

Connection of Ganoderma Lucidum with Health

Ganoderma Lucidum'un Sağlık ile İlişkisi

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ABSTRACT Ganoderma lucidum (G. lucidum) has been called the “mushroom of immortality” for 2.000 years. The mushroom is composed of bioactive components, such as various proteins, sterols, lectins, and fatty acids, including polysaccharides and triterpenoids. The bioactive components of G. lucidum, as a medical mushroom, has been widely used to improve public health and to treat diseases in many populations for a long time. Clinical and pharmacological studies showed that G. lucidum is composed of hundreds of bioactive components with immunomodulatory, antioxidant, antiaging, antiviral, antitumor, antiobesity, and protective effects on the liver and neurons and against human immunodeficiency virus (HIV)/ acquired immune deficiency syndrome (AIDS) through different parts of the mushroom, such as the fruit, mycelium, and spores. In addition, the components of G. lucidum are one of the important prebiotics used to strengthen the bacterial flora. The prebiotic property of G. lucidum is thought to be due to the presence of various polysaccharides. It does not show any negative or toxic effect while exhibiting its potential health effects and its cost is lower than drugs. It prevents the formation and progression of various diseases. Further study will benefit the determination of the efficacy of G. lucidum, the elucidation of other possible biological activities, the development of recommendations, and the provision of evidence in relation to other diseases. In this study; bioactive components and health effects of G. lucidum were reviewed through selected web sites including MEDLINE, Embase, Cochrane Central, www.ClinicalTrials.gov, PubMed, Science Direct, Google Scholar.

Keywords: Ganoderma lucidum; antioxidants; immunomodulation; anti-obesity agents; toxicity

ÖZET Ganoderma lucidum (G. lucidum), 2000 yıldır “ölümsüzlük mantarı” olarak adlandırılmaktadır. Bu mantar; polisakkaritler ve triterpenoitler dahil olmak üzere çeşitli proteinler, steroller, lektinler ve yağ asitleri gibi biyoaktif bileşenlerden oluşmaktadır. Tıbbi bir mantar olarak G. lucidum'un biyoaktif bileşenleri, halk sağlığını geliştirmek ve birçok popülasyondaki hastalıkları tedavi etmek için yaygın olarak birçok ülkede kullanılmaktadır. İnsan sağlığını koruması ve birçok hastalığın tedavisinde kullanılması nedeniyle G. lucidum'un toz formu, çayları, kahvesi, diyet suplemanı gibi sayısız çeşidi piyasaya sürülmüştür. Klinik ve farmakolojik çalışmalar G. lucidum'un meyve, miselium ve sporlar gibi farklı kısımlarından elde edilen biyoaktif bileşenlerinin güçlü anti-kanser aktivitesinin olduğunu, tümör oluşmadan önce kanser hücrelerini arayabilen ve yok edebilen bağışıklık sistemini geliştirdiği, immünomodülatör, antioksidant, antiaging, antiviral, antidiyabetik, antiobezite, nöronlar, karaciğer ve İnsan İmmün Yetmezlik Virüsü (HIV)/Kazanılmış Bağışıklık Yetersizliği Sendromu (AIDS)'e karşı koruyucu etkisinin olduğu bildirilmektedir. Ayrıca, G. lucidum'un bileşenleri, bakteri florasını güçlendirmek için kullanılan önemli prebiyotiklerden biridir. G. lucidum'un prebiyotik özelliğinin, çeşitli polisakaritlerin varlığından kaynaklandığı düşünülmektedir. Olası sağlık etkilerini gösterirken herhangi bir olumsuz ve toksik etki göstermemekte ve maliyeti açısından da ilaçlardan daha avantajlı olmaktadır. İleriki çalışmalar, G. lucidum'un etkinliğinin, diğer olası biyolojik aktivitelerin aydınlatılmasının, önerilerin geliştirilmesinin ve diğer hastalıklarla ilgili kanıtların sağlanmasının belirlenmesinde faydalı olacaktır. Bu derlemede; G. lucidum'un biyoaktif bileşenleri ve sağlık etkileri MEDLINE, Embase, Cochrane Central, www.ClinicalTrials.gov, PubMed, Science Direct, Google Scholar gibi seçilmiş web siteleri aracılığıyla irdelenmiştir.

Anahtar Kelimeler: Ganoderma lucidum; antioksidanlar; immünomodülasyon; antiobezite ajanları; zehirlilik

Ganoderma lucidum (G. lucidum) has been called the “mushroom of immortality” for 2,000 years.¹⁻⁴ This mushroom is known as lingzhi in China, youngzhi in Korea, reishi in Japan, and ganoderma

in the United States of America.³ Clinical and pharmacological studies showed that G. lucidum is composed of hundreds of bioactive components with immunomodulatory, antioxidant, antiaging, antiviral,

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antitumor, antiobesity, and protective effects on the liver and neurons and through different parts of the mushroom, such as the fruit, mycelium, and spores.^{1,2,4-6} Various forms of *G. lucidum*, such as powder, tea, coffee, and dietary supplement, have been introduced because of their use in protecting health and treating many diseases.⁷

BIOACTIVE COMPONENTS OF *G. LUCIDUM*

G. lucidum was first identified in England in 1781 (Figure 1).¹ Approximately 90% of *G. lucidum* is water. The remaining 10% includes protein (7.9%), fat (5.1%), carbohydrates (85.2), ash, and some vitamins and minerals (1.8%) (Table 1).⁸ In addition, the mushroom is composed of bioactive components, such as various proteins, sterols, lectins, and fatty acids, including polysaccharides and triterpenoids.^{2,7,9} Active ingredients of *G. lucidum* should be accu-



FIGURE 1: *Ganoderma lucidum*.

