1/2 and PI3K/Akt pathways.[130] This is reminiscent of the effect of BDNF on stimulating the sprouting of serotonergic neurons.[131] Whether the promotion of neuritogenesis can contribute to the antidepressant-like effects of *G. lucidum* needs to be investigated. Currently, clinical studies involving *G. lucidum* focus on patients experiencing depression-related symptoms, with the exception of the study on neurasthenia, which is associated with

a Chinese form of depression.[29,79,82] Collectively, these studies support the beneficial effects of *G. lucidum* in alleviating depression and anxiety. Nevertheless, future research should prioritize clinical trials specifically targeting MDD patients to directly assess the antidepressant effects of *G. lucidum* in humans. Incorporating a broader range of depression-related biomarkers in these studies would provide valuable understanding into their potential role in alleviating depression and the underlying mechanisms. It is noteworthy that most herbal medicines are used as complementary treatments alongside conventional pharmacotherapies for depression. Therefore, investigating whether their use enhances the efficacy of conventional antidepressants in clinical trials could not only provide valuable insights but also facilitate physician-patient communication and support clinical decision-making. However, it is equally important to be aware of potential interactions between herbal medicines and antidepressants to avoid adverse effects, unintended drug interactions, or compromised treatment outcomes during clinical trials.

In the past few decades, there has been a trend for patients to use natural remedies such as herbs for various diseases including depression and anxiety, since they are regarded as safer with less side effects compared to conventional pharmacotherapy.[132] Medicinal herbs were found to be useful for depression in both preclinical and clinical studies. For example, polyphenols of *Camellia sinensis*, the tea plant, alleviate depression-like behaviors through decreasing serum levels of corticosterone.[133] Moreover, *Hypericum perforatum*, St John's Wort, has a long history of use in treating depression.[134] *Hypericum perforatum* extract demonstrated antidepressant effects comparable to conventional medications, but with fewer side effects in MDD patients.[135] Therefore, future research could explore the commonalities and differences in the mechanisms of action of these herbal medicines while also comparing their efficacy and side effects. Imperatively, other herbal medicines also contain polysaccharides and triterpenoids, which exhibit diverse bioactive properties. For instance, β-glucan polysaccharides have been extracted from *Lentinula edodes* (Shiitake), while pentacyclic triterpenoids are widely found in *Glycyrrhiza* and *Gymnema* species.[136,137] Interestingly, some of these bioactive compounds such as acidic polysaccharide portion of *Panax ginseng* and glucan extract of *Hericium erinaceus* also demonstrated antidepressant-like effects in animal models of depression.[138,139] Therefore, future research could not only investigate whether similar bioactive compounds from other herbal medicines exhibit antidepressant-like effects but also compare and contrast already-established antidepressant-like compounds from different herbs in terms of their chemical structures, pharmacokinetics, bioavailability, mechanisms of action, receptor interactions, and metabolic pathways. Such studies would help elucidate their shared and distinct properties, deepening our understanding of their therapeutic potential and facilitating the development of safer and more effective antidepressant drugs.

Conclusion

Studies have shown that polysaccharides and triterpenoids, the two major bioactive compounds of *G. lucidum*, can exert antidepressant-like effects in animal models of depression. Clinical studies in non-MDD patients have also shown that *G. lucidum* can ameliorate some common depression-related symptoms, such as anxiety, fatigue, and mood disorders. These antidepressant-like effects were found to be mediated through the regulation of monoamine and neuroendocrine systems, the BDNF pathway, and the peripheral or central immune system. However, our understanding of the mechanisms underlying the antidepressant-like effect of *G. lucidum* is still incomplete and requires future studies, particularly in MDD patients. Overall, *G.* lucidum could potentially be used clinically in parallel with the conventional antidepressant medications to improve treatment efficacy in MDD patients.

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Authors' Contributions

Conceptualisation, funding acquisition, resources, project administration, & supervision: LWL, AK, & KHW. Writing (original draft, review & editing), data curation, formal analysis, investigation, validation, & visualization: HJ, AK, KHW, & LWL. Intellectual inputs & writing (review & editing): LA, BCH, TS, MLF, GLT, EK, AB, YT, ZL, and AK. All authors have read and agreed to the published version of the manuscript.

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