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Review Article

Available chemical constituents and activities of *Ganoderma lucidum* (Lingzhi or red Reishi) utilizing in disease treatment: A mini review

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Abstract

Medicinal mushrooms are known and used to be nutraceuticals for centuries to enhance health benefits and treat several diseases. Among them, *Ganoderma lucidum* (i.e., *G. lucidum*, red Reishi, or Lingzhi) is appreciated as a medicinal mushroom or significant herbal food for treating diseases, extending life, and developing drugs. It is detected in different locations, likely contributed confusing concerning its classification. Concomitantly, it has been utilized as tea, alcoholic drinking, and complementary medicine to bestow numerous health benefits. Thereby, it is essential to identify chemical constituents and provide its activities in health benefits regarding these products. In this mini-review, we try to show the advantages of *G. lucidum* which may encourage its production and usage in disease treatment.

Introduction

As known, Reishi has many species. However, only six types are studied (based on the color, i.e., black, white, purple, blue, yellow, and red Reishi) to provide essential health advantages (Table 1).[1] Especially, black and red Reishi are much employed in the global market to be a complementary health medicine because they have manifested appreciable effects in improving health. Red Reishi (*Ganoderma lucidum*) is regarded to be superior to black Reishi (*Ganoderma sinensis*) because of its higher polysaccharide content. However, black Reishi is still considered to be a moderate herbal cordial.[1]

Specifically, *Ganoderma Lucidum* (red Reishi) was concerned to be a well-known herb for enhancing healthy benefits and the most significant herbal food in Asia (i.e., China, Korea, Japan, etc), especially in Chinese traditional medicine. In China, it is believed to be a perfect remedy to treat many different illnesses or diseases (i.e., hepatitis, hypertension, cancer, chronic bronchitis, etc) (Figure 1).[2-4] Mostly, its benefits are probably built upon the studied laboratory and clinical data. Concomitantly, there are a few conducted clinical studies to be still doubtful. Nevertheless, from laboratory studies with the expected findings, *G. lucidum* has several potential benefits for patients.

Thereby, it is important to identify the available chemical constituents and activities that can be applied in drug development after the reliability is proved. In this mini-review, we try to show the advantages of *G. lucidum* which may encourage its production and usage in disease treatment.

Chemical constituents of *Ganoderma lucidum*

The major extract components of *G. lucidum* contain 68.9% of positive material, 7.3% of protein, 11.1% of glucose, and 10.2% of metals (i.e., Mg, K, and Ca).[5,6] Nonetheless, its chemical constituents depend on various conditions (i.e., origin, classifications, extracting, and planting processes) to attain qualitative and quantitative differences of these products.[7] Generally, *G. lucidum* contains numerous active chemical constituents which belong to polysaccharides, triterpenoids, proteins, nucleotides, steroids, sterols, fatty acids, peptides, etc.[8] Two important active constituents, polysaccharides, and triterpenoids, are mostly considered in recent researches.

Polysaccharides are sugar molecules with long connected chains of glycosidic bonds, which may probably prevent cancer progression.[9] Mostly, its possible structures are heteropolymers with a high molecular weight (Figure 2A).[10] Also, for various branching conformations of each polysaccharide (in *G. lucidum*), which can offer varied responses and effects[10] (especially for the soluble

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Table 1. Various Reishi types

Common color	Possible taste	Common function
Black	Salty	Influencing to functions of lung.
White	Hot	Using to shield kidney.
Purple	Sweet	Improving functions of eyes junctions and supporting complexion.
Blue	Sour	Improving sight for eyes and functions of liver.
Yellow	Sweet	Enhancing functions of spleen.
Red	Bitter	Supporting/improving for memory and internal organs.

polysaccharides). Besides, *G. lucidum* also includes an insoluble polysaccharide like chitin, causing in large an indigestible part and a physical stiffness of this mushroom.