TABLE 1: Energy and nutrient composition of *Ganoderma Lucidum* (100 g).⁸

Energy and nutrient	
Energy (kcal)	138.3
Total carbohydrate (g)	85.2
Soluble polysaccharide (g)	10.9
Fiber (g)	59.2
Dietary Fiber (g)	70.1
Reducing sugar (g)	15.1
Protein (g)	7.9
Fat (g)	5.1
Ash (g)	1.8

rately detected to avoid inaccurate treatment of diseases and complications associated with mushroom toxicity.¹⁰

POLYSACCHARIDES

The largest bioactive components of *G. lucidum* are polysaccharides that are present in all particles of the mushroom. Such polysaccharides have a heteropolymer structure and contain xylose, mannose, galactose, and fucose with different natures.² Majority of *G. lucidum* polysaccharides (GL-PS) consist of β -1-3 and β -1-6 D glucans that present a wide bioactivity, including antioxidant, antidiabetic, anti-ulcer, antitumor, and immunostimulating effects.^{3,11-14} The polysaccharides are usually obtained from the mushroom by extracting with hot water after precipitating with ethanol or methanol, but they can also be extracted with water and alkali.²

TRITERPENOIDS

G. lucidum contains high amounts of triterpenoid. However, the triterpenoid content differs in different parts of the mushroom. The triterpenoid content may be used to measure the quality of different *G. lucidum* samples.^{10,15} Two new triterpenoids (ganoderic acids A and B) that depend on lanostan in structure have been isolated from the dried epidermis of *G. lucidum*.^{3,16} Although more than 100 triterpenoids have been reported within the composition of the mushroom, the majority of these triterpenoids consist of ganoderic and lucidenic acids.² The *G. lucidum* triterpenoids, such as ganoderic acids, are low-molecular-weight compounds that are similar to steroid hormones in terms of formation and believed to provide different benefits, such as apoptosis, cell cycle regulation, lipid lowering, and antioxidant and angiogenic effects.^{10,15}

PROTEINS

G. lucidum contains some active proteins. These proteins contain essential amino acids such as phenylalanine (39.8%), histidine (6.3%), isoleucine (6.2%), eucine (3.4%), valine (2.9%), lysine (1.9%), threonine (1.3%) and methionine (1.2%).^{17,18} A previous study detected that the protein with mitogenic and immunomodulatory characteristics was ling zhi-8 (Lz-8).³ Lz-8 protein exhibits immunomodulatory activity

by regulating interleukin 2. This molecular mechanism is thought to be an effect of essential amino acids although it is not clear.¹⁹ The protein Lz-8 isolated from the *G. lucidum* micelle and purified was observed to cause stress-dependent autophagic cell death in gastric cancer cells. The study pointed out that the mechanism described was neither a caspase-dependent cell death nor apoptosis, which may serve as a new strategy for cancer treatment.²⁰ According to the results of an American study; glutamic protease is an important protein in water extracts from *G. lucidum* and has an angiotensin converting enzyme (ACE) inhibitory effect. Also various enzymes (glycoside hydrolases and proteases) in water extracts from *G. lucidum* have been reported to play an important role in the production of anti-tumor polysaccharide from the cell wall.²¹

FATTY ACIDS

G. lucidum contains highly polyunsaturated fatty acids.¹⁸ The most abundant fatty acids *G. lucidum* were linoleic (C18:2n6c), oleic (C18:1n9) and palmitic (C16:0) acids.²² C16 and C18: 1 fatty acids from *G. lucidum* have been shown to prevent DNA damage and prevent aging and cancer.²³ Gao et al. and Hou et al., found the C-19 fatty acid on *G. lucidum* spores and the antitumor activity of this C-19 fatty acid.^{24,25} Gao et al. discovered that ethanol extracts of *G. lucidum* spores inhibit tumor cell proliferation, and HL-60 cells induce apoptosis. The most common fatty acids in *G. lucidum* are C18: 1 and C16: 0, C18: 2, C18: 0, C14: 0 and C15: 0. a small amount of C19: 0, C19: 1 and C17: 0 fatty acids are also present. They also emphasized the active compounds with aforesaid effect were long-chain fatty acids, C-19, in particular.²⁴

STEROLS

Steroids play an important role in maintaining the normal structure and function of the cell membranes and also act as a precursor in the synthesis of steroid hormones.²⁶ Several sterols (ganoderin A, chaxine B, ergosterol, stellasterol) have been isolated from *G. lucidum* spores in studies conducted in recent years.^{27,28} Chen et al. have isolated 14 ergosterol derivatives (Compounds 1-14) in their studies. Different parts of *G. lucidum* were found to contain ergosterol. Ergos-

terol peroxide (a steroid) obtained from *G. lucidum* is thought to upregulate multiple tumor suppressors and prevent cancer growth. Compounds 9-13 displayed both anti-tumor and anti-angiogenesis activities against two types of human tumor cells and human umbilical vein endothelial cells (HUVECs). Compound 2 had significant selective inhibition against two tumor cell lines, while 3 exhibited selective inhibition against HUVECs.²⁶

ALKALOIDS

Four polycyclic alkaloids, lucidimine A-D (C16 H15NO, C15H13NO2, C16H15NO3, C17H 17NO4) were isolated of *G. Lucidum*.²⁹ There is not much data about the biological activities of alkaloids obtained from *G. lucidum*. Chen and Lan conducted a study on MCF-7 cells and Lucidimine B showed the best antioxidant and antiproliferative effect. Lucidimine B arrested the MCF-7 cell cycle in the S phase by inducing DNA fragmentation.³⁰

