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REVIEW PAPER

PHARMACOLOGICAL PROPERTIES AND USE OF *GANODERMA LUCIDUM* IN MODERN MEDICINE*

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Abstract

Currently, lignicolous fungi, commonly referred to as polypores, belonging to the division of *Basidiomycota* (basidiomycetes), are of great interest. *Ganoderma lucidum* is one of the representatives. They grow and develop in the wood of trees and shrubs, both living and dead ones. These fungi belong to the world's most valued and sought-after medicinal plants, used as dietary supplements and applied in medicine. Fungal extracts can be used both for the purposes of prevention and treatment of the acute and chronic diseases. Clinical studies have confirmed the unique characteristics of parasitic medicinal fungi: wide possibilities of application, a high supportive and enhancing role taking into account the effects of treatment of various diseases, non-toxicity and a lack of the side effects of use. Triterpenes and immune-active polysaccharides, mainly β -D-glucans and polysaccharide peptides as well as proteins, are of the greatest health-promoting importance. Glucans that have been most widely used in medicine include: lentinan (from *Lentinula edodes*), krestin (*Trametes versicolor*), schizophyllan (SPG), isolated from *Schizophyllum commune* (splitgill). However, not all glucans have anti-cancer properties

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since this property depends on their water solubility, size and molecular weight, degree of branching and form of occurrence. High-molecular-weight β -glucans, containing mainly β -(1-3) bonds, display the highest anti-cancer activity. These polysaccharides do not induce allergic reactions or side effects in the human body; however, they show cytotoxic effects against neoplastic cells, as confirmed by *in vitro* and *in vivo* studies. A bibliometric analysis on *Ganoderma lucidum* in the period 1995-2021 was completed in the study. The literature review was conducted searching through the PubMed, SCOPUS and Google scholar databases. The criterion of thematic classification was implemented to carry out an analysis of bibliographic data.

Keywords: *Ganoderma lucidum*, fungi, anti-cancer effect, Chinese medicine, pharmacologically active substances

INTRODUCTION

Herbal medicine of the ancient East (China, Japan, Mongolia, Korea) and especially Traditional Chinese Medicine (TMC) and Traditional Japanese Kampo Medicine (KAMPO) make use of indigenous medicinal plants, of which particular attention is drawn to adaptogenic raw materials, which include fungi. According to preliminary estimates, more than 700 species of fungi growing around the world are considered to have medicinal properties. They were attributed with the power to prolong life of the elderly people and keep them in good physical and mental condition as well as having anti-cancer effects and the ability to reduce the risk of recurrence of the neoplastic disease or spread of metastases, to stimulate the immune system and create antibiotic effects (Pravettoni et al. 2014, Rahman et al. 2016, Bi et al. 2018, Sohretoglu et al. 2018, Zeng et al. 2018).

The nutritional value of fungi results mainly from the presence of digestible proteins and dietary fibre, which regulates the digestive process although it is indigestible to humans on its own. Other (nitrogenous) compounds present in fungi are exo- and endogenous amino acids (constituting the building blocks of proteins), amines, nucleic acids, urea and chitin. On the other hand, due to their high water content, fungi are low in calories (Turlo 2013). In addition to their nutritional effect, they also have a health-promoting effect and therefore meet the requirements of functional foods. Polysaccharides (e.g. grifolan, lentinan, pleuran, schizophyllan, scleroglucan) and polysaccharide-protein complexes (e.g. ganoderan, krestin) constitute the best-known health-promoting active substances of fungi. Functional foods include, e.g. low-calorie cakes rich in protein, fibre, zinc, magnesium, copper, potassium and iron with dried shiitake or crisps made from oyster mushrooms and shiitake as well as beer made from *Ganoderma lucidum* extract containing amino acids, fatty acids, carbohydrates and triterpenes valuable to health and dried *Ganoderma lucidum* for brewing (Manzi et al. 2004, Kalac 2009).

