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Unlocking the immunomodulatory potential of *Ganoderma lucidum*: A comprehensive review

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ABSTRACT

Ganoderma lucidum, popularly known as Reishi is a medicinal fungus used in traditional Chinese medicine for its immunomodulatory characteristics. It has been demonstrated that the bioactive substances extracted from *Ganoderma lucidum* alter the immune system, affecting both innate and adaptive immunity. Bioactive compounds like polysaccharides, proteins have exhibited immunostimulant activity by enhancing the activation and differentiation of various immune cells, which include T-lymphocytes, B-lymphocytes, macrophages and natural killer cells. They also increase the synthesis of cytokines which are essential for maintaining immune homeostasis. Additionally, some of the bioactive substances exhibited immunosuppressive activity by inhibiting the histamine release from mast cells and suppressing the production of pro inflammatory cytokines. There by it exhibits anti-allergic, anti-inflammatory and anti-tumor activity. Reishi can be demonstrated as a potential therapeutic agent in treating immune related diseases and may be involved in the development of new immunomodulatory medication. This review aims to provide a comprehensive overview of the immunomodulatory effects of *Ganoderma lucidum*.

Keywords: Immunomodulatory, *Ganoderma lucidum*, Cytokines, Lymphocytes, Anti-inflammatory.

INTRODUCTION

The basidiomycetes fungus, *Ganoderma lucidum* commonly referred as Reishi or Lingzhi has a lengthy history in Asian medicine. Chinese and Japanese emperors have included it in their diets because of its reputations for boosting vitality and longevity. Its fruiting bodies, spores and mycelia have been shown to contain bioactive substances such as polysaccharides, proteins and terpenoids. Its immunomodulatory properties have been emphasized in recent research, indicating that it may boost immunity and aid in disease prevention. *G. lucidum* may be used as a treatment for a number of illness because to its pharmacological qualities, which include immunomodulatory anti-tumor and anti-inflammatory qualities [1-3].

Taxonomical Classification

Kingdom: Fungi
Phylum : Basidiomycota
Class : Agaricomycetes
Order : Polyporales
Family : Ganodermataceae
Genus : *Ganoderma*
Species : *lucidum*

The double-layered spore wall of *G. lucidum* is likely due to the presence of pilocystidia, which are thick-walled, specialized cells submerged in melanin-rich extracellular matrix [2]. The powdered fruiting bodies of mycelium spores are used medicinally [4].

Habitat

In temperate regions of Europe, Asia, and North America, this annual mushroom is frequently found on deciduous trees such as oak, maple, elm, sweet gum, and locust. It is also occasionally seen on conifers and on the roots of decomposing trees [5].

Morphology

Ganoderma species are found all over the world and are distinguished by a number of traits such as host specificity, geographic origin and fruit body form and colour (such as red, black, blue, white, brown and yellow). However, natural genetic processes (mutations, recombination) with in species and cultivation

conditions can cause morphological traits to vary [6].

Fruit Body Details

- Size: 7-12 cm in length, 11-19 cm in width, 1.5cm thick.
- Texture: Corky to woody.
- Attachment: Sub sessile to laterally stipitate, with a kidney-shaped stalk.
- Upper surface: Purplish and dark crimson with yellowish shift towards the edge.
- Spore surface: Milky coffee to creamiest in hue, rounded with five spores per mm.
- Tubes: 2-2 mm long, initially brown with age or brushing.
- Context: Brown 9mm broad, free of hard deposits [7].

Microscopic Features

- Cutis: Made up of clavate cells with strong walls and branching extensions at base.
- Measurements: 6-8 micrometer width and 35-42 micrometer length.
- Trimitic Hypothalamic system: Generic Hyphae, Skeleton Hyphae, Binding Hyphae.
- Basidiospores: Yellowish brown, 8.23-10 micrometer long, 6.6 micrometer broad, spore index- 1.6 [7].

