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http://dx.doi.org/10.19104/jfnd.2015.101

Review Article | Journal of Food Nutrition and Dietetics | Open Access

Ganoderma lucidum Polysaccharides and Terpenoids: Profile and Health Benefits

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Received Date: April 16, 2014, **Accepted Date:** May 10, 2015, **Published Date:** May 29, 2015.

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Abstract

Recent studies have shown that mushrooms are recognized as a promising source of functional and nutraceutical compounds. The species *Ganoderma lucidum* (also called Reishi or Lingzhi) is a mushroom used in medicine because Chinese attributes to this fungus better health and longevity. Among the numerous bioactive compounds identified in *G. lucidum* are polysaccharides mostly *β*-glucans, heteropolysaccharides or glycoproteins, terpenoids mostly ganoderic acids and derivatives, as well as many other bioactive proteinases that contribute to health and diseases prevention. The aim of this review is to report on the profile of the most bioactive compounds, particularly polysaccharides and terpenoids of *G. lucidum*.

Keywords: Polysaccharides; Terpenoids; Glycoproteins; *Ganoderma lucidum*

Introduction

From ancient civilizations and modern medicine raised by Hippocrates who stated that our food should be our first medicine, people have always been trying to merge natural remedies like herbs and spices with conventional medicine even though they failed to cure many diseases such cancer, some infections and allergies [1-3]. Chinese and Egyptians were among the first peoples to appreciate the medicinal value of mushrooms. Egyptians associated mushrooms with immortality and since they revered their Pharaohs, they included mushrooms as a specialty in the diet of the royal family [4].

Some misconceptions about mushrooms have always been admitted, for example mushrooms have low nutritional value. Nevertheless, the development of analytical chemistry is reporting that apart from being low in calories, mushrooms contain many specific biologically active compounds for example L-ergothioneine [5], known as an effective physiologic cytoprotectant [6].

Classification of *Ganoderma lucidum*

The *Ganodermataceae* family, term composed by "Gano" meaning shiny or bright and "derma" meaning skin, is a wide family of saprophytic fungi feeding on wood and having a bright or shiny skin covering the fruiting body. The genus *Ganoderma* includes fungi species like *G. lucidum* as well as other fungi such as *Ganoderma applanatum*. Indeed, the species *G. lucidum* is known by some features that separate it from others in the *Ganoderma* genus. Among these features are (i) its association with hardwood trees that is necessary, and (ii) *G. lucidum* has hyphal walls that are thicker than other *Ganoderma* species [7,8].

Medicinal properties of *G. lucidum*

Known also as Reishi, *G. lucidum*, is a mushroom used in medicine only, and is not considered as food because of the hard texture and bitter taste. In Chinese medicine, it was used for better health and was supposed to contribute to longevity [9], and recent research considers this fungus a real therapeutic factory [10]. Medicinal users claim that *Ganoderma* can be used against, liver diseases, lung problems, diabetes, cancer [2,3,11,12], heart disease, HIV [13], antiherpetic activities [14], and many other diseases. Other protective effects of *G. lucidum* were also reported for example DNA protection from strand breakage caused by hydroxyl radicals or UV irradiation [15], enhancing immune system [16] and antifibrotic effects [17].

Although containing different phytochemicals and pharmacological compounds, the most important biologically active constituents of *G. lucidum* are Polysaccharides and triterpenoids [18], and this review aims to screen mainly the profile of these two categories of phytochemicals of *G. lucidum*.

Polysaccharides of *G. lucidum*

The history of the health benefits of polysaccharides began with the discovery of fructans by Rose (1804). When known at the turn of the past century considerable developments on fructans have been achieved with Edelman's proposal concerning their metabolism in higher plant. More recently, research on bioactive polysaccharides has known a considerable progress especially with the molecular biology tools, thus the scope of prebiotics and other benefits research has expended from basic to applied science [19-22].

The extensive research carried out has revealed that many mushrooms contain different biologically active polysaccharides having among others immunomodulating, prebiotic, antioxidant, and antimicrobial properties. From the pure chemical and structural points of view, the polysaccharides of *G. lucidum* are mostly composed of *β*-glucans, heteropolysaccharides and glycoproteins [23-25].