A number of substances with pharmacological effects have also been detected in fungi, such as:

- bactericidal ones, including polyporene, merulinic and unguinic acids, betulinic, sulphuric and eburic acids, fomanosin, fomannoxin, cinnabarin, lenzitin, merulidial and fomentariol;
- fungicides, including merulidial, biforminic acid, biformin and lenzitin;
- antibiotic and antiviral ones, e.g. coriolan, lucidumol;
- immunostimulatory and anticancer agents, e.g. coriolan, inotodiol, schizophyllan, pleuran, fomentariol, terpene compounds (lucidenic acid, ganodermanediol, ganoderiol) and merulidial (Panda et al. 2021).

Some polysaccharides obtained from fungi grown on wood are registered in China, Japan, Korea and New Zealand as medications applied in the treatment of cancers (gastrointestinal, breast, cervical or lung cancer):

- grifolan (GRN) – a polysaccharide fraction isolated from the fruiting bodies and mycelium of the maitake (*Grifola frondosa*);
- krestin (a polysaccharide, PSK, and a polysaccharide-protein complex, PSP) isolated from the mycelium of the turkey tail (*Trametes versicolor*), administered orally;
- lentinan, a polysaccharide fraction isolated from the fruiting bodies of the shiitake (*Lentinula edodes*), administered intravenously and intraperitoneally;
- schizophyllan (soniphyllan, sisophyllan, SPG), a polysaccharide fraction isolated from the culture medium of the splitgill (*Schizophyllum commune*), administered intravenously and intraperitoneally (Jakopovic et al. 2021).

Until recently, specifics obtained from lignicolous fungi were very expensive and rarely available outside the Eastern countries. However, since their high health properties have been scientifically confirmed, fungiculture has begun in numerous countries around the world. It is also worth mentioning a specific Tibetan fungus belonging to the *Ascomycota* (sac fungi) division – *Cordyceps sinensis* (*Ophiocordyceps sinensis*, caterpillar fungus, yartsa gunbu, Totsu kasu, Yarchakunbu, Aweto, Himalayan Viagra). The previous attempts at its cultivation have been unsuccessful. It is only found in the soil of high mountain meadows in the Tibetan Highlands and the Himalayas and develops in the larvae of the ghost moth, forming an elongated brown fruiting body. It is attributed with anti-cancer, anti-inflammatory, antimicrobial, antidiabetic, anti-asthmatic, immunomodulatory and hepatoprotective activities (Winkler 2008, Chiba et al. 2010, Ivanova et al. 2014).

The objective of this study was to present the potential use of the world's best-known representative of the medicinal fungal species *Ganoderma lucidum* in modern medicine.

CHARACTERISTICS OF *GANODERMA LUCIDUM*

Ganoderma lucidum is the best-known representative of medicinal fungi in the world. This species is also described in the literature under other names: *Boletus lucidus* (Fr.), *Polyporus lucidus* Curt. (Fr.), *Polyporus polychromus* Curt. (Fr.), *Ganoderma polychromum* Curt. (Fr.), *Ganoderma sessile* Curt. (Fr.), *Ganoderma japonicum* (Fr. Lloyd), *Fomes lucius* (Curt.Fr.) Sacc. This fungus is commonly called Ling Zhi in China, Reishi, Mannentake, Mannen Dake and Sachi Dake in Japan, and lacquered bracket in Poland (Siwulski et al. 2015). These fungi have been used in ancient Chinese medicine for more than 2,000 years and are among the oldest fungi cultivated for their medicinal use as the anti-cancer abilities of Reishi mushrooms are legendary.

Dried and then powdered Reishi mushroom was used as a popular substitute for chemotherapy in the treatment of cancer as far back as ancient China. Modern pharmaceutical companies continue to add Reishi extracts to specific anti-cancer medications, such as MC-S. In the Chinese medical works from the Han (206 BC - 220 AD) and Ming (1368-1644) dynasties, the fungus *G. lucidum* was placed first out of 120 medicinal plants that were considered to be outstanding. It was believed to have an effect on the body and soul and as a result it was called the 'mushroom of immortality', 'mushroom of spiritual power' or 'gift of the gods'. Thanks to its unique medicinal properties, the fungus has been used for more than 4,000 years in Southeast Asian countries as a 'cure for old age', and talismans of various kinds made from it were thought to symbolize immortality, protect against illness and attract good fortune (Siwulski et al. 2013, Schulten 2016). Numerous legends about *G. lucidum* have also been written, including the Legend of the Yellow Emperor and the Han Wudi Emperor and the miraculous mushroom with its unique form. The first fruiting bodies of *G. lucidum* as food for longevity were consumed by the Emperor of China, the builder of the Great Wall of China, Shinh-huang (259-210 BC). Since the fruiting bodies of this fungus are rare in nature, anyone who found and delivered them to high-ranking officials received a high reward. This tradition persisted in China for quite a long time, until the 1950s. Nowadays, the ever-increasing demand for preparations from *G. lucidum* has resulted in a growing interest among modern mycologists in this fungal species (Siwulski et al. 2013).

