

***Ganoderma*: The mushroom of immortality**

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Abstract

Ganoderma is the genus from order Aphyllophorales with more than 300 species. *Ganoderma* contains various compound that showed many biological activities e.g. enhancer of immune system, antitumor, antimicrobial, anti-inflammatory, antioxidant and acetyl cholinesterase inhibitory action. These bioactive compounds related to the triterpenoids and polysaccharides classes. Proteins, lipids, phenols, sterols, and others, are also recorded. *Ganoderma* is currently an important source in the pharmaceutical industry and is one of the most promising projects in the world of food and medicine, which is being highlighted these days. In Egypt seven species of *Ganoderma* were recorded by Abdel-Azeem (2018). Among cultivated mushrooms, *G. lucidum* is unique in that its pharmaceutical rather than nutritional value is paramount. A variety of commercial *G. lucidum* products are available in various forms, such as powders, dietary supplements, and tea. These are produced from different parts of the mushroom, including mycelia, spores, and fruit body. The commercial cultivation of *Ganoderma* in Egypt not started yet. In this article the most important bioactive materials produced by *Ganoderma*, their applications and business opportunity in Egypt will be discussed.

Keywords – Egypt, Lingzhi, Triterpens, Polysaccharides, Anti-HIV, Anti-cancer

Introduction

Ganoderma is a historical fungus that used for promoting health and longevity in China, Japan, and other Asian countries. It is a large, dark mushroom with a glossy exterior and a woody texture. The Latin word *lucidus* means “shiny” or “brilliant” and refers to the brown varnished appearance of the surface of the mushroom (Fig. 1). In China, *G. lucidum* is called lingzhi, whereas in Japan the name for the Ganodermataceae family is rishi or manntake.

The name lingzhi represents a combination of spiritual potency and essence of immortality, and is regarded as the “herb of spiritual potency,” symbolizing success, well-being, divine power, and longevity. Among cultivated mushrooms, *G. lucidum* is unique in that its pharmaceutical rather than nutritional value is paramount. A variety of commercial *Ganoderma* products are available in various forms, such as powders, dietary supplements, and tea. These are produced from different parts of the mushroom, including mycelia, spores, and fruit body.

The specific applications and attributed health benefits of lingzhi include control of blood glucose levels, modulation of the immune system, hepatoprotection, bacteriostasis, and more. The various beliefs regarding the health benefits of it are based largely on anecdotal evidence, traditional use, and cultural mores. However, recent reports provide scientific support to some of the ancient claims of the health benefits of lingzhi (Wachtel-Galor and Benzi 2011). The family Ganodermataceae describes polypore basidiomycetous fungi having a double-walled

basidiospore (Donk 1964). In all, 219 species within the family have been assigned to the genus *Ganoderma*, of which *G. lucidum* is the species type (Moncalvo 2000). Basidiocarps of this genus have a laccate (shiny) surface that is associated with the presence of thick-walled pilocystidia embedded in an extracellular melanin matrix (Moncalvo 2000).



Fig 1 – Basidiomata of *Ganoderma lucidum* (Courtesy of Prof. Ahmed M. Abdel-Azeem).

Ganoderma species are found all over the world, and different characteristics, such as shape and color (red, black, blue/green, white, yellow, and purple) of the fruit body, host specificity, and geographical origin, are used to identify individual members of the species (Zhao and Zhang 1994; Woo *et al.* 1999; Upton 2000).

In Egypt Abdel-Azeem (2018) recorded seven species of *Ganoderma* namely *G. Adpersum* (Schulzer) Donk, *G. applanatum* (Pers.) Pat., *G. carnosum* Pat., *G. colossus* (Fr.) C.F. Baker, *G.lucidum*(Curtis) P. Karst., *G.mbrekobenum* E.C. Otto, Blanchette, Held, C.W. Barnes & Obodai, and *G. resinaceum* Boud.. Recently Abdel-Azeem and Nafady (2019) recorded *Tomophagus colossus* (= *G. colossus*) as a new record in Egypt.

