Ganoderma lucidum – FROM TRADITION TO MODERN MEDICINE

ABSTRACT: Ganoderma lucidum has a long tradition of use in folk medicine of the Far East, which is documented in the oldest Chinese pharmacopoeia, written in the first century B.C, declaring it a superior medicine. The healing properties of G. lucidum reflected on folk names such as: Reishi, Mannentake, Ling Zhi etc., which mean “herb of spiritual power”, “mushroom of immortality” or “10,000-year mushroom”, respectively. It has been known, for thousands of years, that this species extends life span, increases youthful vigour and vitality and it was used in the treatments of hepatitis, kidneys’ disease, hypertension, arthritis, asthma, bronchitis, arteriosclerosis, ulcers and various types of cancer. However, Western civilisation did not discover its healing properties until the 20th century. Modern scientific researches and numerous clinical trails, conducted in recent decades, have confirmed the ancient knowledge of Eastern nations and given them a scientific basis. These studies have demonstrated many biological activities of G. lucidum extracts and compounds, including: immunomodulating, antioxidative, cytotoxic, hypoglycaemic, anti-inflammatory, antiallergic, antimicrobial, etc. It has been reported that its extracts play important role in detoxification of the body and protecton of the liver, as well as in reducing cardiovascular problems, stress and anxiety. However, its most important effect is undoubtedly immunostimulating one as it is the basis of many other positive effects. The Japanese government introduced G. lucidum on the official list of auxiliary agents for the treatments of various cancers, Alzheimer’s disease, diabetes and chronic bronchitis. Many chemical components have been isolated from G. lucidum, but polysaccharides and terpenoids are the main carriers of its bioactivities.

KEYWORDS: Ganoderma lucidum, traditional usage, modern studies, bioactivities

Ganoderma lucidum IN TRADITIONAL MEDICINE

Ganoderma lucidum (Curt.: Fr.) P. Karst. has been the important part of the traditional medicine in the Far East, especially in China and Japan, for several thousands of years. The people of these countries appreciated G. lucidum, not only because of its medicinal but also for its spiritual power. It was considered as a symbol of good luck, prosperity, good health, longevity and immortality.

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*G. lucidum* was also believed to have the power to keep from evil and was treasured in homes as a talisman (Wasser and Weis, 1997). In the ancient China, it was known as “God’s herb”, because it was believed to prolong life, enhance the youthful spirit and maintain vitality. Its fruiting bodies were rarely found in nature, so anyone who brought it to the imperial court was richly awarded (Wasser and Weis, 1997). *G. lucidum* was a part of the daily diet of monks and Taoist magi throughout Asia because of the belief that it calmed the mind, prevented tension, strengthened the nervous system and heart, improved memory and concentration, strengthened willpower, and therefore helped the achievement of wisdom. The importance of *G. lucidum* in the Far East tradition is best demonstrated by the fact that as the “King of Herbs” it was celebrated in many stories and legends and depicted in the art works, the paintings, embroidered fabrics and carvings, along with the Gods and immortals. It was a common theme on dishes, furniture, and even ladies’ hairpins, perfume bottles, always as a symbol of longevity and good fortune (Osuji *et al.* 2016). The significance of *G. lucidum* in traditional oriental medicine is testified by the oldest Chinese medical record, “Shen Nung Pen Tsao Ching”, written more than 2,000 years ago. This document presents the first world’s pharmacopoeia which was based on studies of medicinal plants and fungi, conducted by the founder of traditional Chinese medicine, Shen Nung, about 5,000 years ago. Namely, 365 plants and fungal species were described and classified based to their medicinal properties into the superior ones, which included about 120, the above-average ones (the same 120) and the average ones with about 125 species. The group of superior medications, otherwise called “God’s weeds”, included those used for maintaining the vitality, preserving mental health and increasing longevity. The members of the second group, above-average one, were taken as tonics, while those from the average category were used to treat certain diseases. That pharmacopoeia also emphasized that patients should be careful with the amount of average and above-average medications which are taken and that they should not be used continuously. On the contrary, the superior class of drugs can be taken in unlimited quantities, without any negative side effects. The top place on the list of superior remedies is reserved for *G. lucidum* (Wasser and Weis, 1997).

