Therapeutical Properties of Bioactive Compounds Extracted from *Ganoderma lucidum* Species on Acute and Chronic Diseases

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Abstract

Ganoderma lucidum or Reishi is a medicinal mushroom of significant importance that is being used for the prevention and treatment of various diseases, due to its numerous pharmacological and therapeutic properties. The Ganodermataceae family is diverse, but the focus is on the lucidum species because of its specific biologically active macromolecules such as polysaccharides, triterpenoids, steroids, phenolic compounds, lactones, and fatty acids that were isolated from the mycelia and fruiting bodies. Ganoderma lucidum species have many benefits over the immune system (promoting health) and properties such as: anti-tumoral, anti-inflammatory, anti-allergic, anti-viral, anti-bacterial and antioxidant. Based on the literature, triterpenoids and polysaccharides are the most abundant active compounds that possess anti-diabetic, hepatoprotective, cytotoxic and anti-hypertensive effects. A review of the literature showed that there are very few papers that studied semisolid dosage forms preparations based of Ganoderma lucidum extract to have been used on damaged skin and skin diseases, neither have there been enough studies on its anti-aging properties.

Keywords: Ganoderma lucidum, polysaccharides, anti-inflammatory, anti-tumoral, antioxidant

Introduction

Currently, medicine based on plant extracts or other medicinal herbs is in great demand by the population, since most are looking for a way to live healthy or looking for alternative medicine based on herbal extracts. Still, fungus extracts are in great

demand, especially those from Ganodermataceae family due to its promotions over the years, which shows through statements and studies that is still a wonder-mushroom [1]. It is known that medicinal mushrooms have been used in over the years to treat many disorders, for promoting health and longevity in Asian countries. Among Eastern population, the name Reishi or Mannentake is commonly used by Japanese people and is the symbol of good health. In Chinese and Korea, it is known as LingZhi and represents a combination of spiritual potency and essence of immortality [2]. *Ganoderma lucidum* (*G. lucidum*) also known as Reishi and LingZhi, is the most known medicinal macrofungal species, with a long history in promoting health in different countries, especially in China and Japan. The medicinal activity of *G. lucidum* fungus is localized, for example, inhibiting the activity of the enzyme cyclooxygenase in the anti-inflammatory response [3] and proliferation of the immune system by inhibiting its activity in cases of overstimulation [4].

Various formulations and products based on this fungus species are now available on the market. These are extracted from different parts of the fungus: mycelium, spores, and fruiting body. Most products are in the form of tea, tonics and coffee, powders, and encapsulated food supplements [4].

Botanical description

G. lucidum is a kidney-shaped mushroom [4] with glossy surface and woody texture [5]. *Ganoderma* genus can be found all over the world, mainly in tropical and subtropical climates [6], but different characteristics of the fruiting body, soil specificity and geographical origin are used to identify individual species of this medicinal fungus. The Ganodermataceae family consists of many fungi from the *Ganoderma* genus [6] and the taxonomy classification of this species is related into Table 1.

This species grows on multiple hosts, on living trees or stumps of oak and is growing rarely on coniferous trees [2]. In Europe, specially in Romania, it can be found in the Sub Carpati mountain chain region. The medicinal mushroom, *Ganoderma lucidum*, taken in work, weighs 0.25 grams, is 9-10 cm wide and 9-10 cm long and is quite bulky, has a dark reddish shiny surface and a woody texture, see Fig. 1.

Table 1 Taxonomy classification of species G. lucidum [6, 7]

Kingdom	**Fungi**
Phylum	Basidiomycota
Class	Basidiomycetes
Sub-class	Homobasidiomycetes
Family	Ganodermataceae
Genus	*Ganoderma*
Species	*lucidum*

Fig. 1 Ganoderma lucidum (personal archive)

Polysacharides and Triterpenes of *Ganoderma lucidum* extract

Polysaccharides and triterpenes are the most abundant biocomponents in the composition of *G. lucidum* [1]. The most important functions of polysaccharides are reported by numerous studies, and there are: normalizing blood glucose levels, restoring the enzymatic balance in the intestinal tract due to the probiotic effect [8], reducing damage through antioxidant effect on free radicals formed in oxidation reactions. Anti-diabetic and anti-tumor effects have also been reported for both the polysaccharide and triterpenoid components [9]. In addition to these effects, triterpenoids have an immunomodulatory effect, proven by in vivo and in vitro studies. Beside these two major bioactive compounds, the mushroom contains in significant quantities proteins, lipids, carbohydrates and sodium chloride [10].