β-glucans

Different bioactive polysaccharides have been isolated from the bodies of *G. lucidum* and these are considered as one of the main bioactive substances in the *Ganoderma* genus. Numerous researches reported on the isolation, structural characterisation and biological activities of *Ganoderma* polysaccharides. Results indicated that the *α*- or *β*-(1→3)-, (1→6)-glucans and other heterosaccharides conjugated to glucose, mannose, galactose, xylose, fucose and arabinose were the most predominant. Numerous polysaccharides have been isolated and structurally elucidated, however, the modern analytical chemistry is still revealing new polysaccharides from the species *G. lucidum* [26]. The major polysaccharides identified in *G. lucidum* bodies showed to have a backbone of *β*-(1→3)-linked D-glucopyranosyl residues, with branches of mono-, di- and oligosaccharide side chains substituting at the C-6 of the glucosyl residues in the main chain. The studies carried out on these polysaccharides are also suggesting that the degree of substitution of the backbone chain and the length of branching chains might have some importance in determining the biological activities of *β*-(1→3)-linked glucans [4,27].

Later Bao et al. [28] isolated three glucans, one holo- and two hetero-, and their study showed these isolated three glucans enhanced the proliferation of T- and B-lymphocytes in vitro and exhibited an

immune-stimulating activity. The isolated holo-glucan consists of a highly branched composed of 1,3-linked β-D-glucopyranosyl residues substituted at O-6 with 1,6-linked glucosyl residues. The two hetero-glucans, one consisting of 1,4-linked α-D-glucopyranosyl residues and 1,6-linked β-D-galactopyranosyl residues branched at O-6 of glucose residues and O-2 of galactose residues, respectively, and composed of terminal glucose, 1,6-linked glucosyl residues and terminal rhamnose. The second hetero-glucan consists of 1,3-, 1,4- and 1,6-linked β-D-glucopyranosyl residues and 1,6-linked β-D-mannopyranosyl residues. Huang et al. [29] isolated another novel water-soluble polysaccharide that showed a linear chain consisting of (1→4) -di-β-glucoseopyranose and 1,4,6-tri-β-glucoseopyranosyl, while the branched chains consist of (1→4) and (1→6) -di-β-galactoseopyranosyl residues.

Other polysaccharides of *G. lucidum*

A galactose rich extracellular polysaccharide composed of galactose, mannose, glucose, arabinose and rhamnose in different molar ratios and molecular weight was also isolated and identified in *G. lucidum* [30,31], and later Pan et al. [32] isolated another neutral hetero-polysaccharide containing galactose, rhamnose and glucose in mole ratio of 1.00:1.15:3.22, respectively. Other polysaccharides containing xylose, fructose, glucose, sucrose and maltose in different molar ratios were also isolated and identified, and analysis has shown that maltose yielded more than 50% of the total saccharides [33].

More recently, another high molecular weight polysaccharide was purified, and the analysis showed it contains 95.9% total carbohydrate, with chemical structure consisting of β-(1→3)-linked D-glucan with a (1→6)-β-D-glucopyranosyl side-branching unit on every third residue [34]. To date, researches are still running to isolate and characterise other polysaccharides from this fungus.

Terpenes or Terpenoids

Terpenoids (or isoprenoids), secondary metabolites subclass of the prenyllipids (terpenes, prenylquinones, and sterols), represent the oldest group of products synthesized by plants, and are probably the most widespread group of natural products. From the chemical point of view, terpenoids are modified terpenes, where methyl groups are moved or removed, or oxygen atoms added, although the term "terpenes" is more broadly used to include the terpenoids. Although considered as "cellular waste", terpenoids are present at low levels, play diverse and vital roles in plant physiology, and might have several functions in cellular membranes [35,36].