According to the traditional belief, *G. lucidum* can possess one of 5 flavors: bitter, salty, sour, sweet and hot, and each of them is aligned with one of the internal organs (heart, kidney, liver, lung and spleen) (Denisova, 2001). Likewise, in Japan, it is thought that depending on the colour and taste of *G. lucidum* fruiting bodies, they heal different organs. Thus, gray and the acidic ones improve vision; red and bitter regulate the functioning of the internal organs and improve memory; yellow and sweet ones affect the spleen and “soothing soul”; red and hot act on the lung and increase the courage and boost will; black and the salty ones protect kidneys; and sweet ones improve hearing, act on joints and muscles and improve the complexion. One Chinese doctor has also written: “The superior treatment consists of treating the disease before it occurs, the average treatment means treatment when the disease is detected and inferior treatment cures the disease that has already manifested itself”. The highest value of *G. lucidum* is in the fact that it can be successfully used
in all three stages of treatment. This species has been used for several thousands of years in the treatment of hepatitis, kidney disease, hypertension, arthritis, asthma, bronchitis, arteriosclerosis, ulcers and various types of cancer (Berovič et al. 2003).

_Ganoderma lucidum_ IN THE MODERN MEDICINE

Although the Far East traditional medicine has highly valued _G. lucidum_ for several millennia, its healing properties were unknown to Western civilisation until the 20th century. The current researches and numerous clinical trails conducted in recent decades have confirmed the ancient knowledge of the Eastern nation and given them a scientific basis. These studies have demonstrated many biological activities of _G. lucidum_, including immunomodulating, cytotoxic, antioxidative, antimicrobial, anti-inflammatory, hypoglycemic antiallergic, neuroprotective, etc. (Chang et al. 2006; Zhou et al. 2010; Bishop et al. 2015). However, its most important effect is undoubtedly immunomodulating, which is the basis of many other activities, and therefore Japanese government has put this species on the official list of auxiliary agents for the treatment of various cancers, Alzheimer’s disease, diabetes etc. According to Mizuno et al. (1995a, b, c), _G. lucidum_ also helps in treatments of numerous disorders, such as neurasthenia, dyspnea, insomnia, chronic hepatitis, pyelonephritis, high blood cholesterol level, hypertension, coronary heart disease, leukopenia, rhinitis, chronic bronchitis, bronchial asthma, gastropathy, and duodenum ulcer. A number of reports indicate that this fungus increases the resistance of laboratory mice to the exposure to radiation and therefore its extracts are used as a component of suntan lotion to protect against UV radiation (Wasser and Weis, 1997). It was also demonstrated that it increases the resistance of the animals to the effects of muscarine and nicotine so it is also used as an antidote in poisonings with different poisonous mushrooms (Wasser and Weis, 1997).

The results of the clinical trail including 2,000 patients suffering from chronic bronchitis who had been treated with _G. lucidum_ tablets for 2 weeks, showed an improvement of the clinical picture in about 60%–90% of patients (Chang and But, 1986). Likewise, it was confirmed that the extract of this species decreased the blood and plasma viscosities in patients with hypertension and hyperlipidemia who were recovering from cerebral thrombosis (Wasser and Weis, 1997). The usage of _G. lucidum_ in the treatment of hepatitis, in particular in the case of severe liver damage, has proved rather effective. Namely, in 355 patients who suffered from hepatitis B and used a preparation Wulingdan Pill with a high content of _G. lucidum_ fruiting bodies, the improvement was noted in 92% of patients (Chang and But, 1986).

Since _G. lucidum_ fruiting bodies are rare and the demand for them is great, nowadays this species is successfully commercially cultivated and it is available in various forms on the world market. Currently, _G. lucidum_ is a popular dietary supplement, with annual global market value amounting to $1.5 billion (Liu et al. 2010).
THE BIOACTIVITY OF CRUDE *Ganoderma lucidum* EXTRACTS

A wide spectrum of bioactivities (immunomodulatory, antioxidative, citotoxic, antimicrobial, genoprotective etc.) was demonstrated for *G. lucidum* extracts, their efficiency depending on extractant (water, ethanol, methanol, chloroform, ethyl acetate etc.), the fungal part (basidiocarp, mycelium, spores, cultivation broth) and extraction technique. It has been shown that alcohol extracts (ethanol, methanol) contain compounds which reduce the blood cholesterol and glucose levels, regulate blood pressure and inhibit the release of histamine from the cells, and have citotoxic, antiviral and hepatoprotective effects (Lu et al. 2004).