PHENOLIC COMPOUNDS

Among these bioactive chemical molecules obtained from *G. lucidum* are phenolic compounds (1.35/ mg/1 g *G. lucidum*). The phenolic compound content of *G. lucidum* in a study were found ganoderic acid, ferulic acid, rutin, coumaric acid, caffeic acid, kercetin.³¹ These phenolic compounds are important antioxidants.^{31,32} The major flavonoids with active antioxidant activity in ethanol extracts from *G. lucidum* were quercetin, myricetin and morin.³³ Recent studies have emphasized the importance of phenolic compounds as well as other bioactive components.³⁴ But in a study it was reported that the significant amount of phenolic compounds is strongly bound to glucans and thus reduces antioxidant capacities.³⁵

HEALTH EFFECT

The bioactive components of *G. lucidum*, which has been used for traditional medical treatment, are used to treat many health problems. Recent studies especially report the therapeutic effects of the mushroom on cancer, asthma, allergies, autoimmune diseases, neurological diseases, diabetes, hypertension, obesity, liver diseases, and many other conditions (Figure 2).³⁶⁻⁴⁴

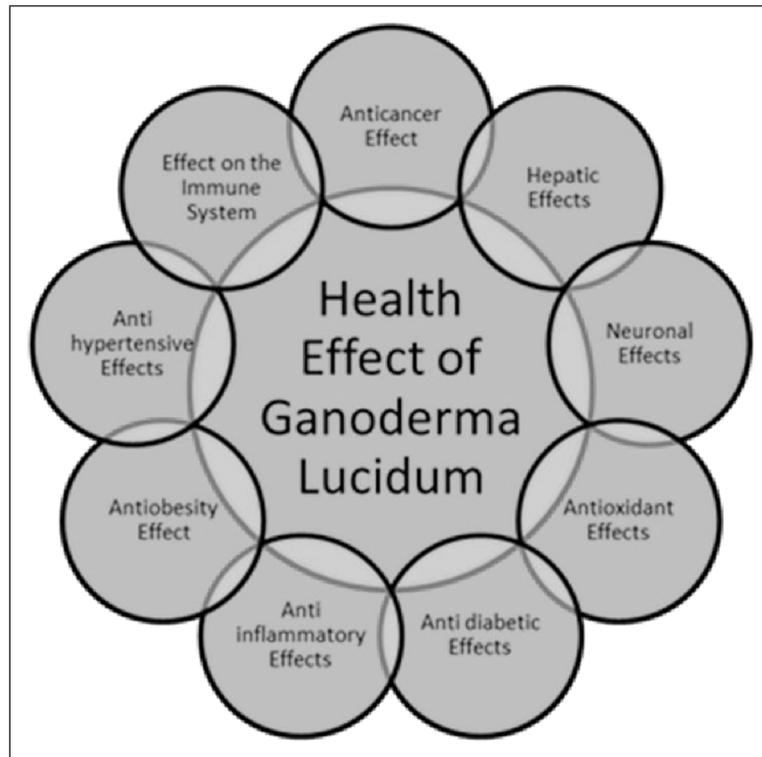


FIGURE 2: Health effect of ganoderma lucidum.

ANTICANCER EFFECT

Studies discovered that medical mushrooms like *G. lucidum* produce polysaccharides with several anti-tumor characteristics within a culture medium; therefore, reports by the American Institute of Cancer suggest these mushrooms could be used as active substances in drugs.^{45,46} Indeed, *G. lucidum* that has been used to develop a healthy life and to increase the lifetime in Far East countries for many years is considered to play an important role in preventing and treating many health problems. The gradual increase of interest in *G. lucidum* among cancer patients led to studies that evaluate its clinical anticancer effects.¹⁵ *G. lucidum* contains different bioactive components. However, among these, triterpenoids and polysaccharides (β -glucan, in particular) are the most important components that contribute to anticancer functions.^{15,47-49} *G. lucidum* extracts present an anticarcinogenic effect on different cancer cell lines.¹⁰ Recent studies demonstrate many mechanisms where *G. lucidum* extracts present anticancer activities.^{10,49} Such mechanisms are summarized as follows:

Cytotoxic Activity

Normal cells divide with a certain rate during the cell cycle process. However, when this process gets out of control, the cell cycle becomes modified, which leads to abnormal cell proliferation that causes cancer formation.¹⁵ Direct killing of these cells or inhibition of cell proliferation is defined as cytotoxicity.⁵⁰ Anti-cancer drugs specific to cell cycle phases also fight with cancer through cytotoxic activity. However, cytotoxic drugs with chemotherapeutic effect show toxic effects against cells by causing DNA damage and programmed cell death. Cytotoxic drugs can stop the rapid proliferation of cancer cells through cell cycle arrest; however, they do not kill these cells directly.¹⁵ *G. lucidum* is considered to be the most active cytotoxic mushroom species against cancer cells.⁵⁰ Many studies showed that *G. lucidum* triterpenoids present cytotoxicity against cancer cells, have antioxidant effect and reduce cell damage.^{5,16,47,51-53}

Antimetastatic Activity

Metastasis is common in cancer patients and is the leading cause of death.¹⁵ Preventive effects of *G. lu-*

cidum triterpenoids on cancer metastasis have been shown previously.⁵⁴⁻⁵⁶ A recent study demonstrated that *G. lucidum* inhibited migration and adhesion of highly metastatic breast cancer cells by suppressing the focal adhesion kinase (FAK)-SRC Paxillin cascade pathway.^{15,57} In another study, it was reported that *G. lucidum* extract could reduce breast-lung cancer metastases by down-regulation of genes responsible for cell invasion.⁵⁸