In addition to the above-mentioned polysaccharides, triterpenoids are the main active compounds related to the various health advantages (Figure 1B, C).[5,6] Triterpenoids are terpenes with six isoprene units that probably create different structures like a ring or linear chains. Specifically, chemical structures of possible triterpenoids are isolated from *G. lucidum* consisting of ganoderic acid (Figure 2B) and ganoderiol (Figure 2C) constituents. It means that these triterpenoids are various two linear and four cyclic isoprenes. Moreover, triterpenoids have low molecular weight to probably aim cells when interacting directly with molecular targets (i.e., cycle tuning of the cell, apoptosis, and angiogenesis).[11,12] At the same time, they also demonstrate anti-inflammatory activities like several non-steroidal compounds such as indomethacin.[13,14]

Furthermore, other necessary active compounds of *G. lucidum* could probably be used as pharmacological agents. For instance, nucleotides/nucleosides/steroids, platelet inhibitors, proteoglycans/glycans, hypoglycemic activities, peptidoglycans, blood pressure stability, cytotoxic polysaccharides, etc.[5,6] Besides, different oils, vitamins, inorganic ions (i.e., Zn, Mg, Ca, Fe, Cu, Ge), and coumarin-glycosides were also found in *G. lucidum*.[7,8] In particular, an organic compound (bis-β-carboxyethyl-germanium-sesquioxide, or GE-132) was recently found in *G. lucidum*, suggesting that this organic compound could reduce γ-interferon to make macrophages active and affect malignancies and rheumatoid arthritis.[15] Overall, *G. lucidum* is a frequently used mushroom with a long history in Asia (e.g., China, Korea, Japan), which contains lots of chemical compounds with pharmacological activities that would probably serve in treating various diseases.

Activities of *Ganoderma lucidum* in disease treatments

As known, *G. lucidum* (red Reishi, or Lingzhi) is one of the most widely-utilized medicinal mushrooms (or herbal food) in Chinese traditional medicine, which can treat different illnesses and diseases such as hypertension, migraine, headache, arthritis, bronchitis, asthma, gastritis, anorexia, hemorrhoids, hypercholesterolemia, dysmenorrhea, nephritis, hepatitis, constipation, leukopenia, traumatic wounds, and cardiovascular problems.[2] For instance, *G. lucidum* was appreciated due to memory improvement and age-related obliviousness; However, several therapeutic reports of this medicinal mushroom may be overstated. This is truly important to be illumined; consecutively updated research has likely indicated its active effects and drug development in the future.

A reduction of cognitive and daily function is occurred continuously in Alzheimer's and Parkinson's diseases due to the loss of functions related to neurons and synapses.[16] Thus, effective treatments of these diseases have been explored. Several researchers have suggested that non-steroidal anti-inflammatory drugs could slow the progress of these diseases during a long-time ingestion.[17-21] Besides, *G. lucidum* polysaccharides prevent neural injury due to reoxygenation/hypoxia in vitro.[22] The oil from *G. lucidum* spores could also shield dopaminergic neurons and improve involving deficits in rats with Parkinson's disease.[23] A 50 years old patient with Parkinson's disease for 5 years was treated with Lingzhi for three months, resulting in a notable increase in mindfulness after the treatment.[24] Thereby, this patient had small positive changes in some affective behaviors. Concomitantly, Huang et al studied both polysaccharides and water extract of *G. lucidum* to reduce cognition deficits and advance hippocampal neurogenesis in transgenic mice with Alzheimer's disease.[25] Moreover, Lucca have been treating normal aging people for 37 years (648 women, 1417 men),[26] indicating that non-steroidal anti-inflammatory drugs are utilized to reduce the incidence of Alzheimer's disease probably. This can approve the previous reports where *G. lucidum* was appreciated due to the improvements in memory and age-related obliviousness. Also, the active mechanism of inflammatory drugs is grounded on their prevention capability to prostaglandins' biosynthesis.

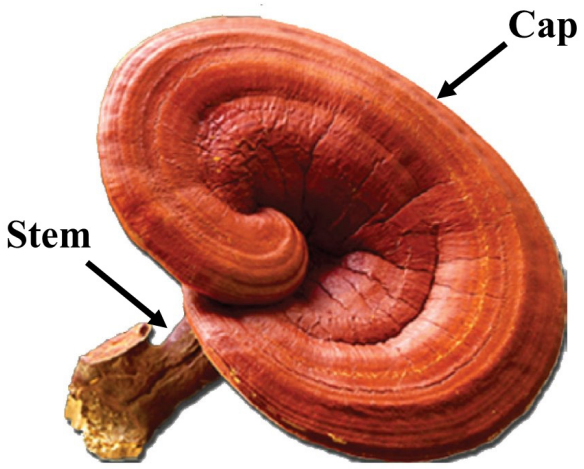

Figure 1. Illustration body of *Ganoderma lucidum*.