Major bioactive components in *Ganoderma*

Ganoderma contains a wide variety of bioactive molecules, such as terpenoids (Fig. 2), steroids, phenols, nucleotides and their derivatives, glycoproteins, and polysaccharides. Mushroom proteins contain all the essential amino acids and are especially rich in lysine and leucine. The low total fat content and high proportion of polyunsaturated fatty acids relative to the total fatty acids of mushrooms are considered significant contributors to the health value of mushrooms (Chang and Buswell 1996; Borchers *et al.* 1999; Sanodiya *et al.* 2009).

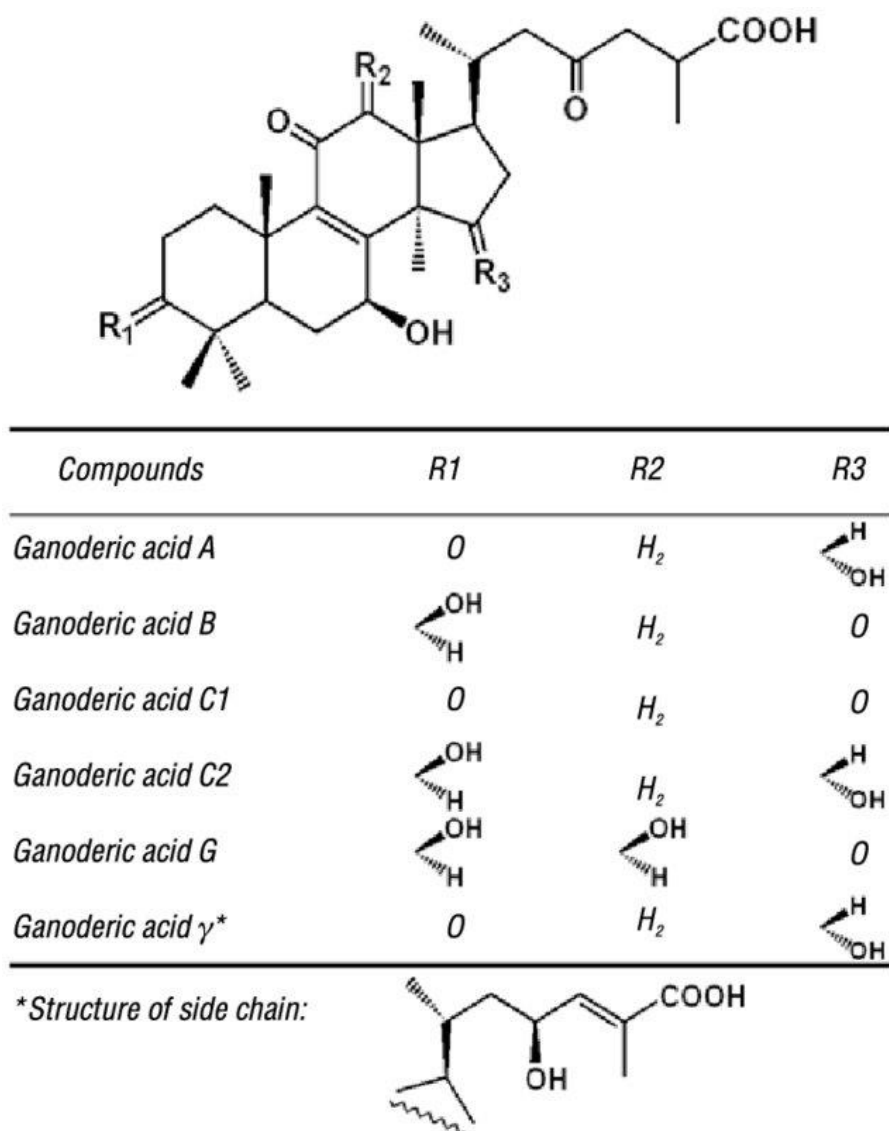


Fig 2 – General structure of terpenoids in *Ganoderma lucidum*.

Triterpenes

The Terpenes are a class of naturally occurring compounds whose carbon skeletons are composed of one or more isoprene C5 units. Terpenes have also been found to have anti-inflammatory, antitumorigenic, and hypolipidemic activity. Terpenes in *Ginkgo biloba*, rosemary (*Rosemarinus officinalis*), and ginseng (*Panax ginseng*) are reported to contribute to the health-promoting effects of these herbs (Mahato and Sen 1997; Mashour *et al.* 1998; Haralampidis *et al.* 2002).