Anti-inflammatory Activity

Inflammation is a group of cellular events as a response against infection and tissue damage.⁵⁹ Chronic inflammation cause 25% of all cancer cases. Anti-inflammatory treatments are successful for the prevention and treatment of inflammation-associated cancer.¹⁵ Many studies showed that *G. lucidum* has an anti-inflammatory effect. The possible mechanisms for its anti-inflammatory effect were found to be associated with reduction of myeloperoxidase (MPO) and lipid peroxidation levels and regulation of multiple pro-inflammatory cytokines.^{49,59-61}

Immunomodulation Activity

Tumor cells produce transforming growth factor- β 1, interleukin (IL)-10, and vascular endothelial growth factor that all may prevent the functions of immune cells.¹⁵ Tumor-associated macrophages are transformed into M2 macrophages and cause an immune reaction on the host, and tumor cell invasion and attack following this immune response increase tumor growth and metastasis.⁶² Many studies showed the immunomodulator effect of GL-PS, in particular by affecting the immune cells or by directly affecting the tumor cells.⁴⁷⁻⁴⁹

Furthermore, *G. lucidum* may safely increase chemotherapeutic efficiency (boosting the chemotherapeutic effect by increasing the dose of chemotherapeutic drug accumulated on the cell).⁶³ A study found that *G. lucidum* polysaccharides increase the effect of cyclophosphamide and cisplatin and may provide a protection against bone marrow suppression.³⁶ However, more studies are required to identify quantitatively the treatment for prostate adenocarcinoma, in particular, and specific tumoral diseases like other cancers during the course of the individualized treat-

ment.⁴⁹ Some studies conducted on *G. lucidum* and anticancer effect are summarized in Table 2.

Despite the limited number of human studies investigating the anticancer effects of *G. lucidum* in recent years, many in vivo and in vitro studies have been performed. In the randomized controlled human trials, it was emphasized that the group receiving *G. lucidum* supplementation had better disease stability and reduced viability of cancer cells.^{64,66} In studies investigating *G. lucidum* spores and β -glucagon effects in rats, it has been reported that they inhibit inflammatory markers and tumor cells and increase survival of rats.^{5,62,67,68} Different results can be obtained depending on the cell type in studies performed in cancer cells. Ruan et al. conducted a study on different cancer cells have reported that HepG2 cells do not induce apoptosis, although they cause apoptosis in HeLa and Caco-2 cells.⁵⁷ Nevertheless, in vitro studies have shown that they inhibit cancer cells and show high cytotoxic activities.^{5,16,47,49} It has been shown in these studies that *G. lucidum* has played an important role in cancer treatment and prevention.

Studies also reported that *G. lucidum* may cause serious problems on patients who receive cancer treatments. The knowledge that using *G. lucidum* does not have any side effect, such as liver failure and death, was expressed as inaccurate. A study reported that use of this mushroom during, before, and after chemotherapy may be problematic because it causes nausea, vomiting, and bleeding and reduces the effects of chemotherapeutic and other drugs.⁶⁹

HEPATIC EFFECTS

The most attractive mushroom that has hepatoprotective effects is *G. lucidum*. The polysaccharides and triterpenoid components of *G. lucidum*, in particular, are suggested as bioactive components responsible for protection against toxin-induced hepatic damage.^{37,70} Chronic alcohol consumption is associated with secretion of pro-inflammatory cytokines, which play an important role in the development of ethanol-induced steatotic liver. Such oxidative stress and pro-inflammatory factors may cause inflammation, apoptosis, and fibrosis, as well as ethanol-induced steatotic liver. Oxidative stress also creates an ethanol-originated liver damage through reactive

TABLE 2: Some studies on ganoderma lucidum and its anticancer effect.

Subjects	Study types	Consumption (G. Lucidum extract)	Health effects of fermented foods	References
21 patients with gynaecological cancer	Randomized double blind controlled	G. Lucidum extract (1000 mg) and spores (1000 mg) Control group, Vitamin C (200 mg)	2 cases in the G. Lucidum extract group and 3 patients in the spore lingzhi groups achieved disease stability. All patients in the placebo group presented a progression.	(64)
12 patients with lung cancer	Randomized controlled	G. Lucidum Polysaccharide extract	GI-PS caused suppression of plasma-originated lymphocyte activation in cancer patients.	(65)
96 şndividuals with colorectal adenoma	Randomized controlled	G. Lucidum micelle (MAC) (1.5 g/day)	An increase was detected in number of adenomas in the control group up to 12 months whereas a decrease was observed in the MAC groups (p<0.01). Moreover, total adenoma size increased to 1.73 ± 0.28 mm in the control group whereas decreased to 1.40 ± 0.64 mm in the MAC group (p<0.01).	(66)
Human acute myeloid leukemia HL-60, Human chronic myeloid leukemia K562, Human gastric carcinoma SGC7901, Murine sarcoma S180 Murine hepatoma H22 cell culture	In vitro	G. Lucidum extract and spore oil	Both G. Lucidum extract and spore oil were found to inhibit cell growth on tumour cells.	(5)
Human breast carcinoma cell MDA-MB-231 Hepatocellular carcinoma cell HepG2	In vitro	35 triterpenoids isolated from the fruit part of G. Lucidum	Cytotoxic activities (especially TNF α) were found higher.	(16)
Human cancer cell breast cancer MDA-MB 231 Murine melanoma B16-F10	In vitro	G. Lucidum extracts	G. Lucidum extract significantly inhibited release of IL-8, IL-6, MMP-2 and MMP-9. It also reduced viability of both cancer cells significantly.	(49)
Inflammatory breast cancer (IBC) cells (SUM-149)	In vitro	G. Lucidum extracts (Pharmanex),	This study shows that G. Lucidum selectively inhibits viability of the cancerous cell; however, it does not affect viability of non-cancerous breast epithelium cells; it also inhibits cell invasion.	(47)
Caco-2, HepG2 and HeLa cells	In vitro	G. Lucidum triterpenoid	The mushroom promoted apoptosis in HeLa cells. It caused apoptosis most (29%) on apoptotic cells in Caco-2 cells. It did not cause apoptosis in hepG2 cells.	(57)
Injected into S180 and H22 tumour cells in 60 rats	In vivo	G. Lucidum, (1, 2, 4 g/kg) Ganoderma spore oil flourouracil (5-FU) (1.2g/kg)	Both G. Lucidum extract and spore oil were found to inhibit tumour cells. GL was found safer than fluorouracil (5-FU).	(5)