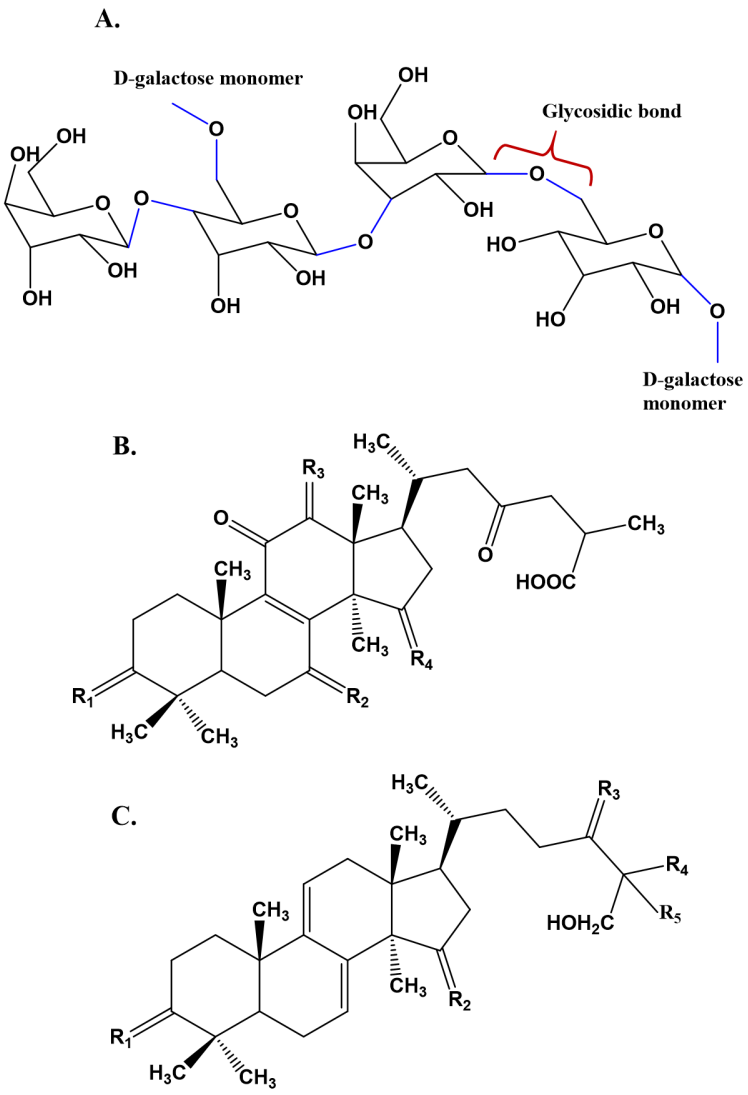

Figure 2. Chemical structures of possible polysaccharides (A) and triterpenoids (B, C) isolated from *Ganoderma lucidum* [constituents of ganoderic acid (B) and ganoderiol (C)].

Thereby, the future Alzheimer's disease treatment strategies can use non-steroidal anti-inflammatory drugs through the incorporation of disease-modifying agents and acetylcholinesterase inhibitors,[27,28] as well as *G. lucidum* triterpenoids also probably become the anti-inflammatory drugs with high effectiveness in the future. Besides, Yu et al[29] also conducted a study on the use of *G. lucidum* triterpenoids in vitro to improve cognitive impairment, inhibit apoptosis, and reduce neuronal damage in cells and tissues of mice with Alzheimer's disease. However, in another study, spore powder of *G. lucidum* was explored to treat patients with Alzheimer's disease for 6 weeks. This resulted in no effectiveness of the spore powder of G. lucidum in this disease treatment, probably due to a relatively short-term intervention.[30] Further clinical trials with large sample size and longer treatment duration are required.

For inflammatory diseases, inflammation can cause the pathogenesis of various diseases.[31,32] Moreover, inflammatory responses also contribute to a host shielding against microbial infection. However, inflammatory mediators are produced excessively or uncontrollably, which can cause various chronic diseases with inflammatory metabolisms (e.g., type 2 diabetes, atherosclerosis, colitis, gout, Alzheimer's disease).[33-36] Therefore, the inflammatory response is a strategy for treating disorders. As known, *G. lucidum* has been widely utilized to treat various diseases (e.g., diabetes, nephritis, and chronic hepatitis),[37-40] as well as protect kidney and liver[41] and act against cancer, hyperlipidemia, and hypertensive disorders.[42-44] In particular, triterpenoids are major components of *G. lucidum*, which also manifest anti-tumor, anti-inflammatory, and antioxidant properties.[13,14] However, the molecular mechanisms underlying triterpenoid inhibition of lipopolysaccharide-induced inflammatory responses and acute liver injury are unknown. Nonetheless, it was not still yet explained clearly in the mechanisms of triterpenoids inhibited