Triderpenoids from the *G. lucidum* mushroom

There are many types of triterpenoid compounds that have been isolated from the *G. lucidum* mushroom, the most common are ganodermic, lucidenic, ganoderals, ganoderols and applanoxidic acids. The most characteristic acids in the composition are ganodermic acid F (Fig. 2), lucidenic acid D1 (Fig. 3), ganoderal A (Fig. 4), ganoderol B (Fig. 5) and applanoxidic acid A (Fig. 6) [9].

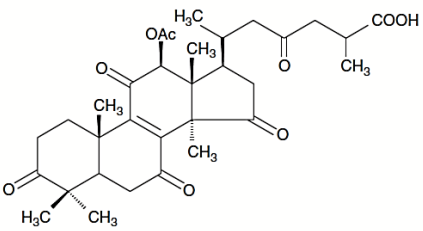

Fig. 2 Ganodermic acid F

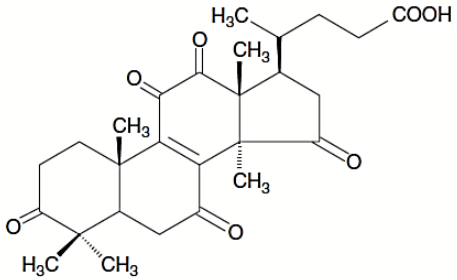

Fig. 3 Lucidenic acid D1

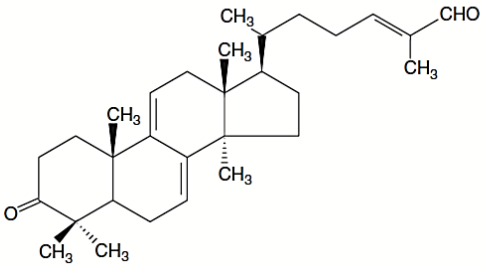

Fig. 4 Ganoderal A

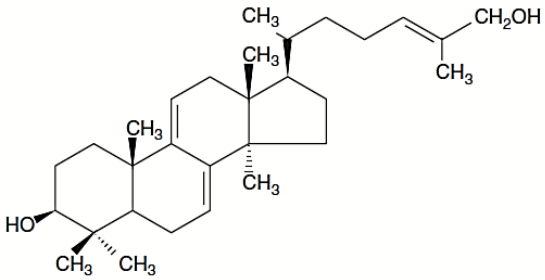

Fig. 5 Ganoderol B

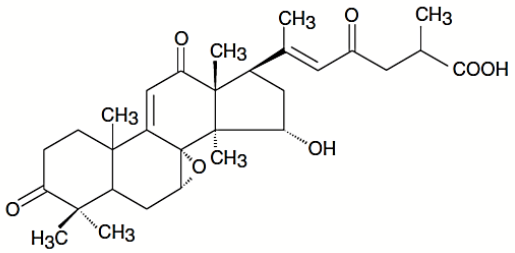

Fig. 6 Applanoxidic acid A

Polysaccharides from the *G. lucidum* species

Polysaccharides are important elements in both the pharmaceutical and food industries, due to their ability to defend the body against pathogens through various mechanisms [11]. These compounds are able to interact with the immune system and to enhance mechanisms of response. Its structure is composed of long-chain sugar molecules linked together by glycosidic bonds. Numerous types of them have been isolated in the *Ganoderma* species. Polysaccharides from this mushroom have heteropolymers with high molecular wight where the major components are glucose, mannose, galactose, and fructose. [12, 13]. Fig. 7 represents the side-chain of β-glucan with protein in polysaccharide-K [14].

