SCIENCE

REISHI MUSHROOM

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GANODERMA LUCIDUM

The reishi mushroom *Ganoderma lucidum* is a white-rot, wood-decaying fungus that is classified within the family Ganodermaceae of Polyporales which show hard fruiting bodies [1, 2]. *Ganoderma lucidum* is a medicinal mushroom which has been widely used in China, where it is called Ling Zhi, and in Japan where it is referred to as reishi or mannentake. This mushroom has been used in each of these regions for hundreds of years for its many health-promoting characteristics.

Presented here is an overview of the medicinal properties of the reishi mushroom as it is described in current scientific literature. Among these benefits are increased life span, strengthened immune response, enhanced cancer-fighting capacities, and improved renal health [2, 3]. There is also compelling evidence showing that *G. lucidum* is effective in treating diabetes and complications related to high cholesterol. Perhaps the most pharmacologically active compounds yet extracted from *G. lucidum* are triterpenoids and polysaccharides, each of which will be discussed in detail in this report. It is shown here that reishi has many properties that improve quality of life and many more are yet to be discovered.

ACTIVE SUBSTANCES

Among the most biologically active compounds found in *G. lucidum* are the triterpenoids and polysaccharides [1]. Triterpenoids extracted from *G. lucidum* are reported to be responsible for many of the pharmaceutical properties of the fungus. Thus far, hundreds of triterpenoids have been isolated in *G. lucidum* and many more are likely to be discovered in the future. Two major types of triterpenoids are ganoderic acids (C30) and lucidenic acids (C27), with the total triterpenoid content in *G. lucidum* ranging from 0.6 to 11 mg/g of dry powder. These triterpenoids were reported to mitigate diabetes and regulate inflammatory pathways in cell culture. Triterpenoids from *G. lucidum* also possess significant chemo-therapeutic potential and exhibit cytotoxic effects on colon carcinoma cells [4]. Moreover, it has been reported that activities that affect tumor growth and metastasis in a triterpenoid fraction of *G. lucidum* containing ganoderic acid F were due mainly to inhibition of tumor-induced angiogenesis. For example, in intrasplenic Lewis lung carcinoma-implanted mice, the triterpenoid fraction of the fruiting bodies of *G. lucidum* inhibited primary solid tumor growth in the spleen and forestalled liver metastasis and secondary metastatic tumor growth in the liver. Other studies report that different triterpenoids of *G. lucidum* have strong anti-HIV-1 protease activity and that triterpenes such as ganodermic acids C and D inhibit histamine release [1].