Cultivation

Lingzhi cultivation techniques have evolved, providing producers with various options for producing fruiting bodies, spores, and mycelial biomass. Solid state mediums are used for fruiting bodies, while liquid state medium is used for mycelial biomass. Popular methods include the synthetic sawdust bag method and short wood log method, which offer quicker growth cycles, higher yields, better quality and copious spore generation [5,8].

Submerged cultivation or liquid medium cultivation is preferred method for extracting fungal cellulose from mycelia. Submerged fermentation produces desired output faster than traditional basidiocarp culture, producing acceptable levels of ganoderic acids and polysaccharides in 2 to 3 weeks. Mycelial biomass production is faster and more efficient, benefiting nutraceuticals and Lingzhi-based medication. There are two types of fermentation techniques: liquid state (LSF) and solid state (SSF). SSF is more economical and suitable for recycling and agriculture waste [3,5,9].

CHEMICAL CONSTITUENTS

Triterpenoids

G.lucidum rich in triterpenes, with over 140 compounds identified, primarily ganoderic acids. Notably, these compounds impart a bitter taste. Researchers have discovered novel triterpenoids, including ganosporic acid A and lanostane-type triterpenoids, in the spores of *G.lucidum*. Interestingly, spores contain significantly higher concentration of ganoderic acids than other parts of the fungus. Additionally, the triterpene composition of the fruit body varies depending on the geographical location where it is cultivated. The spores also contain triterpenes lactones. Based on their structural characteristics and biological activities, these triterpenoids have been classified into 10 categories [5].

Polysaccharides

Reishi is a rich source of polysaccharides, with over 100 types isolated from its various parts, including the fruiting body, spores and mycelia. These polysaccharides have molecular weights ranging from 400,000 to 1,000,000Da and are considered key contributors to the mushroom's pharmacological activity. The main types of polysaccharides found in *G. lucidum* include (1→3)-beta-D-glucans, hetero polysaccharides and glycoproteins have a linear backbone with

varying degrees of branching and they can exist as water-soluble compounds or as complex with proteins and other polysaccharides. Certain polysaccharides, such as protein-bound polysaccharides and glycoproteins containing fucose, have been discovered to possess bioactive characteristics [5,10].

Proteins

A wide variety of bioactive proteins with possible medical uses have been produced by *Ganoderma* species. A wide variety of bioactive proteins with possible medical uses have been produced by *Ganoderma* species. A protein named Lingzhi-8 (LZ-8) has been isolated from *G. lucidum* mycelium is characterized as an immunomodulatory protein. LZ-8 stimulates immune responses and share structural similarities with the immunoglobulin heavy chain there by demonstrating mitogenic activity. Other bioactive proteins including lectins and antifungal peptides have also been identified in *Ganoderma* species demonstrating its anti-proliferative, antioxidant properties. These findings underscore the potential of *Ganoderma* derived bioactive proteins in medicine and agriculture [7,11].

Steroids and alkaloids

Ganoderma species contain steroids in their fruit bodies and spores, with distinct ring configurations and side chains. They also contain alkaloids, nitrogen containing compounds with complex cyclic structures, with alkaline properties and the ability to form salts with acids. Recent studies have isolated novel alkaloids like ganoine and ganodine from certain *Ganoderma* species, with the biosynthesis involving amino acids [7].

Nucleotides and Nucleosides

Researchers YU and Zhai discovered adenine, adenosine, uracil and uridines in *Ganoderma* mycelia. Uridine and uracil reduced serum aldolase levels in mice with myotonia, while adenosine inhibited platelet aggregation. However, conflicting results exist on human platelet aggregation effects. The unique properties of these compounds remain unclear [11].

EXTRACTION METHODOLOGY

G. lucidum fruiting bodies are the primary source of *Ganoderma lucidum* polysaccharides (GLPs). These polysaccharides are extracted using traditional methods 'like Hot water extraction (HWE), recently ultrasound-assisted extraction (UAE) has been developed as an efficient and environmentally friendly technique with shorter extraction times, lower energy consumption, and improved yields [12]. The extraction of GLP was optimized using UAE and HWE methods, with UAE extracting 2g of dried GLP powder, HWE extracting 120g and both solutions treated with activated carbon and deproteinized [13,14]. Microwave-assisted extraction (MAE) was used to isolate bioactive compounds from Lingzhi powder, involving varying concentrations of ethanol and microwave radiation, then reconstituted in distilled water [15].