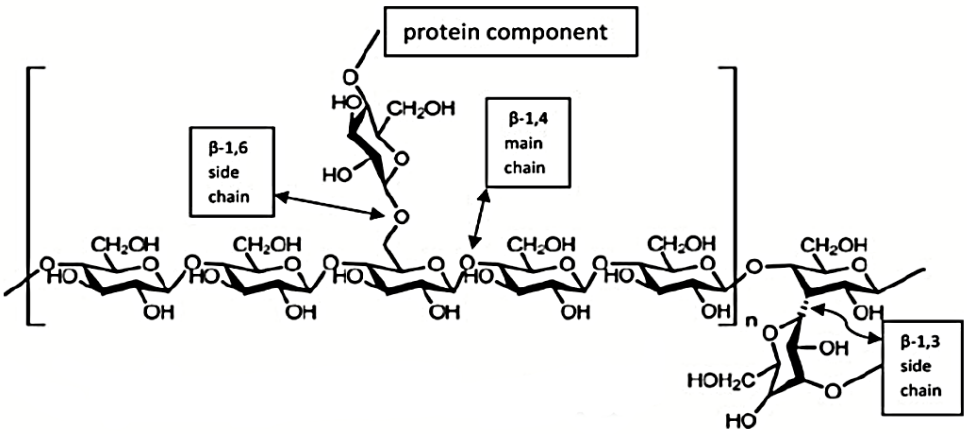

Fig. 7 β-glucan side-chain

Therapeutical applications

Ganoderma lucidum is known to have a very wide range of pharmacological effects. Among these, we list the immuno-modulatory, hypocholesterolaemia, anti-inflammatory and analgesic, antitumor, antibacterial, antiviral, and antifungal, hepatoprotective, antidiabetic, antioxidant effects [5, 12, 15-17]. Today, it is used by a very large number of people especially as an adjuvant medication in the treatment of cancer, hepatitis, diabetes and for anti-aging property [12, 8]. Fig. 8 represents pharmacological actions of both compounds, polysaccharides and triterpenoids.

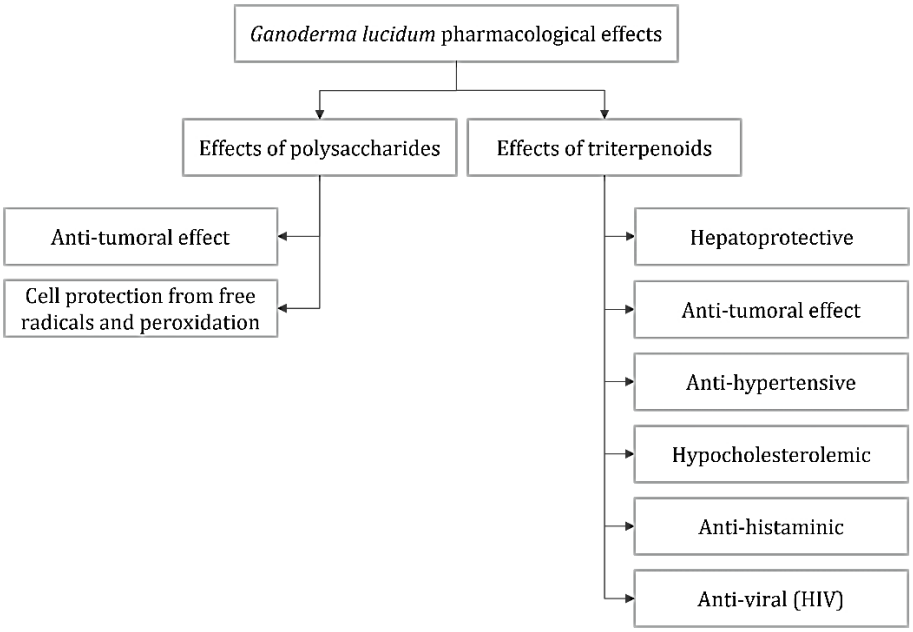

Fig. 8 Ganoderma lucidum pharmacological effects

Anti-inflammatory properties

The anti-inflammatory action is achieved by inhibiting the activity of cyclooxygenase enzymes, which are responsible for the production of prostaglandins. A study related by Joseph et al. [3] showed that the chloroform extract of *G. lucidum* has huge inhibitory potential of the inflammation induced by carrageenan and formalin, in the mice paws. The chloroform extract showed a 73,4% reduction at a concentration of 100mg/kg body weight, and a 63,2% reduction of inflammation at a concentration of 50mg/kg body weight of chloroform extract from the *G. lucidum* for carrageenan-induced inflammation. A reduction in inflammation of 63,4% and 53,4% for the same concentrations was observed in formalin-induced inflammation in the oedematous paw of the mice. For the standard reference, the study used the anti-inflammatory drug diclofenac, which showed an inhibition of oedemas of 53,0% and 40,2% for the same concentrations [3].

