The beneficial effects of *Ganoderma lucidum* on cardiovascular and metabolic disease risk

Sze Wa Chan*, Brian Tomlinson*, Paul Chan and Christopher Wai Kei Lam

*School of Health Sciences, Caritas Institute of Higher Education, Hong Kong SAR, China; Faculty of Medicine, Macau University of Science & Technology, Macau, China; Division of Cardiovascular Medicine, Department of Internal Medicine, Wan Fang Hospital, Taipei Medical University, Taipei City, Taiwan

**ABSTRACT**

**Context:** Various herbal medicines are thought to be useful in the management of cardiometabolic disease and its risk factors. *Ganoderma lucidum* (Curtis) P. Karst. (Ganodermataceae), also known as Lingzhi, has received considerable attention for various indications, including some related to the prevention and treatment of cardiovascular and metabolic disease by ameliorating major cardiovascular risk factors.

**Objective:** This review focuses on the major studies of the whole plant, plant extract, and specific active compounds isolated from *G. lucidum* in relation to the main risk factors for cardiometabolic disease.

**Methods:** References from major databases including PubMed, Web of Science, and Google Scholar were compiled. The search terms used were *Ganoderma lucidum*, Lingzhi, Reishi, cardiovascular, hypoglycaemic, diabetes, dyslipidaemia, antihypertensive, and anti-inflammatory.

**Results:** A number of in vitro studies and in vivo animal models have found that *G. lucidum* possesses antioxidative, antihypertensive, hypoglycaemic, lipid-lowering, and anti-inflammatory properties, but the health benefits in clinical trials are inconsistent. Among these potential health benefits, the most compelling evidence thus far is its hypoglycaemic effects in patients with type 2 diabetes or hyperglycaemia.

**Conclusions:** The inconsistent evidence about the potential health benefits of *G. lucidum* is possibly because of the use of different *Ganoderma* formulations and different study populations. Further large controlled clinical studies are therefore needed to clarify the potential benefits of *G. lucidum* preparations standardised by known active components in the prevention and treatment of cardiometabolic disease.

**Introduction**

Cardiovascular disease (CVD) is highly prevalent, with ischaemic heart disease and stroke being the two leading causes of mortality throughout the world (World Health Organization 2021). Metabolic syndrome is characterised by a cluster of conditions including insulin resistance, central obesity, hypertension, dyslipidaemia, and low-grade chronic inflammation (Eckel et al. 2005). Several drug treatments for CVD have been derived from plant sources, such as digoxin and reserpine. Herbal medicines are now becoming more popular, representing a potentially cost-effective class of substances for combating CVD if safe and effective therapies can be identified. The common herbal medicines used in the West include Asian ginseng, astragalus, flaxseed oil, garlic, ginkgo, grape seeds, green tea, hawthorn, milk thistle, and soy (Liperoti et al. 2017). Herbal formulæ are widely used in the clinic in China for hypertension, dyslipidaemia, coronary heart disease, and heart failure (Liu and Huang 2016).

*Ganoderma* (Ganodermataceae) is a kind of woody mushroom that can be found all over the world. Individual members of the species are identified according to different characteristics, such as shape and colour (red, black, blue/green, white, yellow, and purple) of the fruiting bodies, host specificity, and geographical origin (Upton 2000; Wachtel-Galor et al. 2011). *Ganoderma lucidum* (Curtis) P. Karst. (Curtis 1781), known as Lingzhi in China and Reishi in Japan, has been used in traditional Chinese medicine (TCM) for over 2000 years for a broad range of indications including improving general health, well-being, and longevity (Bishop et al. 2015; Klupp et al. 2015).

A variety of commercial products from *G. lucidum*, such as powders, dietary supplements, and tea (Wachtel-Galor et al. 2011), are available. They have been shown to possess a range of activities against CVD, including effects on lipids, blood pressure, obesity, diabetes, and antioxidant and radical scavenging properties (Liu and Tie 2019; Meng and Yang 2019; Winska et al. 2019). However, scientific evidence supporting the beneficial medical properties of *G. lucidum* is still inconclusive (Hapuarachchi et al. 2016). Many of the commercial products from *G. lucidum* may not have undergone effective standardisation, so it is difficult to compare results from different studies with different products. Many different herbal supplements or nutraceutical commercial products bearing the names Lingzhi, Reishi, or *Ganoderma*, etc., contain extracts from various parts of *G. lucidum*, often in combination with other herbal components. Ganopoly™ (Encore Health), which is a product
containing water-soluble *G. lucidum* polysaccharides, has been used in some animal and clinical studies.