continue →

TABLE 2: Some studies on ganoderma lucidum and its anticancer effect (continue).

Subjects	Study types	Consumption (G. Lucidum extract)	Health effects of fermented foods	References
Rats of which Lewis lung carcinoma (LLC1) were injected	In vivo	Celecoxib(Pfizer) or G. Lucidum β-glucan	G. Lucidum β-glucan significantly increased IL-12 and IFN-γ mRNA expression; however, IL-6, IL-10, COX-2 decreased. It provided transformation of TAMs into M1 macrophages and reduced transformation of TAMs into M2 macrophages.	(62)
Rats exposed to 4-Gy or 8-Gy radiation dose	In vivo	β-glucan	A death rate of 100% was detected when no radioprotective agent was used; and β-glucan was found to save 66% of the rats from death. When combined with amifostine, a radioprotective agent, survival rate increased to 83%. Furthermore, a significant decrease was found in bone marrow deviations (secession from normal) in the rats which were treated with β-glucan before.	(67)

oxygen species (ROS) that does not cause direct oxidative damage. *G. lucidum* draws attention because of its antioxidant capacity and anti-inflammatory effect on ethanol-induced steatotic liver.^{71,72} A study detected that the liver of the rats that consumed alcohol for 20 days enlarged. The alcohol-induced liver enlargement in the rats that were regularly provided alcohol was significantly suppressed by consumption of *G. lucidum* [during 4 weeks, The Reishi suspension (33 mg/ml) and water (1 mL)], which reduced their neurotransmitter imbalance.⁷³ Chung et al. administrated *G. lucidum* to the rats with ethanol-induced fatty liver. They discovered that the cholesterol and triglyceride levels of the rats decreased; their antioxidant enzymes (superoxide dismutase [SOD], catalase [CAT], and glutathione [GSH]) increased; their inflammation proteins (Inducible nitric oxide synthase (iNOS), Cyclooxygenase2 (COX2), tumor necrosis factor (TNF)-α nuclear factor-kappa B (NF-κB), and IL-6) decreased, and their hepatic injury biomarkers (aspartat aminotransferaz, alanine transaminase, and alkalenfosfataz) improved.⁷² In another study carried out on adult rats, GL-PS was administered as extracts for 14 days (250-500 mg/kg/d), and plasma malondialdehyde (MDA) and plasma 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels were found significantly lower in the groups that were administered GL-PSs. Furthermore, the Cu-Zn SOD level of the liver tissue in the GL-PS group significantly increased. Such results showed that GL-PS reduce oxidative stress and protect DNA against liver tissue damage.⁷⁴

Moreover, 26-oxygenosterole, isolated from *G. lucidum* species, was found to decelerate cholesterol synthesis in the plasma and liver and/or to accelerate cholesterol metabolism and decrease the total cholesterol level (25%).⁷⁵

NEURONAL EFFECTS

Given that *G. lucidum* was considered to have neurological benefits from ancient ages, it is used for its analgesic and muscle-relaxant characteristics.¹⁰ *G. lucidum* is known to have neuron-protective components that prevent neuronal differentiation and apoptosis of neuron cells.⁷⁶ GL-PS, protects the neurons against in vitro hypoxia/reoxygenation damage; and the spore oil protects the dopaminergic neurons. A previous study found that it improved through anti-inflammation of the behavioral deficiencies in a rat model with Parkinson's disease. GL-PS extracts significantly prevented the production of microglia-derived proinflammatory and cytotoxic factors, including nitric oxide (NO), TNF-α and IL-1β.⁷⁷ The recent data show that GL-PS starts neuronal differentiation of pheochromocytoma cell