Anti-tumoral activity

The anti-tumoral effect of different *G. lucidum* extracts has been intensively studied by several groups of researchers. A study showed that the ethanolic extract of *G. lucidum*, which contains a high number of phenolic compounds, indicates antiproliferative activity in human cervical carcinoma, human alveolar basal adenocarcinoma, and human colon carcinoma [19]. Following the analysis, the author related an important correlation between the antiproliferative activity against human cervical carcinoma and the total phenolic compounds, and antiproliferative activity against human alveolar basal adenocarcinoma and total glucans content. The most abundant phenolic compounds were hesperetin and naringenin, for each analysed sample of the study [19]. In another study, an important part of the antiproliferative activity against cancer cell line is attributed to the high content of total phenolic compounds such as resveratrol and apigenin. Quantitative analysis of the total polyphenolic compounds showed that from 13,991.10 mg of total polyphenolic compounds per 100g of the extract, resveratrol was the most abundant with 5155,70 mg and apigenin with 4039.08 mg [20].

The clinical potential and a wide acceptance of extracts obtained from *G. lucidum* in terms of its antitumoral activity as an alternative therapy have developed interest in the research of its molecular mechanisms. [21]. In table 2 and 3 are related applications, activities, and mechanism of action of different *G. lucidum* extracts and for purified Ganoderic acids on multiple types of cancer cells.

Tabel 2 G. lucidum extracts- applications, activities and mechanism of action

Ganoderma lucidum extracts	Antitumoral applications	Mechanism of action	References
Dried powder of G. lucidum dissolved in boiled water	Invasive breast cancer Prostate cancer	Produces down-regulation of transcription factors AP-1 and NF-κB in cancer cells.	[22]
Hot water extraction	Drug-sensitive (H69) and multi-drug resistant (VPA) human SCLC (small-cell lung cancer) cells.	Both cells show equal cytotoxicity	[23]
Ethanolic extract of G. lucidum	Human Urothelial cells (bladder cancer)	In vitro – ethanolic extract exhibits a potent inhibition and induces	[24]

		growth arrest and cell migration	
Methanolic extract	Inhibit several cancer cell lines including hematological cell lines (lymphomas and multiple myelomas)	Upregulation of p21/p27 Induction of cell line arrest	[25]

Tabel 3 Subtypes of Ganoderic Acids- applications, activities and machanism of action

Subtypes of Ganoderic Acids	Antitumoral applications	Mechanism of action	References
Ganoderic Acid X (GA-X)	Hepatoma cells Colorectal carcinoma Acute promyelocyte leukemia	In Human Hepatoma (HuH-7) cells – GAX caused immediate inhibition of DNA systhesis and activation of ERK and JNK mitogen-activated protein kinases. *In vitro* – inhibate topoisomerases I and IIα	[26]
Ganoderic Acids T (GA-T)	Human metastatic lung carcinoma (95-D)	Apoptosis induction and cell line arrest at G (1) phase Induce cytotoxicity in human carcinoma cell lines in a dose-dependent manner, less toxic to normal human cell lines.	[27]

Anti-allergic property

The first line in the treatment of minor allergies are histamine H1 receptor antagonists. However, they respond poorly to acute hives or pruritic diseases [16]. Thus, studies to develop new adjuvant treatments based on *G. lucidum* extract against symptoms that are resistant to antihistamines are ongoing. Studies have shown that the properties of mushrooms from the Ganodermataceae family are able to restore the balance between TH1 and TH2 immune states [28]. In addition, there have been studies linking the potential of polysaccharides extracted from *G. lucidum* to the process of restoring IL-2 production that has been inhibited by the aging process observed in mice [29]. Powell studied the efficacy of unfractionated *G. lucidum* to determine the role of the medicinal fungus in managing the histamine-mediated immune response. The experiment took two males of different ages into the study. The first man aged 39, who had suffered from hay fever as a child, was initially given a dose of *G. lucidum* tablets of 3g per day (6 tablets x 500mg) with maintenance of this dose until symptoms subsided. The process of maintaining and decreasing the dose to 1. 5g per day (3 tablets x 500mg) showed a significant decrease in symptoms after 10 days of treatment. The second subject, a 5-year-old male who developed hay fever at the age of 4, was given an initial dose of 1g per day (2 tablets x 500mg) maintained until the end of the season. For the youngest subject, a 90% reduction in symptoms was achieved after one week. A review article, reported by Sanodiya et al. 2009 [6], synthesized studies showing inhibition of histamine release by mast cells from rat subjects, finding that ganoderic acids C and D, for the first time, played an important role in the inhibition of histamine release. Also, the compound cyclo-octasulfur found in *G. lucidum* composition inhibited the release of histamine from peritoneal mast cells of rat subjects, justified by membrane proteins interaction for inhibiting the Ca^{2+} uptake causing for the benefit, blockade of histamine release [18].