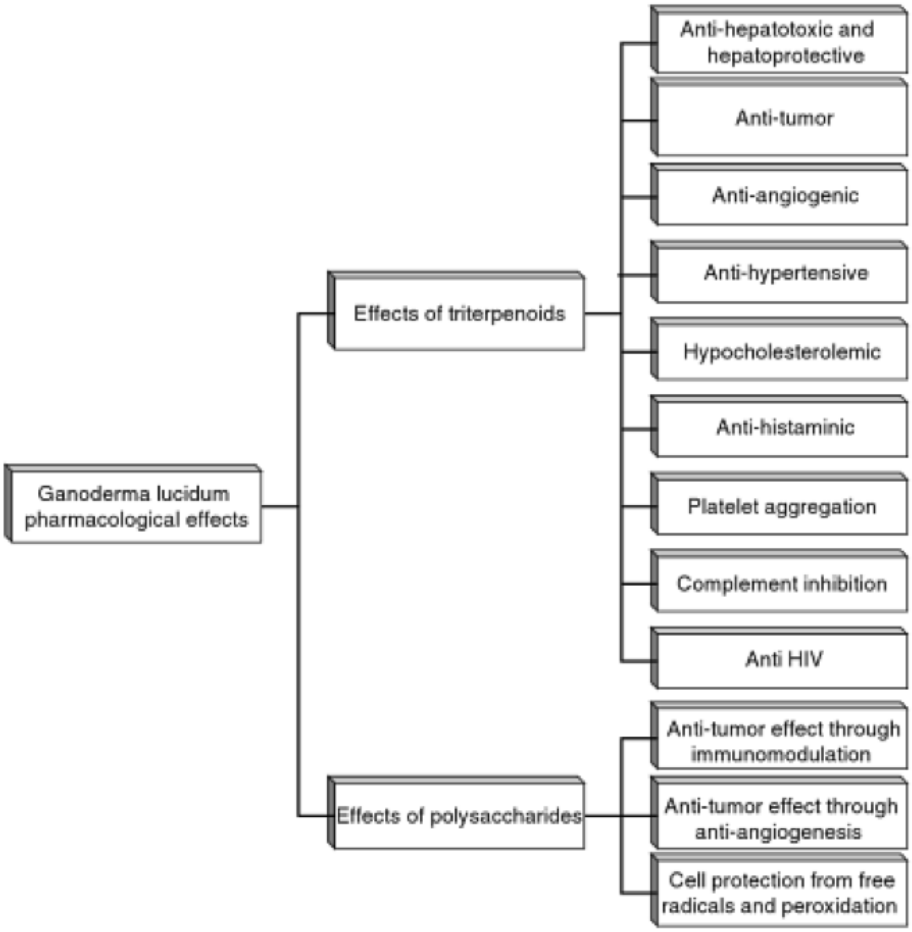

Figure 1.

Main pharmacological effects of Ganoderma lucidum (ref. 1).

Polysaccharides isolated from *G. lucidum* stimulate release of cytokines and activate immune cells. Among the polysaccharides implicated in this activity are β-D-glucans which are known to have anti-tumor effects [3, 5]. Figure 1 shows the main pharmacological effects of *G. lucidum* triterpenoids and polysaccharides.

Other active compounds extracted from *G. lucidum* are adenosine which inhibits platelet aggregation, lectins that affect mitosis, and various alkaloids, fatty acids, vitamins, and essential minerals [1].

ANTIOXIDANT PROPERTIES AND TREATMENT OF DIABETES

Previous studies have reported a protective effect of *G. lucidum* polysaccharides on pancreatic islets that were damaged by alloxan, an oxygenated pyrimidine derivative. This particular effect was dose-dependent and manifest as increased serum insulin and reduced serum glucose in alloxan-induced diabetic mice that were pretreated intragastrically for 10 days. It was found that homogenates of pancreas had higher lipid peroxidation products in alloxan-treated mice than in animals treated with *G. lucidum* polysaccharides[1]. Thus, it is hypothesized that scavenging of free radicals by *G. lucidum* polysaccharide protects pancreatic islets from oxidative stress.

Jia et al. [6] demonstrated in their study with diabetic rats that orally administrated *G. lucidum* ameliorates hyperglycemia and may normalize plasma and liver that was compromised by oxidative damage. Such promising antioxidant properties and diabetes-mitigation effects may open new avenues in the treatment of diabetes and its complications.

In a separate study, a clinical trial was conducted to test the combined effects of orally administered capsules of *G. lucidum* and regular hypoglycemia drugs on human patients suffering from type 2 diabetes mellitus. After two months of treatment, the formulation-treated patients showed a significant improvement in clinical symptoms compared to controls who only received the regular drugs for hypoglycemia. This result suggests that extract of *G. lucidum* acts synergistically with medications already approved for treatment of type 2 diabetes [1].

CHOLESTEROL-LOWERING PROPERTIES

The components in *G. lucidum* that may lower cholesterol are not well characterized. However, there are many candidate compounds isolated in previous studies and may include ganoderan-type glucans, hetero-ß-glucans, glucan-protein complexes (e.g., xyloglucans, uronic acid-ß-glucans), other fibers, lectins, terpenoid triterpenes, ergostane sterols, and highly oxygenated ganoderic acid-type, lanostanoid triterpenes. *Ganoderma lucidum* fibrous components could affect cholesterol absorption and bile acid recycling, whereas lipophilic components could affect cholesterol synthesis[7].