cultures and protects the neurons against a possible invasion and apoptosis between extracellular signal-regulated kinase1/2 and response element-binding protein signal paths. GL-PS reduced expressions of pro-inflammatory and cytotoxic factors from microglia and efficiently protected dopaminergic neurons against inflammation.⁴⁰ Moreover, Zhang et al. suggested that *G. lucidum* spores protect injured spinal motor neurons by up- or down-regulating the expression levels of the proteins that play an important role in axon degeneration.⁷⁸ Such results show the nerve protection and antioxidant characteristics of *G. lucidum* extracts. The outcomes of a study revealed that both GL-PS and methylprednisolone (MP) (30 mg/kg) treatments significantly inhibit apoptosis on injured spinal segments. Levels of MPO and pro-inflammatory cytokine TNF- α were measured to assess neuroinflammation following a spinal cord injury (SCI). An increase was detected in mean MPO and TNF- α levels in the trauma group when compared with those in the control and sham groups. The treatment with GL-PS and MP possibly suppressed MPO and TNF- α production associated with the anti-inflammatory activity of GL-PS. The spinal cord levels of MDA, which is a balanced product of lipid peroxidation, significantly increased after a traumatic SCI. Treatment with both GL-PS and MP inhibited lipid peroxidation and significantly lowered MDA levels (Trauma group: 5.68 ± 0.58 nmol/mg-protein; MP group: 2.22 ± 0.21 nmol/mg-protein; GL-PS group: 2.05 ± 0.27 nmol/mg-protein).⁴⁰ Matsuzaki et al. found in their study performed on rats that *G. lucidum* mycelium (MAC) has an antidepressant-like potential and anxiety reducing-like effects on memory-associated and/or stress-induced anxiety because of the antagonism of serotonin precursor 5-hydroxytryptamine receptor 2A receptors.⁷⁹ Another study performed on rats found an increase on neural progenitor cell (NPC) proliferation by oral administration of GL-PS to increase neurogenesis and to relieve cognitive disorders in the rats with transgenic Alzheimer's disease. GL-PS also stimulated self-renewal of NPC in the cell culture. These findings motivated us to consider the possible use of GL-PS for the treatment of cognitive disorders as a regenerative therapeutic agent.⁸⁰ Xuan et al. conducted a study on

the brains of rats with type 2 diabetes and found a significant suppression by MAC on superoxide production in ischemic penumbra, neuronal cell death, and vacuolization. They showed that such suppression accompanies the reduction in the number of caspase-3 positive cells. They observed that MAC also reduced the receptor-interacting protein kinase 3 mRNA, which is a key molecule for necroptosis and protein expression. Depending on the aforesaid results, they reported that MAC would provide a resistance to apoptotic and necroptotic cell death and relieve the cerebral ischemic damage caused by H/I.⁸¹

ANTIOXIDANT EFFECTS

Free radicals and ROS are produced as side products of metabolic processes including redox enzymes and bioenergetic electron transfer along with exposure to some external chemicals. ROS and free radicals may damage the cells through oxidation and causes different age-dependent diseases. *G. lucidum* is known to increase the activity of SOD and CAT, which are crucial in ROS removal.¹⁰ A study conducted on rats with ovarian cancer found that the polysaccharides obtained from *G. lucidum* significantly reduce MDA and increase the activity of antioxidant enzymes in the serum.⁸² A study carried out on 300 birds with similar body weight found that a diet contaminated with aflatoxin B₁ (AFB₁) suppresses the growth performance, antioxidant capacity, and immune functions of the birds. However, the addition of *G. lucidum* into the diet significantly eliminated the negative effects of AFB₁, increased growth performance, and decreased oxidative stress and immune suppression.⁸³ Chiu et al. carried out a study on 42 healthy individuals and divided the participants into two groups. They administered *G. lucidum* and placebo (225 mg after lunch and dinner) to the participants and followed them by a six-month interval for one year. The antioxidant capacity (TEAC; 79.33-84.04) and antioxidant enzyme activities of the participants in the *G. lucidum* group were higher. Furthermore, the hepatic steatosis state rate decreased through examining the hepatic enzyme activities and conducting an ultrasound.⁸⁴ Another study analyzed content of eight mushroom species and found *G. lucidum* to have the highest total phenolic content (TPC)

(39.3±0.07 mg GAE/g), total flavonoid content (TFC) (15.1±0.04 mg GAE /g) and the strongest free radical scavenging activity (IC50=3.66 mg/mL). TPC of the other mushroom examined in the study ranged from 3.9±0.04 (*Tremella fuciformis*) to 11.8±0.06 (*Agrocybeaegerita*) mg GAE/g and TFC ranged from 0.75±0.04 (*Grifolafrondosa*) to 4.29±0.04 (*Auricularia auricula-judae*) mg GAE/g.⁸⁵

ANTIDIABETIC EFFECTS

Insulin resistance-associated type 2 diabetes characterized by hyperglycemia is the most common metabolic disease almost worldwide and has significantly increased in developing countries.³⁹ A study pointed out that natural antioxidant treatment may reduce diabetic complications, and discovery of useful antioxidants is necessary for fighting against diabetic complications.⁸⁶ Triterpenoids, polysaccharides, glycoproteins, and proteins are known to have an antidiabetic effect.⁸⁷ Polysaccharides prevent hyperglycemia by regulating the expression of some important enzymes on the glucose metabolism pathway.¹⁴ Triterpenoids present preventing activities for aldose reductase and α -glucosidase associated with glucose metabolism.⁸⁸ The protein Lz-8 (*G. lucidum*) positively affects anti-type 1 diabetes activity. The mitogenic activity of Lz-8 is considered to be one of the mechanisms that reduce plasma glucose concentrations.³⁹ In a study performed on rats, GL-SP (*G. lucidum* spores powder) was administered to the rats to reduce their blood glucose level (21.0 %), and lipid synthesis in the GL-SP groups significantly decreased after four weeks when compared with that in the control group. The GL-SP administration significantly relieved the oxidative stress, and the lipid metabolism-associated genes and glycogen synthesis-associated genes increased in diabetic rats. Furthermore, it was shown that GL-SP consumption may be beneficial because it promotes glycogen synthesis and inhibits gluconeogenesis to reduce blood glucose levels. The GL-SP treatment was associated with improved lipid profile (the blood triglyceride levels decreased by 49.0% and total cholesterol decreased by 17.8% as compared to the non-treatment group). As a result, GL-SP may be used as a component to reduce diabetes mellitus through antihyperglycemic

and antihyperlipidemic activities.⁸⁶ Another study reported that *G. lucidum* extracts presented the best dependent inhibitor activity at 4.88 mg/ml against IC50 and α -glucosidase and aldose reductase preventing potential by 9.87 mg/ml IC50 level.⁸⁵