Kuo et al. (2006) noted stimulatory effect of *G. lucidum* mycelial extract on TNF-α, IFN-γ and IL-6 production, which led to improvement of innate immune response. Numerous studies have also confirmed a considerable antioxidative potential of various extracts of *G. lucidum* basidiocarps, mycelium and cultivation broth (Mau et al. 2002; Sun et al. 2004; Tseng et al. 2008; Ćilerdžić et al. 2014; 2016a,b). Namely, overproduction of reactive oxygen species, caused by numerous environmental factors and lifestyle, exceed the defence capacity of an organism and leads to the oxidative stress that could be the trigger of many diseases and disorders. Despite the existence of numerous commercial, synthetic antioxidants, finding new natural antioxidants without negative side effects is very important. Mau et al. (2002) and Saltarelli et al. (2009) have reported that the extracts may significantly enhance the non-enzymatic and enzymatic antioxidative response and remarkably reduce the level of lipid peroxidation. The extract property to inhibit lipid peroxidation was also base for improvement of heart function (Wong et al. 2004).

*G. lucidum* basidiocarp ethanol extract, cultivated under laboratory conditions on different substrates showed a great genoprotective as well as citotoxic activity against human cervix adenocarcinoma HeLa and human lung adenocarcinoma epithelial A549 cell lines (Čilerdžić et al. 2014; 2016c). Likewise, Müller et al. (2006) noted significant apoptosis effect of methanol basidiocarp extract on leukemia, lymphoma and multiple myeloma cells, and Harhaji Trajković et al. (2009) antiproliferate effect on melanoma, fibrosarcoma, and astrocytoma cell lines.

Uncontrolled usage of commercial antibiotics and antimycotics in the treatment of infectious diseases leads to the appearance of numerous resistant strains of microorganisms. On the other hand, these antimicrobial medicaments also induce various side effects, and finding of new antimicrobial agents of biological origin is the trend of current science. Various *G. lucidum* extracts showed an outstanding antimicrobial potential against Gram – and Gram + bacteria as well as numerous micromycetes, which depends on extractant and extraction method that affect extract composition (Sridhar et al. 2011). Several studies demonstrated higher antimicrobial potential of compounds insoluble in water so their content is higher in extracts obtained by non-polar organic solvents, such as chloroform. Thus, Keypour et al. (2008) noted that chloroform basidiocarp extract strongly inhibited development of *Bacillus subtilis* and
Staphylococcus aureus, while methanol extract had inhibitory effect on Escherichia coli, Salmonella spp. and B. subtilis. The ethanol extract of basidiocarps obtained on alternative substrate showed a considerable antibacterial and antifungal capacity against S. aureus and Micrococcus flavus, Acremonium strictum, Aspergillus glaucus and Trichoderma viride (Čilerdžić et al. 2014). Klaus and Nikšić (2007) reported that bacteriolytic enzymes i.e. lysozymes and acid protease are carriers of antimicrobial activity in aqueous extract.

Peculiarly, it should be emphasized that the latest findings indicate the positive effect of G. lucidum extracts on inhibition of acetylcholinesterase and tyrosinase, enzymes which high activities cause appearance of neurodegenerative disorders, especially the most frequent Alzheimer’s and Parkinson’s diseases (Hasnat et al. 2013; Taofiq et al. 2016).

THE BIOLOGICALLY ACTIVE COMPOUNDS OF Ganoderma lucidum

A wide range of different chemical compounds with medicinal properties have been isolated from the fruiting bodies, mycelium and spores of G. lucidum, but the most important ones are polysaccharides, triterpenoids, phenols and proteins (Berovič et al. 2003; Paterson, 2006; Leskošek-Čukalović et al. 2010).