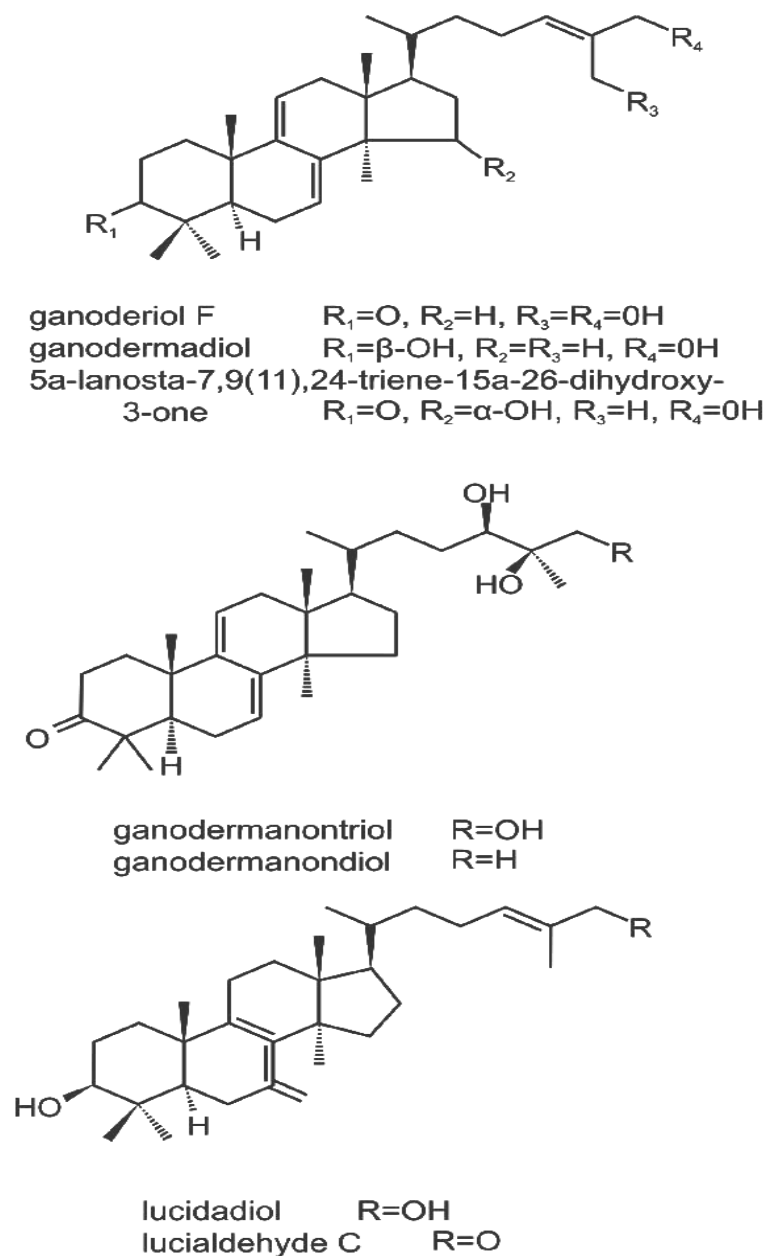


Fig 3 – Some examples of triterpenoids extracted from *Ganoderma*.

The triterpenes (Fig. 3) are a subclass of terpenes and have a skeleton of C₃₀ and have molecular weights ranging from 400 to 600 kDa and their chemical structure is complex and highly oxidized (Mahato and Sen 1997; Zhou *et al.* 2007). In *Ganoderma* the chemical structure of the triterpenes is based on lanostane, which is a metabolite of lanosterol, the biosynthesis of which is based on cyclization of squalene (Haralampidis *et al.* 2002). Extraction of triterpenes is usually done by means of methanol, ethanol, acetone, chloroform, ether, or a mixture of these solvents. The extracts can be further purified by various separation methods, including normal and reverse-phase HPLC (Chen *et al.* 1999; Su *et al.* 2001).