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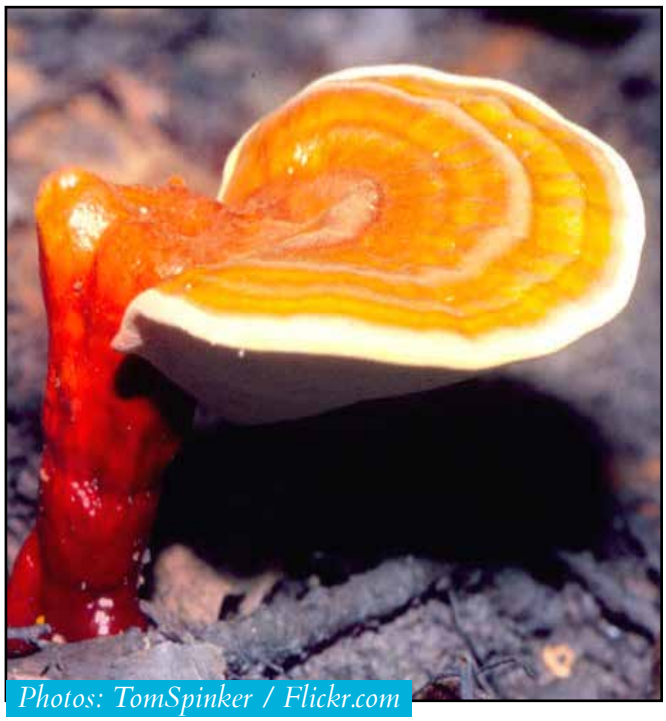
Berger et al.[7] tested the effects of *G. lucidum* on cholesterol metabolism in hepatic T9A4 human cells, a hamster small animal model, and a larger minipig animal model that has a different lipoprotein cholesterol distribution than the hamster model. Animal models were fed cholesterol-containing diets. The fact that the aqueous phase from *G. lucidum* was ineffective at inhibiting cholesterol synthesis suggests that hydrophilic molecules such as glucans and fiber in *G. lucidum* do not affect conversion of acetate to cholesterol. Such molecules may however affect cholesterol absorption and bile acid recycling. Hamsters were fed a low-cholesterol chow-based diet with no added exogenous cholesterol or saturated fat. Under these conditions, there was not sufficient cholesterol to redistribute cholesterol from the HDL to LDL pool. This is why in hamsters, 5% *G. lucidum* and lovastatin, a statin used to lower cholesterol, together reduced D18 total cholesterol and HDL, but not LDL. Using the same type of diet, lovastatin was similarly found to preferentially reduce HDL in hamsters; and only when dietary saturated fat was added, were both LDL and HDL reduced. Another factor contributing to a weak effect in hamsters, and the total lack of effect in minipigs, may be that the dose of lovastatin was insufficient to induce a reduction in cholesterols.

In summary, *G. lucidum* was found to have cholesterol lowering potential in vitro, ex-vitro, and in two animal models, with some differences between the two animal models. It is possible that oxygenated lanosterol derivatives in *G. lucidum* contributed to this cholesterol lowering by decreasing cholesterol synthesis [7].

ANTI-CANCER EFFECTS

Previous studies showed that *G. lucidum* inhibits proliferation and apoptosis in leukemia, lymphoma, and myeloma cells. Moreover, the inhibition of acute myoloblastic leukemia cells was associated with cell cycle arrest and apoptosis, whereas the inhibition of lymphoma was mediated by the upregulation of expression. *Ganoderma lucidum* inhibits distinct signaling pathways in different cancer cells. Anti-cancer effects of *G. lucidum* are associated with triterpenoids, polysaccharides, or immuno-modulatory proteins, and operate via inhibition of DNA polymerase, inhibition of post-translational modification of the Ras oncoprotein, or the stimulation of cytokine production [8].

Calviño et al. [5] tested the effects of *G. lucidum* fractions on NB4 human leukemia cells. Three different extracts were obtained from *G. lucidum* including two aqueous extracts and one methanol extract. The aqueous extracts slightly reduced cell viability and induced DNA fragmentation in NB4 cells. Methanol-extracted, semi-purified fraction at dilutions down to 15% or 40% of the initial fraction concentration significantly reduced the viability of these leukemia cells via induction of DNA fragmentation and induction of apoptosis. Calviño and colleagues also showed that NB4 cells treated with the methanol extract avoided apoptosis by reducing p53 and Bcl-2 and, concomitantly, by increasing the levels of the protein Bax



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that promotes apoptosis. Moreover, NB4 cells suffer a reduction in Erk and pErk2 which suggests a role for this kinase in cell death induced by *G. lucidum*. Several observations show that activation of Akt may induce anti-apoptotic effects in culture. In conclusion, Calviño et al. showed that induction of apoptosis and alterations in signal transduction kinases Akt and Erk are produced by active fractions of *G. lucidum* on human leukemia cells. These data are of particular relevance to the antitumor properties of *G. lucidum*.
Ruan et al. [4] used a bioassay-guided approach to identify *G. lucidum* fractions that are cytotoxic and induce apoptosis in cultured human colon carcinoma cells (Caco-2). Ruan and coworkers are the first research group to demonstrate induction of apoptosis from specific triterpenoids in cultured human colon carcinoma Caco-2 cells, a finding that may advance understanding of the diverse pharmaceutical properties of *G. lucidum* triterpenoids as chemo-preventative agents.