The genus *Ganoderma* was established by Karsten in 1881. The typical species was *Polyporus lucidus*, now known as *Ganoderma lucidum* and classified in the order of *Polyporales*, family of *Ganodermataceae* and genus of *Ganoderma* (Siwulski et al. 2013, Lisiecka et al. 2015).

OCCURRENCE AND MORPHOLOGICAL VARIETIES OF *GANODERMA LUCIDUM*

Ganoderma lucidum is most common in the deciduous forests in Asian countries, both on living and dead trunks of the trees, such as black alder,

birch, beech, poplar, Japanese plum and magnolia. On the other hand, it is rare in Poland and is a protected fungus, growing singly or in groups on a variety of deciduous trees, most commonly oaks. Fresh fruiting bodies appear in the summer and autumn, whereas older fruiting bodies occur throughout the year (Siwulski et al. 2013).

Ganoderma lucidum produces a fruiting body in the form of a flat cap of the diameter of 6-20 cm, which has a shiny, usually furrowed surface of varying colour (initially from light yellow-red, darkening with age to purplish, purplish-brown and finally reddish-black). The underside of the fruiting body is characterized by long tubes of length of 5-20 cm, small pores, initially white, turning brownish with age. The flesh is spongy, white, ochre-coloured just above the tubes, indistinctly streaked, without a specific taste or smell. The produced spores are yellow-brown with an oval shape. The lateral stipe of this fungus is shiny, 5-15 cm long and 1-2 cm thick. *Ganoderma lucidum* is usually kidney-shaped, however, depending on the growth conditions, a peculiar feature of this astonishing fungus is revealed - the ability to assume different shapes. An extremely rare form is the specimen known as 'Rokkaushi' or 'horned stag' that occurs only in darkened areas and is therefore considered particularly useful for medicinal purposes, causing its market price to be very high (Siwulski et al. 2013). In nature, there is also a *Ganoderma carnosum*, which grows on coniferous trees and whose fruiting bodies are darker.

As the demand for preparations from *Ganoderma lucidum* increased, several methods of the so-called artificial breeding of this fungus were developed, yet, the most important ones were based on cultivation on solid wood and intensive breeding on sawdust in a bioreactor. Production of this fungus on an industrial scale began in Japan in 1937 and later in other Asian countries.

Due to the use of different morphological varieties of *Ganoderma* in production, the quality and content of the biologically active substances are differentiated. They largely depend on the producer, its location, growing conditions, the growth type of the fungus as well as the processing and purification procedure (Boh et al. 2007).

MEDICAL PROPERTIES OF *GANODERMA LUCIDUM*

The mycelium and fruiting bodies contain pharmacologically active substances, such as carbohydrates, amino acids, proteins, steroidal compounds, triterpenes, lipids, alkaloids, volatile oils and vitamins: B2, C and calcium, zinc, iron, copper and organic germanium ions (Boh et al. 2007, Lisiecka et al. 2015, Schulten 2016). Particular health-promoting importance is attributed to triterpenes and polysaccharides (Figure 1).