Polysaccharides

Polysaccharides are the main biologically active macromolecules and the most responsible for the therapeutic application of G. lucidum acting as immunomodulators and carcinostatics (Berovič et al. 2003). They are present in fruiting bodies, mycelia, spores and cultivation broth of G. lucidum. More than 200 different polysaccharides were isolated from G. lucidum, 50 of them showing antitumor activity and some hypoglycemic effect (Wasser and Weis, 1997; Fang and Zhong, 2002). Most of the biologically active polysaccharides are 1,3-β-D- and 1,6-β-D-glucans consisting of a large number of D-glucose molecules linked by glycosidic bonds and known as homopolysaccharides (Yang et al. 2000; Paterson, 2006). They are branched and side chains occur after a certain number of glucose units in the main chain. Numerous studies have shown a positive correlation between the degree of polysaccharide branching and its immunomodulating effect as well as the length of the side chain and bioactivity degree (Zhang et al. 2001). Likewise, the majority of anticancer glucans are insoluble in water and have an average molecular weight of 1050 kDa (Paterson, 2006). However, Hsieh and Yang (2004) demonstrated a strong anti-tumor activity of water soluble G. lucidum polysaccharides against Sarcoma 180, which inhibited proliferation of even 95% cells.

The most of the researches conducted with G. lucidum polysaccharides are dedicated to their immunomodulating activities (Berovič et al. 2003). Thus, Wasser and Weis (1997) demonstrated that 1,3-β-D-glucan is the main carcino-
static agent, which is not toxic for the organism contrary to the conventional chemotherapy and with effect based on the strengthening of the host immune system. It was shown that the inhibition of tumor growth is carried out through the enhancement of the host immune response by stimulating the production of the cytokinin, interleukin (IL), tumor necrosis factor (TNF) and interferon (IFN). Namely, incubation of human macrophages and T-lymphocytes with polysaccharides isolated from fresh *G. lucidum* fruiting bodies caused increasing production of IL-1, IL-6, TNF-α and IFN-γ (Wasser and Weis, 1997). However, several researches showed that the antitumor activity of pure polysaccharides extracts is lower than crude extracts which support the fact that other substances also contribute to the bioactivity of *G. lucidum* (Liu et al. 2002).

**Terpenoids**

Terpenoids, besides polysaccharides, are the most important bioactive metabolites and ones of the main carriers of *G. lucidum* medicinal properties. Until now, 130 *G. lucidum* terpenoids have been isolated and characterized from the basidiocarps, mycelium and spores (Paterson, 2006). According to the number of carbon atoms, structure and functional groups, terpenoids were classified into the non-volatile triterpenoids (C30) and a less volatile diterpenes (C20) (Leskošek-Čukalović, 2010). Anticancer activity of *G. lucidum* triterpenoids is based on direct cytotoxicity against tumor cells, contrary to the polysaccharides with activity based on the strengthening of the organism immune response (Paterson, 2006). Thus, Ganoderic acid T, purified from the methanol extract of *G. lucidum* mycelium, showed cytotoxicity on human lung cancer cell line (95-D), in a dose-dependent manner, via apoptosis induction and cell cycle arrest (Tang et al. 2006). Some triterpenoids have inhibition effect on the growth of human hepatoma Huh-7 cells causing cell cycle arrest in G2 phase, without any effect on the normal liver cells (Lin et al. 2003).

*G. lucidum* triterpenoids also have significant antiviral activity, i.e. they play an important role in the inhibition of HIV-1 and HIV-2 protease, as well as HIV-1 reverse transcriptase. It was demonstrated that Ganosporeic acid, isolated from *G. lucidum* spores, is active hepatoprotective agent (Paterson, 2006).

**Proteins**

The bioactive proteins have also been isolated and characterized from *G. lucidum*. The immunomodulatory protein known as Ling Zhi-8 (LZ-8) constructed of 110 amino acid residues, with the molecular mass of 12 kDa has been isolated from mycelium (Tanaka et al. 1989). The recent studies showed that peptides present one of the main carriers of antioxidant activity and a polysaccharide-peptide complexes (Gl-PP) have antitumor and antiangiogenesis activities (Sun et al. 2004; Cao and Lin, 2006). *G. lucidum* protein, ganodermin,
has antifungal activity against various micromycetes, especially against some phytopathogens, such as *Botrytis cinerea*, *Fusarium oxysporum* and *Physalospora piricola*, while glycoproteins have a direct antiviral effect on a herpes simplex virus types 1 and 2 (Liu *et al.* 2002; Paterson, 2006).