lipopolysaccharide to inflammatory responses and liver damages. Especially, Hu et al[45] identified that the use of ethanol extract and triterpenoids from *G. lucidum* could inhibit inflammatory response with lipopolysaccharide, as well as ganodermanontriol, which inhibits liver damage with lipopolysaccharide. Concomitantly, the aforementioned inhibiting mechanisms were found in this study. Thereby, *G. lucidum* triterpenoids could be potential therapeutic agents for inflammatory diseases.

As known, *G. lucidum* has various bioactivities suchlike anti-aging, anti-tumor, anti-diabetes, immunomodulation, etc.[9] It is used to be a potential anti-cancer drug. However, it should be truly studied further to quantify its effects, such as specific tumor disease treatments involving prostate adenocarcinoma and other cancers.[46] Thereby, Barbieri et al[47] conducted a study comparing the treatment influences of curcumin (*Curcuma longa*, or Indian spice turmeric) and *G. lucidum* extracts at different concentrations in order to evaluate their influences on cell viability and pro-inflammatory cytokine secretion. The results showed that a mixture of polyphenols and carbohydrate-flavonoid complexes obtained from *G. lucidum* extract could be well utilized in anti-inflammatory and anti-cancer treatments against breast and melanin cancer. Thus, the use of *G. lucidum* extracts may open a new cancer treatment tool during breast cancer and melanin cancer chemotherapies, especially regarding its anti-metastatic and anti-inflammatory actions. Furthermore, formaldehyde exposure is almost common because of the inhalation, which is mainly metabolized by the liver at the exposure to formaldehyde via any route. As such, this metabolism will gravely affect the liver and cause hepatotoxicity at certain concentrations. In order to prevent the deleterious influence, Oluwafemi Adetuyi et al[48] used *G. lucidum* triterpenoids to improve the above-mentioned toxicity markers of the liver in vivo. Their study aimed to evaluate the protective effect of *G. lucidum* triterpenoids on the rats' livers with formaldehyde exposure.

Obesity, a metabolic disorder with surplus lipid deposition which leads to an increase in the mass of adipose tissues based on the size (hypertrophy) or number (hyperplasia) of adipocytes.[49,50] Especially, adipocyte hypertrophy can disarray adipocyte hormone and increase inflammatory cytokines, impacting insulin resistance, chronic inflammation, and other problems.[51,52] Also, obesity is the cause of various metabolic disorders, especially type 2 diabetes, hepatic steatosis, atherosclerosis, and cancer.[53,54] Besides, 3% extract powder of *G. lucidum* could improve insulin resistance, dyslipidemia, and type 2 diabetes in mice 55, which leads to improving glucose metabolism and insulin sensitivity. Thereby, these indicate that *G. lucidum* can be applied to prevent obesity well and improve insulin resistance. Moreover, for type 2 diabetes mellitus, it is known to be one of chronic metabolic diseases basing on hyperglycemia, inflammation, insulin resistance, and mostly affects lipid/glucose/protein metabolism.[56,57] This disease involves a combination of genetic and environmental relations (i.e., gut microbiota, lifestyle, diet, and obesity).[58] For instance, Seto et al[59] showed that water extracts of *G. lucidum* could contribute to reduction of serum glucose and offer beneficial influences in treating type 2 diabetes mellitus. In particular, polysaccharides, ganoderic acid, and adenosine are considered majority bioactive compounds in *G. lucidum*, especially the polysaccharides which possess antioxidant, anti-tumor, hypoglycemic and immunomodulatory activities.[60,61] Besides, *G. lucidum* polysaccharides could also decrease obesity by controlling the gut microbiota and acting to be prebiotics.[62] As such, the gut microbiota may be concerned to be a potential target for *G. lucidum* polysaccharides to improve related diseases, such as type 2 diabetes mellitus. Gut microbiota dysbiosis can result in disorders of endogenous metabolites along with other damages, so the polysaccharides that can modify the gut microbiota could be a new target for treating diseases like type 2 diabetes mellitus. Chen et al[63] conducted a study to investigate the changes of gut microbiota composition through the use of *G. lucidum* polysaccharides. Proton nuclear magnetic resonance (^{1}H-NMR) was applied to analyze the metabolic changes of this study. At the same time, the relationship between the gut microbiota changes and metabolites with *G. lucidum* polysaccharides were also analyzed and explained based on the possible mechanisms of *G. lucidum* polysaccharides in decreasing type 2 diabetes mellitus from both fecal metabolites and the gut microbiome. As a result, the use of *G. lucidum* polysaccharides rapidly reduced the blood insulin and glucose levels; besides, it decreased lots of harmful bacteria (i.e., *Ruminococcus, Aerococcus, Proteus,* and *Corynebacterium*) as well as raised the level of *Dehalobacterium, Parabacteroides, Blautia*, and *Bacteroides*. In addition, *G. lucidum* polysaccharides could recover the metabolisms in carbohydrates and disturb amino acids, inflammatory substances, and nucleic acid in type 2 diabetes mellitus rats. As such, the disordered gut microbiota of type 2 diabetes mellitus rats could be recovered via the use of *G. lucidum* polysaccharides. These polysaccharides could reform the host metabolites to perform their anti-diabetic effects.