The biological activity of *G. lucidum* is mainly due to the polysaccharides present in them which constitute 10-50% of the d.m. (dry matter) of the fruiting bodies. More than two hundred of them have been isolated from dif-

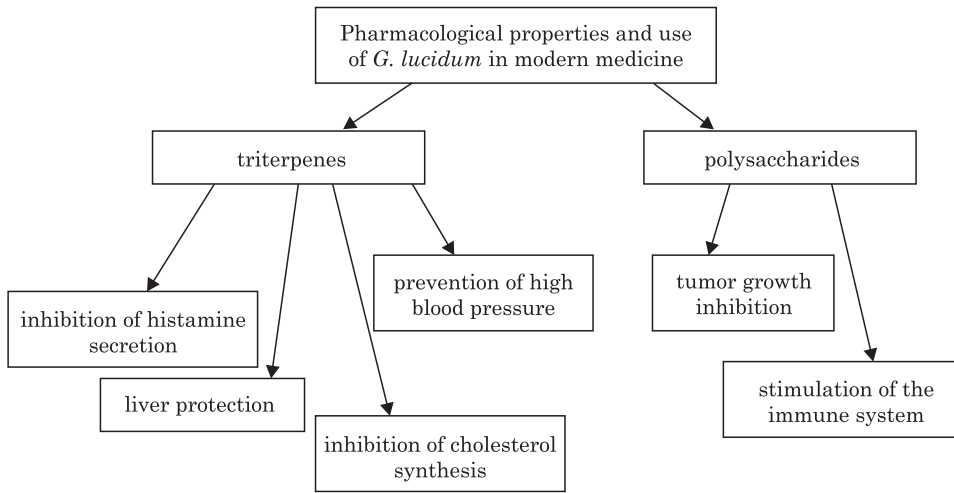


Fig. 1. The main pharmacological substances contained in *G. lucidum* and their health-promoting effects

ferent parts of the fungus (Boh et al. 2007). They are most often in the form of β -glucans and arabinoxylglucans that show immunomodulatory (mainly immunostimulating) and anti-cancer effects (Sliva 2006, Boh et al. 2007). Triterpenes contained in them, derivatives of Ganoderma, including ganoderic acids A-Z (Figure 2), ganoderals A and B, ganoderiols A and B, epoxyganoderiols A-C, ganolucidic acids A-F and lucidenic acids A-M (Figure 3). These compounds normalize blood cholesterol levels, lower blood pressure, reduce pain, improve detoxification, have anti-cancer and antioxidant effects (Boh et al. 2007).

In addition to the above-mentioned substances, special attention is also given to, among others: cyclo-octo-sulphur which inhibits histamine secretion; adenosine which has a relaxing effect on muscles, reduces blood viscosity, improves circulation, increases oxygen supply to the heart and brain; organic germanium which shows stronger properties as compared to germa-

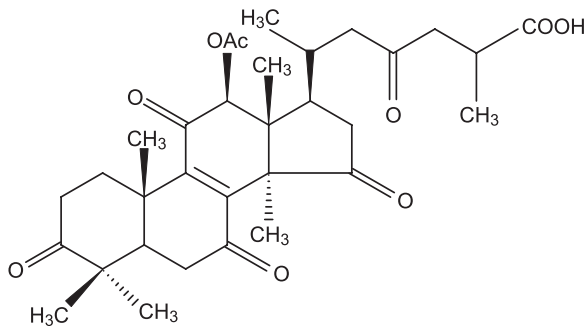


Fig. 2. Formula of ganoderic acid F (Boh et al. 2007)

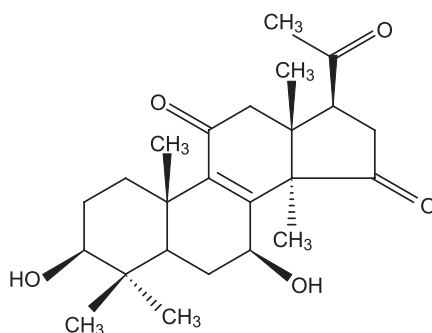


Fig. 3. Formula of lucidenic acid (Boh et al. 2007)

nium found in ginseng or garlic. Since the 1970s, numerous studies have been conducted on the use of germanium in supportive therapy in the treatment of neoplasms. Germanium, particularly in combination with beta-1,3-D-glucan shows strong anti-cancer effects (mainly lung, liver and brain cancers) and combats suffering in the final stages of the disease (Ferreira et al. 2010, Pi et al. 2013, Pazzi et al. 2021).