Ganoderic acid types

Different ganoderic acids, known to be highly oxygenated triterpenoids, have been extracted, isolated and characterised from *G. lucidum*, and many have been identified in the genus *Ganoderma* only [37]. Other ganoderic acid derivatives were also isolated from the fruiting bodies of *G. lucidum*, and results showed the presence of ganoderiol F, ganodermanontriol, ganoderic acid B, ganoderiol B, ganoderic acid C1, ganoderic acid α, ganoderic acid H and ganoderiol A [13]. Later, other terpenoids have been isolated and their chemical structure elucidated among them lucidenic acid O, lucidenic lactone and cerevisterol [38]. With the development of modern analytical techniques, especially the GC and LC coupled to mass spectrometry (GC-MS and LC-MS), Yang et al. [39] investigated the terpenoids profile of *G. lucidum* and this investigation led to the characterisation of 32 different structures of triterpenoids among them six new ones. Further terpenoids have also been identified for example ganoderol B [40], ganoderic acid C6, ganoderic acid G, and ganoderenic acid D [41], ganoderic acid DM [42], and lucidone D [43].

Other terpenoids of *G. lucidum*

Other chemically close triterpenoids have been additionally isolated from the fruiting bodies of G. lucidum. Lee et al. [44] isolated two lanostane triterpenes, methyl ganoderate A acetonide and n-butyl ganoderate H, together with 16 other known compounds. Therefore, these results are indicating that new analytical tools, especially metabolomics, will help in the future to likely isolate and elucidate the structures of many more terpenoids in *G. lucidum*.

Glycoproteins and Conjugated Proteins

Glycoproteins

From the last three decades, mushrooms have also been recognized as a good and promising source of novel proteins as many of them have demonstrated bioactive characteristics [45], and the examples are given by lectins [46,47], protease inhibitors [48,49], and hydrophobins [50,51]. These bioactive glycoproteins might offer solutions to several medical and biotechnological issues such as microbial drug resistance.

In *G. lucidum*, different glycoproteins have been found. Wang et al. [52] isolated a fucose-containing glycoprotein from the water-soluble extract of *G. lucidum*, and this hetero-protein stimulates the expression of cytokines, and this stimulation is caused by the presence of fucose. Later, another glycopeptide consisting of ca. 90% carbohydrate and 8% protein was isolated, and the polysaccharide moiety was composed by D-Glc, L-Fuc, and D-Gal with equal ratio of Glc and Fuc, while Gal was four folds higher. The structure elucidation of this glycoprotein has shown a backbone chains of (1→3) and (1→6) α- galactoseopyranosyl, and branched chains of (1→2) -β-fucanosyl residues [53]. Later, Ye et al. [54] isolated another proteoglycan composed by 95.3% carbohydrates and 3.3% protein. The methylation analysis of this proteoglycan has showed that the polysaccharide moiety has a backbone of 1,4-di-glucopyranosyl and 1,2,6-tri-glucopyranosyl residues, while the branching chains consist of 1-glucopyranosyl residues attached to 1,2,6-tri-glucopyranosyl residue via O-2 or O-6 positions.

Lectins

Although having different features from glycoproteins, many mushroom lectins exhibiting diverse chemical characteristics, have been isolated. Some of them, including G. lucidum lectins, have been extensively characterised. Studies have shown they can be monomeric, dimeric, trimeric or even tetrameric, with a molecular weight and sugar content -mainly galactose, lactose and N-acetylgalactosamine- ranging from 12 to 190 kDa, and 0 to 18%, respectively [55]. Other varying lectins have also been isolated from G. lucidum [55-57]. The development of proteomics can also be a good and valuable tool to isolate, characterise, and assess the bioactivities of other potential proteins in this species.

Mechanisms of action of *G lucidum* polysaccharides and terpenoids

The ancient and traditional Chinese medicine has been using *G. lucidum* from long time. The fungus was used to prevent or as therapeutic treatment of various diseases such as arthritis, cancer, chronic hepatitis, hepatopathy, hypertension, and many other diseases and pathologies [58,59]. Indeed, it was clear that these beneficial effects on health and diseases prevention are mainly due to the bioactive compounds including the polysaccharides and terpenoids of the fungus.

Although no significant antioxidant, anti-inflammatory, or immunomodulating effects have been demonstrated, G. lucidum may have analgesic effects for patients with active rheumatoid arthritis (RA) [60]. Some studies have been reporting on the mechanisms that would help to elucidate the potential therapeutic effect of *G. lucidum* polysaccharide peptide (GL-PP) in RA. Ho et al. [61] investigated the effects of GL-PP on cell proliferation and cytokine production in RA synovial fibroblasts (RASF), and found that the proliferation of RASF was significantly inhibited by GL-PP.