The first triterpenes isolated is from *G. lucidum* called the ganoderic acids A and B, which were identified by Kubota *et al.* (1982). Since then, more than 100 triterpenes with known chemical compositions and molecular configurations have been reported to occur in *G. lucidum*. Among them, more than 50 were found to be new and unique to this fungus. The vast majority are ganoderic and lucidenic acids, but other triterpenes such as ganoderals, ganoderiols, and

ganodermic acids have also been identified (Nishitoba *et al.* 1984; Sato *et al.* 1986; Budavari 1989; Gonzalez *et al.* 1999; Ma *et al.* 2002; Akihisa *et al.* 2007; Zhou *et al.* 2007; Jiang *et al.* 2008; Chen *et al.* 2010).

Antitumor anticancer activity

The triterpene extracts of *G. lucidum* are known to induce apoptosis of multiple human cancer cell lines. However, the cytotoxic activity of triterpenes varied significantly across different subtypes of triterpenes. Most triterpenoids extracted and identified from *Ganoderma* have shown robust biological activities. The ganoderic acids isolated from *Ganoderma* have shown antiviral, anticancer, antioxidant, hepatoprotective, cytotoxic, antiplatelet aggregation, and inhibition of histamine release and hypocholesterolemic activities. The most abundant triterpenic acid from *G. lucidum* is GA T which shows significant anticancer activity both in vivo and in vitro experiments. GA has been found to inhibit tumor invasion by inhibiting matrix metalloproteinase (MMP)-9 expressions.

Another triterpenic acid GAD has been shown to directly bind to 14-3-3 ζ protein and this binding may contribute to the facilitation of apoptosis observed in human epithelial cell line (HeLa) cell. The triterpene extracts identified from *G. lucidum* and other *Ganoderma* species have shown anticancer property under in vivo conditions. The carcinogenic effects shown by various types of extracts from *G. lucidum* include various cancer cell lines (breast, colon, lung, pancreas, prostate, and skin). The known mechanisms through which the extracts of *G. lucidum* exhibit anticancer activities include direct inhibition of cell proliferation through cancer-specific cell cycle arrest and apoptosis. Various other studies have also shown that the triterpene extracts of *G. lucidum* have antioxidant activity and have the potential to reduce oxidative damage by directly scavenging free radicals generated in the cell due to the increase in the activity of superoxide dismutase and catalase which are enzymes involved in removing harmful free radicals and ROS. Smina *et al.* (2011) revealed in mice that triterpenes from *G. lucidum* showed antioxidant activity which may be due to increased activity of antioxidant enzyme and they further observed that total terpenes from *G. lucidum* prevent radiation-induced DNA damage and apoptosis in splenic lymphocytes of mice under in vitro conditions. In a recent study carried by Smina *et al.* (2016), total triterpenes from *G. lucidum* were highly effective in reducing the levels of lipid peroxidation and protein oxidation to near normal values in both liver and brain tissues in Swiss albino mice under in vivo conditions. Total triterpenes, when administered under vivo conditions, were also found to be successful in restoring the antioxidant enzyme activities and glutathione level in liver and brain of irradiated mice. Administration of total triterpenes, before radiation exposure, significantly decreased the DNA strand breaks.

Anti-Viral activity

El-Mekkawy *et al.* (1998) assayed 13 compounds for anti-HIV activity isolated from *G. lucidum*. El Dine *et al.* (2008) observed anti-HIV-1 protease activity of triterpenoids from *G. colosseum*. The inhibitory activity of triterpenoids isolated from *Ganoderma* species against HIV has also been reported by Cassels and Asencio (2011).

The ganoderic acid isolated from *G. lucidum* showed inhibitory effects on the replication of hepatitis B virus (HBV) in HepG2215 cells (HepG2- HBV-producing cell line) over 8 days. Production of HBV surface antigen (HBsAg) and HBV e antigen (HBeAg) were, respectively, 20% and 44% of controls without ganoderic acid treatment (Li and Wang 2006).