The mushroom spores are rich in betaine, stearic acid, coconut acid, lignoceric acid, ergosterol, acid protease, β -sitosterol, ascorbic acid, gandosterone (a substance with strong liver-protective effects), vitamins B1, B2 and B6, vitamin E, provitamin D, coumarin, mannitol and Mg, Ca, Zn, Fe ions. The fruiting bodies contain sterols, lactates and alkaloids. All the constituents of *Ganoderma* have not been studied yet (Soccol et al. 2016).

According to the Pharmacopoeia of the People's Republic of China (the formal official inventory of medications authorized in China), these fungi allow supplementation of Qi (vital energy), and relieve cough and asthma symptoms. Furthermore, they are recommended for dizziness, insomnia, palpitations and dyspnea as well as for hypertension, high levels of cholesterol, cardiovascular disease, liver and kidney disease, respiratory conditions, chronic fatigue syndrome, stomach ulcers, viral infections (e.g. flu, HIV/AIDS), and relieve the pain that occurs in the course of herpes zoster. Most importantly, however, Reishi mushrooms support the treatment of cancer (Jakopovic et al. 2021).

Researchers from Bellarmine University (USA) found that these fungi reduced proliferation (multiplication) of the neoplastic cells in the cancer-ridden lungs and the effect was a result of the apoptosis of the neoplastic cells caused by polysaccharides and saponin (Zolj et al. 2018).

On the other hand, other studies have found that taking *Ganoderma* extract reduced the number of tumours in people struggling with non-cancerous tumours of the colon and rectum (colorectal adenomas). According to the studies, β -glucan that is found in fungi, strengthens the immune system by increasing the number of macrophages and T lymphocytes, and therefore it can be taken in the states of reduced immunity (Mizuno et al. 1995).

The powder obtained from the fruiting bodies of *Ganoderma* increases sleep time, reduces pain sensation and morphine dependence, dilates blood vessels and increases blood circulation. It is recommended for skin allergies, insomnia, constipation, painful and irregular menstruation, lichen erythematous, epilepsy, gastritis, stomach ulcers, kidney disease, treatment of haemorrhoids and in type A, B and C hepatitis (Grys et al. 2011).

G. lucidum preparations are applied in the prevention and treatment of numerous diseases, including cardiovascular disease, allergies, infections, inflammation, asthma, cancer, sleep disorders, regulation of blood pressure and cholesterol levels and delaying the ageing process (Siwulski et al. 2013).

Ganoderma has a beneficial effect on the circulatory system as triterpenes contained in it are inhibitors of the angiotensin-converting enzyme, thus lowering blood pressure in patients with high blood pressure. Furthermore, *Ganoderma* improves peripheral circulation, dilates the coronary vessels, lowers cholesterol and triglyceride levels, eliminates chest pain and prevents cardiac arrhythmias. In turn, thanks to adenosine, it reduces platelet aggregation and reduces the risk of blood clots, causes skeletal muscle relaxation, has a calming effect and inhibits the stimulating effects of caffeine (Zou 2016, Cheng et al. 2017).

Gandosterone (*Ganoderma* extract) has a protective effect on the liver; it normalizes aminotransferase levels in patients with type B hepatitis. Triterpenoids and polysaccharides of *G. lucidum* have antioxidant and hepatoprotective properties by, *inter alia*, inhibiting oxidative stress. Triterpenoids significantly increased superoxide dismutase and catalase activities as well as decreased malondialdehyde content in the liver (Wu et al. 2016, Chiu et al. 2017, Chen et al. 2018).

Ganoderma also demonstrates hypoglycaemic properties – it increases blood insulin levels. It stimulates the immune system, increasing production and activity of lymphocytes, macrophages and cytokines. It also shows strong antimicrobial activity (including *Helicobacter pylori*, *Pseudomonas aeruginosa*, *P. syringae*, *Micrococcus flavus*, *M. luteus*, *Escherichia coli* (MTCC-443), *Staphylococcus aureus* (MTCC-737), *Klebsiella pneumoniae* (MTCC-2405), *Bacillus subtilis* (MTCC-1789), *Salmonella typhi* (MTCC-531) – Quereshi et al. (2010), antifungal activity (*Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Microsporium canis*, *Trichophyton mentagrophytes*, *Botrytis cinerea*, *Fusarium oxysporum* and *Physalospora piricola*) – Wang et al. (2006), Bhardwaj et al. (2017) and antiviral activity (including hepatitis viruses, influenza A virus, herpes viruses HSV-1 and HSV-2 *inter alia*, inhibits their adhesion and cell penetration/, vesicular stomatitis virus, EBV and also reduces HIV replication) – Zhang et al. (2014). It improves removal of toxins and metabolic by-products from the body, has anti-inflammatory and anti-allergenic effects as it inhibits histamine secretion, and it has adaptogenic effects as it increases cellular oxygen uptake and consumption, thus increasing the ability to cope with stress, counteracts insomnia,