Significant progress on the effects on cancer has been done, but still the mechanism of the anticancer action of *G. lucidum* is not well clear and well understood. Nevertheless, it is suggested that the mechanism behind the antitumor and antimetastatic activities of *G. lucidum* (terpenoid fractions) might result from the inhibition of tumor-induced angiogenesis [62]. Previous and recent studies are also in agreement with the fact that the anticancer activity of *G. lucidum* is resulting from a synergetic action of the immune response activation, the induction of cell differentiation, the induction of Phase II-metabolizing enzymes, the inhibition of angiogenesis, and the inhibition of both the expression of the urokinase-type plasminogen activator (uPA) and its receptor in cancer cells [63]. Another hypothesis on the anti-cancer mechanisms of *G lucidum* was suggested, and it might caused by its consecutive inhibition of the active transcription factors nuclear factor kappa B (NF-.B) and AP-1, and therefore causing the expression inhibition of urokinase type plasminogen activator (uPA) and its receptor uPAR. The same study also reported the potency of *G. lucidum* to reduce tumor invasiveness by suppressing the adhesion and the migration of highly invasive breast and prostate cancer cells [2,64].

Peptides from *G. lucidum* (GLP) have also been studied for their hepatoprotective activity. Shi et al. [65] evaluated the effect of GLP against d-galactosamine (d-GalN) and its induced hepatic injury in mice, their results showed that GLP could afford a significant protection in the alleviation of d-GalN-induced hepatocellular injury.

In animal investigation, polysaccharide and terpenoids fractions of G. lucidum have shown protective effects on liver. In a study carried out by Gao et al. [1], ganopoly (*G. lucidum* extract) appeared to be active against hepatitis B viral (HBV) in patients with chronic hepatitis B. Later, Li et al. [66] investigated the anti-hepatitis B virus activity and hepatoprotective activity of a liquid fermentation broth of *G. lucidum* supplemented with aqueous extract of Chinese herbal medicine (Radix Sophorae flavescentis). Their results clearly showed that the cultured broth had an anti-hepatitis B virus activity in vitro and protected mice from liver damage in vivo. On the other hand, different studies reported the relationship between low plasma cholesterol levels and mushrooms consumption [67-70]. In animal experiments, Kabir et al. [71] investigated the dietary effect of *G. lucidum* on blood pressure and their results showed a significant reduction of the plasma cholesterol level in animals fed with *G. lucidum*, and these observations have been reported previously. Although these results are suggesting that an adequate dietary supplementation might prevent from blood pressure increase and reduce plasma and liver cholesterol levels, the mechanism of this action is still unclear and has to be understood.

Additional research works have also showed that the polysaccharides of *G. lucidum* have a hypoglycemic effect [72]. Hikono et al. [73,74] noticed that the administration of *G. lucidum* fruit bodies triggers hypoglycemic potential, however, the mechanism of this eliciting is not know. One mechanism of hypoglycemic action of *G. lucidum* was suggested by Li et al. [75,76]. The *G. lucidum* polysaccharides might increase the concentration of [Ca2+]i in both T lymphocytes and the macrophages of murine peritoneal. This increase is the consequence of the influx of the intra- and extra-cellular cellular Ca2+.

Conclusion and Perspectives

Conclusively, *G. lucidum* is not only natural therapeutic machinery, but can also be considered as a 'natural pharmacy store" because of the