Clinical studies also show that *G. lucidum* preparations exert synergistic therapeutic effects when used in conjugation with radiation and chemotherapy, and in particular reduce severity of undesirable side effects of treatment. The therapeutic efficacy of *G. lucidum* on cancer patients is mediated by at least three processes: (a) immunomodulation of effector cells that target tumors; (b) promotion of anti-tumor cytokine production and activity; and (c) attenuation of angiogenesis in nascent tumors. *Ganoderma lucidum* abates or eliminates the toxicity caused by other therapies via stimulation of hematopoiesis and amelioration of damage caused by radiation and chemotherapy. In summary, the effect of *G. lucidum* on radiation and chemotherapy is compensatory in that the deleterious effects of the two therapies are offset by enabling the immune system to resist malign factors caused by cancer or traditional cancer therapies [1].

IMMUNE DEFENSE

Ha [9] studied the effect of ingestion of *G. lucidum* mycelium on gut-specific humoral immunity in mice. The specific antibody response was assessed using cholera toxin (CT) as an oral immunogen. It is well documented that ingestion of CT is not only able to generate an intestinal secretory immunoglobulin A (sIgA) response, but that it also induces a strong serum IgG antibody response. sIgA plays an important role in host defense by preventing bacteria and toxins from invading the body through wet mucosae. Thus, depression of the gut-specific sIgA antibody response may weaken host defense against opportunistic mucosal antigens. Ha estimated levels of serum anti-CT IgG and levels of anti-CT IgA found in intestinal luminal contents, fecal pellets, and serum. *Ganoderma lucidum* mycelium depresses mucosal IgA responses when taken orally, a finding that suggests that ingestion of *G. lucidum* mycelium may compromise mucosal immune defense.

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Kuo et al. [3] found in their study that *G. lucidum* mycelia stimulated moderate levels of the proinflammatory cytokines TNF-α, IL-6, and IFN-γ release in human whole blood. They demonstrated that the dried mycelia of *G. lucidum* also induced nuclear factor (NF)-κB activation in murine RAW264.7 macrophage cell line, indicating that NF-κB activation is one of the most important signal pathways. Proinflammatory cytokines can bind to their respective receptors and induce iNOS, which is involved in the immune response, and expression via activation of NF-κB. However, they have found that the induction of NF-κB does not lead to an increase in NO production. It has been found that the expression of the iNOS gene can be regulated at different levels; therefore, *G. lucidum* mycelia may exert adverse post-transcriptional effects on iNOS gene expression.

CONCLUSIONS

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The reishi mushroom *G. lucidum* is a medicinal fungus that has been used hundreds of years for its biological activity. Two of the most important substances of *G. lucidum* are triterpenoids and polysaccharides. Among many beneficial effects, triterpenoids have been shown to reduce toxicity of the liver, abate the growth of cancerous tumors, lower cholesterol, and ameliorate complications related to diabetes mellitus. Polysaccharides of *G. lucidum* also have cancer-fighting properties owing primarily to modulation of the immune system and cellular protection from free radicals.

Research with *G. lucidum* on diabetic mice indicates that free radical scavenging of polysaccharides protects pancreatic islets from oxidative stress. This finding is significant because it suggests that *G. lucidum* may have therapeutic benefits in the treatment of type 2 diabetes.

Ganoderma lucidum also inhibits cancer proliferation and promotes apoptosis of leukemia, lymphoma, and myeloma cells. Clinical studies have also demonstrated that preparations of the fungus exert synergistic therapeutic effects when used in conjugation with radiation and chemotherapy, thereby reducing harmful side effects. The fungus abates or eliminates the toxicity caused by other therapies by stimulating hematopoiesis and repairing damage caused by radiation and chemotherapy.

Results from an investigation of the effects of *G. lucidum* on gut-specific humoral immunity suggest that ingestion of *G. lucidum* mycelia may compromise mucosal immune defense. In addition, *G. lucidum* mycelia may stimulate moderate levels of the proinflammatory cytokines

DISCLAIMER

Statements throughout this publication have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease process.

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