ANTI-INFLAMMATORY EFFECTS

Acute inflammation is an outcome of a complex signal transmission pathway required for protection, recovery, health, and normal welfare of the body. However, chronic inflammation is associated with onset of autoimmune disorders. Some herbal drugs targeting the inflammatory cytokines were detected in the past. Among these herbal products, *G. lucidum* is told to have immunomodulatory and immune-boosting effects and central characteristics of many pathophysiological states in response to inflammation and germ invasion.⁸⁹ Macrophages are important immune cells for regulation of inflammation response and includes numerous inflammatory mediators, such as TNF- α , IL-6, ROS, NO, and prostaglandin E2. Irregular production of these mediators increases the severity or mediate appearance of many diseases, including rheumatic diseases, cancer. In a study performed in the RAW264.7 cell culture, triterpenoids isolated from *G. lucidum* were found to inhibit TNF- α , interleukin-6, and HO-1 activity.⁷ Liua et al. found that *G. lucidum* extracts significantly reduced TNF- α levels in mononuclear cells of peripheral blood in asthmatic patients through rat macrophages. Ganoderic acid C1 (GAC1) is the only compound that lowers TNF- α levels from 15 triterpenoid obtained from *G. lucidum* extracts. GAC1 produced >30% inhibition at 10 μ g/mL. This study showed that GAC1 has a new therapeutic potential for the treatment of asthma.⁹⁰ In a previous study conducted on rats with chronic pancreatitis, the effect of *G. lucidum* strain S3 (GLPS3) was analyzed. For four consecutive weeks, GLPS3 intervention has been reported to relieve the pancreatitis in the rats by reducing lipase, amylase, interferon (IFN), and TNF levels, also increasing SOD and TEAC.⁹¹

ANTI-OBESITY EFFECT

Obesity is closely related to low-grade inflammation that causes insulin resistance, hepatic steatosis, cardiovascular diseases, sleep apnea, and cancer.⁴⁴ Moreover, pieces of evidence show that obesity triggers

irregular endocrine functions. This led situation to consider that the fat tissue is not an inactive tissue anymore.⁹² In a study conducted on rats, obesity and the effects of inflammation decreased on the rats treated with *G. lucidum* mycelium extract (WEGL). These effects are transferred through horizontal feces transmission, which was reported to originate from the effect of WEGL on intestinal microbiota. High-molecular-weight polysaccharides present a WEGL-like healing effect. These results encouraged the researchers to think that high-molecular-weight polysaccharides may be an active ingredient of WEGL, and they are likely to be used as a prebiotic in prevention of obesity.⁴⁴ Another study investigated whether a diet that includes triterpenoids and polysaccharides extracted from *G. lucidum*, a medical mushroom affects adipocyte differentiation and glucose uptake. RM (0, 50, 100 µg/mL) was shown to induce activated protein kinase (AMPK) and to increase glucose uptake by adipocytes. The study reported that RM may control adipocyte differentiation and glucose uptake. *G. lucidum* inhibits key transcription factors (peroxisome proliferator-activated receptor-γ (PPAR-γ), sterol regulatory element binding element protein-1c (SREBP-1c) and CCAAT/enhancer binding protein-α (C/EBP-α)) and gene expression (fatty acid synthase (FAS), acyl-CoA synthetase-1 (ACS1), fatty acid binding protein-4 (FABP4), fatty acid transport protein-1 (FATP1) and perilipin) that are responsible for adipocyte differentiation, synthesis, transportation, and storage. The study further revealed that a standard RM may have antidiabetic effects.⁹²

ANTIHYPERTENSIVE EFFECTS

When compared with other medical mushrooms, *G. lucidum* extracts are known as the most efficient ACE inhibitors.⁹³⁻⁹⁵ Redundancy of phenolic compounds within *G. lucidum* is considered to contribute to this inhibition.³⁸ A previous study found that *G. lucidum* mycelium has a high blood pressure-lowering potential depending on anti-ACE proteins.⁹⁶ However, Lee and Rhee suggested an alternative mechanism of *G. lucidum* extract-mediated hypotension. On the other hand, *G. lucidum* extracts inhibit sympathetic nerve movements in the central nervous system, and this causes a hypotensive effect without

any modification in the heart rate.³⁸ Tran et al. administered automatically digested reishi (ADR) extract to rats for four weeks and detected that ADR significantly reduced systolic blood pressure, and such effect lasted approximately eight hours (reduction to 26.8 mmHg [a decrease of 15%]). Eleven peptides were defined from ADR, and four of these were found to inhibit strongly against ACE. At a concentration as low as 100 µg/mL, ADR showed about 50% inhibition on ACE and the enzyme was nearly completely inhibited at 1670 µg/mL. Consequently, ADR may be a good hypotensive peptide source that may be used with antihypertensive drugs.⁹⁴