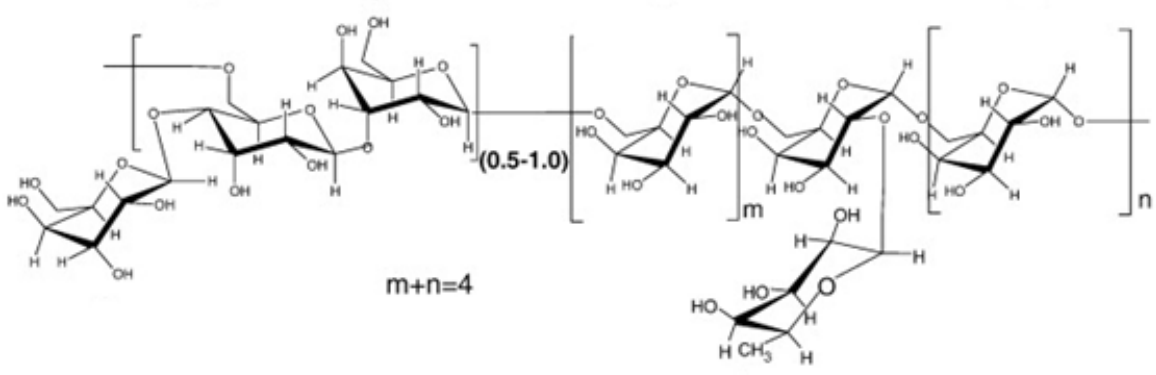

Figure 1: Three-dimensional chemical structure of polysaccharides -proteoglycan repeating units- extracted from *Ganoderma lucidum*.

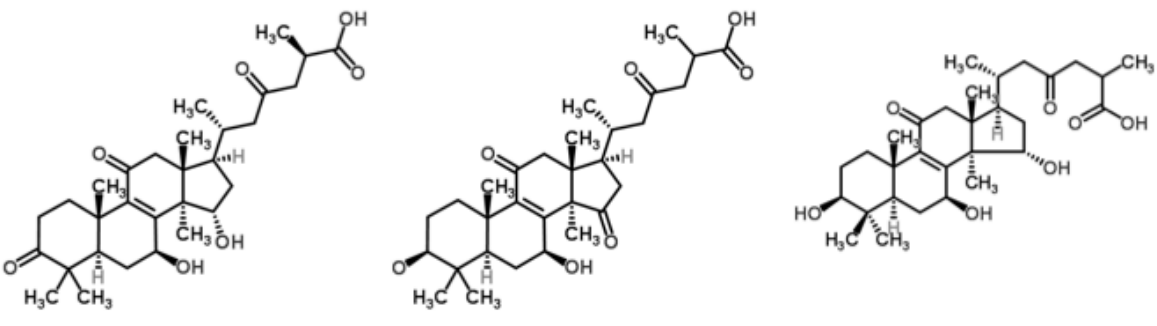

Figure 2: Chemical structures of the main triterpenoids identified from *Ganoderma lucidum.*

large number of bioactive compounds isolated to date and demonstrated to have numerous therapeutic properties. Undoubtedly and from the extensive work carried out, this fungus species offers tangible promises for the development of novel functional foods, nutraceuticals and even therapeutic drugs. On the other hand and because the different active compounds isolated from *G. lucidum* did not show toxic or side effects, the appeal to this fungal as natural remedy, dietary food and health-fortifying food is raising and attracting the interests of the scientific community, and the industrial community as well. Even though and extensive literature is reporting on *G. lucidum* bioactive compounds, however, further clinical studies are still needed to demonstrate their therapeutic efficacy, and more studies regarding the safety and application of these compounds for providing more evidences in order to shift from trial to application stage. These investigations should also focus on the mechanisms of action of *G. lucidum*, because most of them are not or not well-known, and still need to be understood. The understanding of these mechanisms would undoubtedly help to target better the pathologies that can be prevented using this fungus. Moreover, the development of nutraceuticals and functional foods based on *G. lucidum*, and other mushrooms as well seems to have a real potential and promising perspectives in food, nutrition and pharmacology sciences.

Acknowledgements

The photograph of three-dimensional structure of *Ganoderma lucidum* polysaccharides (Figure 1) is a courtesy of Dr. Yan is Giavadis, Technological Educational Institute (TEI) of Thessaly, Karditsa, Greece.

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Received Date: April 16, 2014, **Accepted Date:** May 10, 2015, **Published Date:** May 29, 2015.

Citation: Benkeblia N (2015) *Ganoderma lucidum* Polysaccharides and Terpenoids: Profile and Health Benefits. J Food Nutri Diete 1(1): 101 http://dx.doi.org/10.19104/jfnd.2015.101.