Anti-bacterial and anti-viral activity

There are many studies based on antiviral, antibacterial and antifungal treatment and they are aimed at discovering new herbal therapies. This approach is being considered due to patient neglect of anti-infectious therapies and the triggering of antibiotic resistance and adverse effects. The aim of these studies is to discover new factors that specifically inhibit antiviral and antibacterial activity without affecting the normal cell [30]. According to the literature, numerous experiments have been conducted to prove the efficacy of *G. lucidum* extract for further use as an antimicrobial or antiviral agent. Kim et al. [31], reported anti-herpetic activity of acidic protein bound polysaccharide, isolated from *G. lucidum*. The results showed potent antiviral activity against HSV-1 and HSV-2 [31]. Many studies have shown that antibacterial compounds in *G. lucidum* have inhibitory potential on gram-positive and gram-negative bacteria [32]. Both polysaccharide bioactive compounds and triterpenoids from *G. lucidum* have been shown to be effective in the antibacterial process [33]. Extracts provided from *G. lucidum* have been shown to exhibit antibiotic

properties by inhibiting the growth of gram-positive and gram-negative bacteria [34]. Many studies reporting that these properties have been conducted mostly on *Escherichia coli* and *Bacilus subtilis* [32]. From the studies, different levels of antibiotic activity against *Staphylococcus aureus*, *Salmonella sp*. and *Pseudomonas aeruginosa* are observed [35]. Another study showed that *G. lucidum* extract inhibits *Helicobacter pylori*, responsible for gastric ulcer formation [32]. Different extracts of *G. lucidum* have also been studied, but the methanolic extract showed antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* [36].

Immuno-modulatory and antioxidant property

According to Joseph et al. 2018 [3] study, chloroform extract of *G. lucidum* shows significant superoxide anion, nitric oxide, and lipid peroxidation inhibition activity. Following these tests, *G. lucidum* presents a source of interest for its natural antioxidant properties for the medical, pharmaceutical, and cosmetic industries.

A lot of research has focused on the immune-modulatory activity of *G. lucidum*, a lot of them have shown that its activity is mainly due to the presence of polysaccharides components, proteins, and triterpenoids [37]. An effect of the activation of immune response stimulating T cells, macrophages and natural killer cells was reported in a study that have been carried out on the subjects, mice [38]. The same result has been shown by Wong at al. 2004, too [39].

A study by Shi et al. 2013 [40], defined the antioxidant and immunoregulatory potential of *Ganoderma* extract, obtaining four types of polysaccharide compounds (GLP-I, GLP-II, GLP-III, GLP-IV). For the structural characterization of the compounds, Fourier transform infrared spectroscopy (FTIR) was used, and to determine the monosaccharide composition. This analysis showed that structurally the four identified compounds are similar, but the monosaccharides composition is significantly different. GLP-III and GLP-IV were found to be composed of six types of monosaccharides while GLP-II was found to be composed of three types. The results showed that all four types of polysaccharides performed antioxidant activity in a dose-dependent concentration, moreover, GLP-III and GLP-IV exhibited a significant scavenging effect on hydroxyl radicals, ABTS radicals and DPPH free radicals. The same study showed that 40 μg/mL of GLP, significantly stimulates macrophage proliferation and higher nitric oxide production [40].

Conclusions

Ganoderma lucidum is a traditional medicinal mushroom, appreciated for its many pharmacological effects and is increasingly consumed by the population to support a healthy life or as an adjuvant treatment in various acute or chronic diseases. Due to the numerous studies that have been carried out on both mice and humans, it can be concluded that the pharmacological effects of the medicinal mushroom are confirmed by the abundant presence of polysaccharides and triterpenoids, and in most studies, there was no evidence of renal or hepatic toxicity or changes in DNA genes [41].

However, there is a lack of studies on topical administration of *G. lucidum* extract and its possible pharmacological effects for epithelial regeneration as well as its anti-aging effect.

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