IMMUNO MODULATORY ACTIVITIES

Various bioactive compounds isolated from *Ganoderma lucidum*, exhibits immunomodulatory properties. Polysaccharide (GLP's) play a crucial role in regulating immune responses, activating immune-related cells like B and T lymphocytes, dendrite cells, macrophages and natural killer cells. Mechanisms involved are discussed below

Macrophages

The interaction between GLP's and macrophages receptors triggers a series of signaling events, including the activation of protein kinase C (PKC) and cyclic adenosine monophosphate (cAMP). This process increases intracellular calcium levels, facilitating calcium influx from the external environment. The combined effects enhance immune

function by promoting neutrophil phagocytosis, migration and survival. This interaction has significant implications for understanding immune regulation and developing new therapeutic strategies [4,7,16].

T Lymphocytes

G. lucidum extracts has been shown to boost immunological function especially by activating T cells. Extracts containing polysaccharides and proteins like LZ-8, cause human peripheral blood mononuclear cells (PMBS cells) to produce more cytokines such as TNF- α , interleukins and interferon- γ . These extracts also regulate T cell interactions by increasing the expression of ICAM-1 and facilitating cell aggregate formation. LZ-8, a protein isolated from *G. lucidum*, is a potent activator of T cells, stimulating the production of IL-2 and cytokines like IFN-gamma, TNF-alpha and IL-1beta. The immunomodulatory effects of *G. lucidum* extracts depend on the interaction with integrins, particularly CD11a/CD18 [4,5,17,18].

B-Lymphocytes

G. lucidum has been shown to have immunomodulatory effects on B cells, promoting activation, differentiation and antibody production. GLIS, a proteoglycan that was separated from *Ganoderma lucidum* has been demonstrated to elicit a strong reaction in B-lymphocytes encouraging their maturation, proliferation and activation. The expression of particular surface markers, higher production of immunoglobulins and larger cells are characteristics of this process. The direct stimulation of protein kinase C alpha and gamma expression is associated with GLIS mediated B lymphocyte activation. Additionally, by inducing the expression of Blimp-1, a transcription factor involved in B cell development and antibody production, GLP's interacts to certain proteins such as cell membrane Ig and Toll-like receptors. Further research is needed to fully understand the mechanisms of action and potential therapeutic applications of GLI's [2,19,20,21]. [1, 4, 7, 26]

Natural killer cells

Extracts from *G. lucidum*, especially fucose containing glycoprotein fraction and polysaccharides containing (1 \rightarrow 6)- β -D glucan moiety, have been shown to increase the activity of natural killer (NK) cells, which increases the cell's capacity to eliminate cancer. These substances boost the cytotoxic action of NK cells and promote their activity. By reducing the cytokine synthesis in lymphokine-activated killer (LAK) and Cytokine-induced killer cells, which can cause inflammation and tissue damage, GLP's regulate the immune response. This implies that extracts from *G. lucidum* have immunodulatory activates that increase the activity of NK cells and support the mushroom's anti-tumor qualities [4,7,17,22].

Immuno suppressive action

G. lucidum extracts have been found to possess immunosuppressive properties, preventing systemic anaphylaxis reactions and reducing antibody formation against hepatitis B surface antigen. These effects are specific to antigen-specific antibody production without affecting mitogen responsiveness or T-cell subset populations. Ganoderic acids, oleic acids and cyclo-octa-sulfur are active compounds responsible for inhibiting histamine release from mast cells, which contributes to allergic reactions. GLP's have been found to modulate the immune response, particularly in the context of Rheumatoid arthritis (RA). Research suggests that GLP can influence the balance between Th1, Th2, Th17, and T regulator cells, which is crucial in RA pathogenesis [16,17,23,24].