**Phenolic compounds**

Phenolic compounds are also important biologically active compounds of *G. lucidum*. The dominant phenolic compounds isolated from *G. lucidum* are gallic and protocatechuic acids (Stajić *et al.* 2015). Numerous studies present that the healing properties of some medicinal mushrooms are in direct correlation with their chemical composition, particularly with the content of the phenolic compounds (Yaltırak *et al.* 2009). Polyphenols are the main antioxidative agents because they act either as free radicals’ scavengers or carriers of metal ions (Leopoldini *et al.* 2011). Ćilerdžić *et al.* (2014; 2016b) noted high correlation between amount of these compounds and antioxidative capacity of various *G. lucidum* extracts.

**FUTURE PERSPECTIVES OF *Ganoderma lucidum* IN MEDICINE**

Despite a long history of usage in traditional medicine and current studies that proved medicinal potential of *G. lucidum*, a number of challenges are still in front of scientists with the aim of its usage in a clinical practice. Firstly, the clarifying of the taxonomy is necessary, since other *Ganoderma* species can be mistaken with *G. lucidum*. Further studies on the identification of active ingredients as well as safe doses ranges should be declared for each disease. The important research goal should also be the optimisation of *G. lucidum* cultivation conditions in order to increase yield and to maximise active constituents’ production. Finally, the most important and the most challenging tasks are extensive preclinical and clinical trials which will provide a convincing evidence of the effectiveness of *G. lucidum* based medications. In conclusion, after all findings, we can expect that the slogan “*G. lucidum* a day keeps the doctor away” will be used.

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*Ganoderma lucidum* – ОД ТРАДИЦИЈЕ ДО МОДЕРНЕ МЕДИЦИНЕ

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РЕЗИМЕ: *Ganoderma lucidum* има дугу традицију употребе у народној медицини Далеког истока, што је документовано у најстаријој кинеској фармакопеји, написаној у I веку пре нове ере, у којој је проглашена за супериорни лек. Лековита својства *G. lucidum* су утицала на бројна народна имена као што су: Reishi, Mannentake, Ling Zhi са значењем „биљка духовне моћи“, „гљива бесмртности“ или „10000-годишња гљива“. За *G. lucidum* се хињадама година веровало да продужује животни век, повећава младалачку снагу и виталност и користила се у лећењу хепатитиса, болести бубрега, хипертензије, артритиса, астме, бронхитиса, артериосклерозе, чирева и разних врста канцера. Међутим, западна цивилизација је открила лековита својства *G. lucidum* тек у 20. веку. Савремена научна истраживања и бројне клиничке студије спроведене у последњих неколико деценија потврдила су древна знања далекосточних народа и дала им научну потпору. Резултати ових проучавања су показали многе биолошке активности екстраката и једињења *G. lucidum*, као што су имуномодулаторну, антиоксидативну, цитотоксичну, хипогликемијску, антиинфламаторну, антиалергијску, антимикробну и др. Доказано је да екстракти *G. lucidum* имају важну улогу у детоксикацији организма и заштити јетре, као и у смањењу кардиоваскуларних проблема, стреса и...
анксиозности. Међутим, њен најважнији ефекат је несумњиво имуностимула-торни који је основа многих других позитивних ефеката. Јапанска влада је увела *G. lucidum* на званичну листу помоћних средстава за лечење различитих врста канцера, Алцхајмерове болести, дијабетеса и хроничног бронхитиса. Многа једињења су изолована из плодоносних тела, мицелија, спора и култивационог медијума *G. lucidum* али се полисахариди и терпеноиди сматрају главним носиоцима биолошких активности.

КЉУЧНЕ РЕЧИ: *Ganoderma lucidum*, традиционална примена, савремена истраживања, биоактивности