EFFECT ON THE IMMUNE SYSTEM

G. lucidum is widely used for infectious diseases (bronchitis, asthma, allergies, herpetic conditions, and HIV in recent years) in traditional Chinese medicine because of its ability to affect the immune system.² *G. lucidum* is pronounced to strengthen body resistance and improve structural homeostasis. In a study, GL-PS [low-dose (2.5 mg/kg), intermediate-dose (25 mg/kg), and high-dose (250 mg/kg)] was administered to rats whose immunity was suppressed through injection of cyclophosphamide (Cy, 300 mg/kg), an immunosuppressive antitumor agent, for seven days. In the rats treated with Cy, low-dose GL-PS accelerated the healing of bone marrow, red blood, and white blood cells. In such study, treatment with GL-PS resulted in the accelerated recovery of immunosuppression in the rats treated with cyclophosphamide.³⁶ High-dose GL-PS (2.25 g/kg) were found to strengthen the immune system.⁴¹ In a research, peripheral blood after exercise, absolute neutrophil count, macrophage phagocytic index, serum agglutination valency, and number of the plaque forming cells were found significantly lower in the rats that had severe exercise for a long period and did not receive GL-PS. Medium- and high-dose GL-PS significantly increased peripheral white blood cell, absolute neutrophil count, macrophage phagocytic index, serum agglutination index valency, and number of plaque forming cells. High-dose GL-PS increased the peritoneal macrophage phagocytosis rate. The results show that the immune response of the rats that received GL-PS developed.⁹⁷

EFFECT ON THE GUT MICROBIOTA

Recent developments have shown a link between gut microbiota and many metabolic disorders. Microbiota also regulates energy metabolism.⁹⁸ The components of *G. lucidum* are one of the important prebiotics used to enhance bacterial flora. Polysaccharides from *G. lucidum* are thought to be the source of prebiotic effects.⁹⁹ Li et al. investigated the effects of polysaccharides from *G. lucidum* strain S3 (GLPS3) on intestinal microbiota modulation in mice. GLPS3 altered the diversity of gut microbiota, especially, decreased the relative abundance of bacteroidetes and increased that of Firmicutes. The ratios of Firmicutes to Bacteroidetes (F/B) for GLPS3 (200 mg/kg/day), GLPS3 (300 mg/kg/day), GLPS3 (400 mg/kg/day) and normal control were 0.70, 1.05, 0.84 and 1.00 respectively.⁹¹ In another study, polysaccharide from *G. lucidum* was orally administered to mice to investigate the effects on intestinal barrier functions. In the group of *G. lucidum* polysaccharides, Bacteroidetes and Firmicutes rates were 72.7% and 23.1%, respectively, in the control group and 62.3% and 33.2%, respectively. Moreover microbiota richness in cecum increased.¹⁰⁰ Also in a study using *G. Lucidum* triterpenoids; it has been found to modulate lipid and cholesterol metabolism by modulating gut microbiota in rats.¹⁰¹ *G. lucidum* may act as an immunomodulatory agent to activate gut microbiota and thus may be useful in the treatment of many diseases.¹⁰²

NEGATIVE EFFECT AND TOXICITY

In a study that monitored the biological hepatic markers, renal toxicity, and genotoxicity of *G. lucidum* (220 g fresh *Ganoderma*/kg), no negative evidence about hepatic toxicity, renal toxicity, and genotoxicity was found in healthy individuals after a four-week supplementation.¹⁰³ Another study did not observe any abnormal clinical symptoms or death in Wistar rats. No significant difference was observed on the hematological value, clinical biochemistry value, and organ/body weight rates in Kunming mice. Tests for toxicity were performed, and the outcomes of the current study confirmed that GL-PS is not toxic.⁴¹ No side effect was detected on 250 mg/kg GL-PS administered to mice.³⁶

However, individuals who use antihypertensives, among others, should be monitored because of the blood pressure-lowering effect of *G. lucidum*. *G. lucidum* doses are also reported to cause a significant decrease on blood glucose. Therefore, individuals who use a hypoglycemic agent or insulin should be more careful.² *G. lucidum* extracts prevent blood coagulation, and individuals who use anticoagulant agents, such as warfarin or coumadin, should be more careful or refer to a health care professional for medical advice.¹⁰⁴

CONCLUSION AND RECOMMENDATIONS

G. lucidum, as a medical mushroom, has been used extensively for many years to improve health and prevent or treat diseases. EFSA reported that *G. lucidum* may support the immune system by stimulating cytokine production (i.e., TNF- α and IFN-gamma). The recommended adult dose to support the immune system is 2 to 6 g/day of raw mushroom or 600-1,800 mg (three times a day) of extract, whereas that for physical wellness is 150 to 350 mg/day (EFSA, 2011).¹⁰⁴ Recently, the results of in vitro, in vivo and human clinical studies show that *G. lucidum* has positive effects on health through various biological mechanisms. Many positive effects of *G. lucidum*, such as strong anticancer activity by improving the immune system, which may seek and eliminate cancer cells; strengthening of the liver, neurons, and immune system; as well as antioxidant, antidiabetic, anti-inflammatory, antiobesity, and antihypertensive effects, have been addressed in recent years. Further study will benefit the determination of the efficacy of *G. lucidum*, the elucidation of other possible biological activities, the development of recommendations, and the provision of evidence in relation to other diseases.

The studies conducted regarding the health effects of *G. lucidum* are mostly limited to animal studies. Human studies are lacking. The effects of various doses, forms, and exposure in different periods should be investigated. In addition, although the addition of *G. lucidum* in a diet proved to be reliable at the end of the conducted acute and chronic toxicity test, its safety should be supported through further studies. Further studies on the level of consumption

are also necessary to determine the health benefits of *G. lucidum*.

Ethics statements

This is a review article. It has not involved any human subjects and animal experiments.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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