THERAPEUTIC INDEX

Research on the oral toxicity of Reishi mushroom has shown no adverse effects at doses up to 2000 mg/kg body weight per day in rats. Another study found no clinical sign of toxicity or organ lesions in

Wister rats. The lethal dose 50(LD 50) for Reishi spore powder is greater than 10g/kg. These finding suggest Reishi mushroom has a low toxicity index and a wide therapeutic index. Clinical efficacy was noted as low doses, with optimal efficacy achieved at 1800 mg administered three times a day. However, exceeding this dose, particularly above 3000 mg, may compromise platelet aggregation property and increase bleeding risk. The doses used in these studies fall within the safe or low-toxicity range [25-27].

DOSAGE FORMS

G. lucidum is available in various formulations to suit individual needs. These include injectable solutions, oral preparations such as soups, syrups and teas, as well as solid form like tablets, capsules and powdered medicine. Recommended dosages vary depending on the formulation:

Tincture: 10ml three times daily

Tablets: 1g three times daily

Syrup: 4-6ml daily

In certain situations, such as treating mushroom poisoning, a decoction of dried *G. lucidum* may be administered multiple times daily [5].

SIDE EFFECTS

Reishi is generally safe when used as directed, but high doses may cause temporary side effects like nausea, sweating and insomnia. Rare cases of adverse events include liver damage, low blood sugar and esophagitis. To avoid adverse effects, individuals with anticoagulant and antiplatelet medications should avoid concurrent use of reishi supplements. Patients with gastrointestinal cancer should be cautious due to elevated serum tumor markers. Reishi use has been linked to melena, severe abdominal pain and hypoglycemic shock. Patients with a history of hypoglycemia or ant diabetic medications should avoid reishi supplements [28].

TOXICITY

Preclinical studies demonstrate reishi mushroom's exceptional safety profile, with negligible toxicity observed in various animal models. Aqueous extracts, spore powder and freeze-dried fruit body powder showed no adverse effects, even at high doses. Long term toxicity studies in animals revealed no histopathological changes, confirming reishi's low toxicity potential. *G.lucidum* extracts have shown no toxicity and good tolerability in clinical studies as well. However, high doses or combined with other agents or pre-existing medical conditions may increase the toxicity risks. Reported adverse effects, include hepatitis, aplastic anemia, pancytopenia and dermatitis, often linked to prolonged use, high doses or interactions with other medications [28].

Teratogenicity

Zebra fish embryo research shows high reishi concentrations can use developmental abnormalities and toxicity, including increased mortality, tail malformations and growth retardation. This suggests reishi may have teratogenic properties, requiring caution in pregnancy treatment, as limited clinical data exists [29].

ALLERGY

No cases of allergies to reishi are reported instead animal studies demonstrated effectiveness in reducing allergy symptoms in rat models of house dust mite and peanut allergies [28]. [12] Clinical trials suggest reishi extracts may be effective in managing asthma and allergic rhinitis, potentially with fewer side effects than corticosteroids [30,31].

INTERACTIONS

Limited information is available on drug interactions of Reishi. A study has shown that Reishi when given with antibiotics showed an increase in bleeding by synergistic effects [32].

CONCLUSION

The immunomodulatory effects of *G. lucidum* make it an attractive approach for the treatment of various immune-related disorders. Its immunostimulant activity can be beneficial in the treatment of cancer, while its immunosuppressive action can help alleviate autoimmune diseases and reduce inflammation. Furthermore, *G. lucidum* immunomodulatory effects can be exploited to enhance the efficacy of conventional treatments such as chemotherapy and also can be used in the treatment of infectious diseases, by enhancing the immune response and reducing the severity of the diseases. Additional in-depth research is necessary to fully understand the potential of *G. lucidum* in immunomodulation and its therapeutic benefits.

Conflict of interest

The authors declared no conflict of interest.

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