Anti-inflammatory potential

In the present study we evaluated the anti-inflammatory effects of the triterpene extract from *G. lucidum* (GLT) in LPS-stimulated macrophages. Here we show that GLT markedly suppressed the secretion of inflammatory cytokine tumor necrosis factor- α (TNF- α) and interleukin-6 (IL-6), and inflammatory mediator nitric oxide (NO) and prostaglandin E2 (PGE2) from lipopolysaccharide (LPS)-stimulated murine RAW264.7 cells. GLT also down-regulated LPS-dependent expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX-2) in RAW264.7 cells. The anti-inflammatory effects of GLT were mediated by the inhibition of transcription factor NF- κ B as demonstrated by decreased NF- κ B-DNA binding activity, and the suppression of p65 phosphorylation in LPS-stimulated macrophages treated with GLT. Moreover, GLT inhibited LPS-dependent AP-1-DNA binding activity and down-regulated expression of AP-1 subunit c-Jun. In addition, GLT suppressed the activity of MAP kinases as observed by the down-regulation of LPS-induced phosphorylation of ERK1/2 and JNK but not p38. In vivo experiments clearly demonstrated that GLT also inhibited the production of TNF- α and IL-6 in LPS-induced endotoxemic mice. Apart from its anti-inflammatory activity, GLT suppressed cell proliferation of RAW264.7 cells through cell cycle arrest at G0/G1–G2M, which was mediated by the down-regulation of expression of cell cycle regulatory proteins cyclin D1, CDK4 and cyclin B1, respectively. In conclusion, the anti-inflammatory and anti-proliferative effects of GLT on macrophages are mediated through the inhibition of NF- κ B and AP-1 signaling pathways. (Dudhgaonkar s. *et al* 2009)

Polysaccharides extracted from *Ganoderma*

Various polysaccharides have been extracted from the fruit body, spores, and mycelia of *Ganoderma* they are produced by fungal mycelia cultured in fermenters and can differ in their sugar and peptide compositions and molecular weight. *G. lucidum* polysaccharides (GL-PSs) are reported to exhibit a broad range of bioactivities, including anti-inflammatory, hypoglycemic, antiulcer, antitumorogenic, and immunostimulating effects (Miyazaki and Nishijima 1981; Hikino *et al.* 1985; Tomoda *et al.* 1986; Bao *et al.* 2001; Wachtel-Galor *et al.* 2004). Polysaccharides are normally obtained from the mushroom by extraction with hot water followed by precipitation with ethanol or methanol, but they can also be extracted with water and alkali. Structural analyses of GL-PSs indicate that glucose is their major sugar component (Bao *et al.* 2001; Wang *et al.* 2002). However, GL-PSs are heteropolymers and can also contain xylose, mannose, galactose, and fructose in different conformations, including 1–3, 1–4, and 1–6-linked β and α -D (or L)-substitutions (Lee *et al.* 1999; Bao *et al.* 2002).

Branching conformation and solubility characteristics are said to affect the antitumorogenic properties of these polysaccharides (Bao *et al.* 2001; Zhang *et al.* 2001). The mushroom also consists of a matrix of the polysaccharide chitin, which is largely indigestible by the human body and is partly responsible for the physical hardness of the mushroom (Upton 2000).

Numerous refined polysaccharide preparations extracted from *G. lucidum* are now marketed as over-the-counter treatment for chronic diseases, including cancer and liver disease (Gao *et al.* 2003). Various bioactive peptidoglycans have also been isolated from *G. lucidum*, including *G. lucidum* proteoglycan (GLPG; with antiviral activity; Li *et al.* 2005), *G. lucidum* immunomodulating substance (GLIS; Ji *et al.* 2007), PGY (a water-soluble glycopeptide fractionated and purified from aqueous extracts of *G. lucidum* fruit bodies; Wu and Wang 2009), GL-PS peptide (GL-PP; Ho *et al.* 2007), and F3 (a fructose-containing glycoprotein fraction; Chien *et al.* 2004).

Other beneficial components extracted from *Ganoderma*

Phosphorus, sulfur, potassium, calcium, and magnesium are their main mineral components. **Iron, sodium, zinc, copper, manganese, and strontium** were also detected in lower amounts, as were the heavy metals lead, cadmium, and mercury (Chen *et al.* 1998). Significantly, no cadmium or mercury was detected in these samples. *G. lucidum* can also contain up to 72 µg/g dry weight of **selenium** and can bio transform 20–30% of inorganic selenium present in the growth substrate into selenium-containing proteins (Du *et al.* 2008).