dizziness, and nausea. In geriatric treatment, it is particularly recommended for seniors as an agent increasing physical and mental performance (Asai 2010). *Ganoderma* can also be used in arthritis, gastrointestinal disorders (gastritis and ulcers), lichen erythematosus and epilepsy. Administration of *Ganoderma* extract and San-Mio-San to mice with SLE (systemic lupus erythematosus) reduced plasma levels of pro-inflammatory cytokines, including IL-6, IL-10 (Cai et al. 2016).

The most valuable property of *Ganoderma* is the preventive and therapeutic anti-cancer effect (Lisiecka et al. 2015, Schulten 2016), and these fungi are more frequently used in Western countries, mainly in oncology as an adjunct to chemotherapy and radiation in immunocompromised patients at higher risk of disease recurrence.

No side effects of these preparations have been found; however, they should not be used in cases of autoimmune disease due to strong stimulation of the immune system, blood clotting problems (in the event of taking anti-coagulants or antiplatelet medications, e.g. aspirin, non-steroidal anti-inflammatory drugs, warfarin, heparin), with hypertension or hypotension (Wu et al. 2019). Reishi mushrooms may interact with hypertension medications. They lower blood pressure on their own and as a result they may lower it too much when combined with these medications. For this reason, they should not be used by people suffering from hypotension either (Meng et al. 2019, Shaito et al. 2020, Zhang et al. 2020). Wu et al. identified three angiotensin I-converting enzyme (ACE) inhibitor peptides: Gln-Leu-Val-Pro (QLVP), Gln-Asp-Val-Leu (QDVL), and Gln-Leu-Asp-Leu (QLDL). Molecular dynamics simulation suggested that the peptides are responsible for the antihypertensive activity of *G. lucidum* (Wu et al. 2019).

In their research, Tao and Feng volunteered 15 healthy and 33 atherosclerotic patients and found that any dose of germanium above 3g/day can inhibit platelet aggregation. Reishi mushrooms should not be applied at least two weeks before and after surgical procedures due to their blood clotting-lowering properties (Tao, Feng 1990).

CONCLUSIONS

The main obstacle to acceptance of natural products in official medicine is their complex and complicated structure (Grys et al. 2011), which makes it difficult to predict the final effect. On the other hand, their higher pharmacological activity as compared to single isolated substances has been confirmed, this is the so-called synergism effect (Turlo 2013). Clinical studies have demonstrated the unique characteristics of numerous medicinal fungi, including their wide applicability, high supportive and enhancing role in the treatment of various diseases, non-toxicity and lack of the side effects of use. The best-known representative of this type of medicinal fungus in the world

is *Ganoderma lucidum*. Its health-promoting effects have been known for centuries, however, the current analytical possibilities allow us to determine the exact chemical composition of the fruiting bodies and spores. They contain pharmacologically active substances, such as carbohydrates, amino acids, proteins, inorganic salts, steroidal compounds, triterpenes, lipids, alkaloids, volatile oils and vitamins (B2 and C) as well as inorganic compounds (calcium, zinc, iron, copper and germanium ions). Due to the variety of bioactive substances, these fungi constitute 'hope' for modern medicine and an example of the use of traditional Chinese and Japanese medicine. *Ganoderma lucidum* is applied in prevention and treatment of numerous diseases, including: cardiovascular diseases, allergies, infections, inflammation, asthma, sleep disorders and regulation of blood pressure and cholesterol levels. However, its most valuable properties include preventive and therapeutic anti-cancer effects and delaying the ageing process (Soccol et al. 2016, Chen et al. 2018).

Conflict of interest

The authors declare no conflict of interest.

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