In addition, antibiotics are used by poultry industry to promote the growth and prevent infectious disease. However, use of alternative substances to antibiotics in poultry industry such as prebiotics, probiotics, herbs, and plant extracts have been considered.[64-66] Among them, *G. lucidum* possesses lots of pharmacological functions, such as anti-atherosclerotic, anti-tumor, antioxidant, and antiviral properties,[9] as well as being a potent immune regulator (i.e., polysaccharides – major immune active components).[67,68] *G. lucidum* polysaccharides could form cytokine productions and rouse proliferation of T-lymphocyte and splenocyte.[69,70]

Besides, supplementation of *G. lucidum* also enhances immunity and growth performance in the broilers,[71-74] as well as high mortality and poor growth performance in the broilers, which can occur in a bad intestinal microbial environment.[75] Moreover, Chen et al[76] used *G. lucidum* extracts to determine the fecal microbiota, growth performance, and transcriptome in the bursa of Fabricius – a lymphoid organ of broilers. Thereby, it indicated that *G. lucidum* extracts are a possible replacement for antibiotics in the aforementioned poultry industry. Concomitantly, exposure of birds can be a reason to cause disease agents as well as natural infection. The immune system will be disordered and reduce the growth performance of the bird, although the clinical disease cannot probably happen via every exposure. Moreover, outbreaks of disease can still occur with a poor immune system. In infectious bursal disease, the chickens will be affected, and their health and immunity compromised by the immunosuppression.[77] Besides, this disease can be named Gumboro disease – an infectious disease of chickens, which induced high death in chicks and those vaccinated.[77] Thereby, it is truly important to protect the avian immune system to increase the immunity of chickens as well as improving their health, especially for the bursa of Fabricius – a target organ for virus infection of infectious bursal disease. To formulate feeds, nutritionists almost concern the immunity enhancement and stress management.[78,79] In particular, *G. lucidum* polysaccharides provide several necessary benefits such as faster growth, improved resistance and health, and safeguard from pathogens.[80] In addition to enhancing their growth and maintaining their health, the use of *G. lucidum* can decrease residual effects and resistance associated with drugs or antibiotics in the poultry (eggs and meat). Guo et al. surveyed the benefits of using *G. lucidum* in poultry[80]; however, information on its effect in chickens to improve the health and immune response are still limited, and further studies are needed.

Conclusion

In conclusion, *G. lucidum* is one of the superior medicinal mushrooms due to its obvious medical effects and the absence of toxins and adverse by-effects resulting from the consumption. Besides, the use of natural products is being common and considered to prevent or improve diseases. However, in order to attain economic and medicinal benefits from *G. lucidum*, several challenges should be addressed: (i) providing specifically in *G. lucidum* taxonomy; (ii) determining further the active constituents of *G. lucidum*; (iii) offering beneficial (safe) dose ranges of the active constituents in each disease; and (iv) performing necessary clinical trials to prove its benefits against infectious and chronic diseases.

Conflict of Interest

The authors declare that they have no competing interests.

Ethical Approval

Not applicable.

Authors' Contribution

All authors have contributed to the writing of the manuscript. All authors read and approved the final manuscript.

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