Germanium was fifth highest in terms of concentration (489 µg/g) among the minerals detected in *G. lucidum* fruit bodies collected from the wild (Chiu *et al.* 2000). This mineral is also present in the order of parts per billion in many plant-based foods, including ginseng, aloe, and garlic (Mino *et al.* 1980). Although germanium is not an essential element, at low doses, it has been credited with immunopotentiating, antitumor, antioxidant, and antimutagenic activities (Kolesnikova *et al.* 1997). *G. lucidum* contains some other compounds that may contribute to its reported medicinal effect, such as proteins and lectins.

The **protein** content of dried *G. lucidum* was found to be around 7–8%, which is lower than that of many other mushrooms (Chang and Buswell 1996; Mau *et al.* 2001). Bioactive proteins are reported to contribute to the medicinal properties of *G. lucidum*, including LZ-8, an immunosuppressive protein purified from the mycelia (Van Der Hem *et al.* 1995); a peptide preparation (GLP) exhibiting hepatoprotective and antioxidant activities (Sun *et al.* 2004) and a 15-kDa antifungal protein, ganodermin, which is isolated from *G. lucidum* fruiting bodies (Wang and Ng 2006).

The **carbohydrate** and crude fiber content of the dried mushroom was examined and found to be 26–28% and 59%, respectively (Mau *et al.* 2001). Lectins were also isolated from the fruit body and mycelium of the mushroom (Kawagishi *et al.* 1997), including a novel 114-kDa hexameric lectin, which was revealed to be a glycoprotein having 9.3% neutral sugar and showing hem agglutinating activity on pronase-treated human erythrocytes (Thakur *et al.* 2007). Lectins (from the Latin word *legere*, which means to pick up, choose) are non-enzymatic proteins or glycoproteins that bind carbohydrates. Many species of animals, plants, and microorganisms produce lectins, and they exhibit a wide range of functions. In animals, for example, lectins are involved in a variety of cellular processes and the functioning of the immune system (Wang *et al.* 1998).

Also **Metalloprotease**, which delays clotting time; ergosterol (provitamin D₂); nucleosides; and nucleotides (adenosine and guanosine) (Wasser *et al.* 2005; Paterson 2006). Kim and Nho (2004) also described the isolation and physicochemical properties of a highly specific and effective reversible inhibitor of α-glucosidase, SKG-3, from *G. lucidum* fruit bodies. Furthermore, *G. lucidum* spores were reported to contain a mixture of several **long-chain fatty acids** that may contribute to the antitumor activity of the mushroom (Fukuzawa *et al.* 2008 ; Wachtel-Galor *et al.* 2011).

Economic importance of *Ganoderma* mushroom

Cultivation of the *Genoderma* mushroom in the countries of Asia is of great importance to its health benefits as well as the huge economic return from it. For a new business opportunity in Egypt, there are many factors which will help this industry to success, including the appropriate climate, spread of *Ganoderma* in the governorates of the Nile Delta region, the availability of suitable areas for cultivation (no need of special difficult preparations), the low cost and the most important factor are the studies and researchers who are able to develop this project and provide sufficient information to help the workers in it. The *Ganoderma* project can provide employment opportunities for young people, elderly and women for ease of operation, providing foreign currency where the kilogram sold for about 36 dollars, also opening a new market in the field of pharmaceutical industries. In addition, strengthening the market with a natural product has

enormous benefits as reishi coffee and tea both for prevention and treatment of diseases. For more details please read Mansour *et al.* (2018).

Conclusion

There is still little information available concerning the use of advanced fermentation techniques for obtaining *Ganoderma lucidum* mycelium and its valuable components in Egypt. A better understanding of its morphology and physiology is crucial for the development of large scale fermentation processes. Over the past two decades, the *Ganoderma* industry has developed greatly and today offers thousands of products to the markets. Despite the large market, there are problems with the industry which prevent it from establishing an effective market. In Egypt the world *Ganoderma* cultivation, products, industry and research is urgently needed.

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