**Methods**

In this review, the major studies of the whole plant, plant extract, and specific active compounds isolated from *G. lucidum* in relation to the main risk factors for CVD with particular emphasis on the more recent studies, are summarised. Electronic literature searches were performed using PubMed, Web of Science, and Google Scholar (published from 1961 to 2021). The search terms used were *Ganoderma lucidum*, Lingzhi, Reishi, cardiovascular, hypoglycaemic, diabetes, dyslipidaemia, anti-hypertensive, and anti-inflammatory. A total of 4224 articles were identified. The bibliographies of all relevant articles thus located were also scanned for further relevant references. S.W.C and B.T. extracted all articles independently based on the relevance, quality, and strength of the studies; only a shortlist of 115 studies or representative findings are discussed below.

**Active constituents of *G. lucidum***

*G. lucidum* is thought to have numerous different biologically active constituents, the main ones being various triterpenes, polysaccharides, and proteins (Ahmad 2018; Ahmad et al. 2013). The pharmacologically active compounds are present in different amounts in various parts of the mushroom such as the fruiting bodies, mycelium and spores.

**Triterpenes**

Triterpenes are a large and diverse group of naturally occurring compounds derived from the branched C5 carbon skeleton of isoprene. Triterpenes are a subclass of terpenes and are derived from squalene, a C30 hydrocarbon (Abdullah et al. 2012). They can be classified based on the number of cyclic structures making up the compounds. Up to now, more than 150 triterpenes have been identified from the spores, fruiting bodies, and mycelia of *G. lucidum* (Xia et al. 2014; Baby et al. 2015). The methods of extraction of triterpenes usually involve methanol, ethanol, chloroform, ether, acetone, or a mixture of these solvents. The extracts can be further purified by various separation methods such as normal and reverse-phase high-performance liquid chromatography (HPLC) (Chen et al. 1999). The majority of triterpenes identified are ganoderic acids and lucidinic acids; other important triterpenes include ganoderic acids, ganoderans, and ganodериols (Wachtel-Galor et al. 2011). The strong bitterness of *G. lucidum* originates from the triterpenoid compounds and the bitterness depends on the strain, cultivation conditions and manufacturing processes (Seo et al. 2009). Triterpenoids have been reported to exhibit various biological activities including anti-hypertensive, lipid-lowering, anti-acetylcholinesterase, antioxidant, and anticancer activities, etc. (Abdullah et al. 2012; Chen et al. 2017).

**Polysaccharides and peptidoglycans**

*G. lucidum* polysaccharides are macromolecules with a molecular mass of above 500 kDa. Many different polysaccharides, including (1→3), (1→6)-α/β-glucans, α-ᴅ-glucans, α-ᴅ-mannans, and polysaccharide-protein complexes, have been identified from the spores, fruiting bodies and mycelia of *G. lucidum*. These compounds are reported to have immunomodulatory and anti-cancer activities (Xu et al. 2011; Kao et al. 2013). Glucose, together with xylose, mannose, galactose, and fucose in different conformations, forms the major component of the polysaccharide molecules. Polysaccharides are the major component by weight among all constituents in the spores. Several of the mushroom polysaccharide compounds have proceeded through Phase I, II, and III clinical trials and have been used in some Asian countries to treat various cancers and other diseases (Wasser 2010). The contents of polysaccharides differ among commercial Lingzhi products (Wachtel-Galor et al. 2011). A polysaccharide-based product extracted from the spores of *G. lucidum* originally named ‘Ji 731 Injection’ was used since 1973 in China for treating myopathy (Zeng et al. 2018). The drug was renamed ‘Ji Sheng Injection’ in 1985 and subsequently ‘Polysaccharidum of *G. lucidum* Karst Injection’ (Lin Bao Du Tang Zhu She Ye) and is still used for intramuscular injection for various types of immune-mediated muscle diseases. Various bioactive peptidoglycans possessing antiviral (Li et al. 2005) and immunomodulating activities (Zhang et al. 2019), such as ganoderans A, B, and C, have also been isolated from *G. lucidum*.

**Bioactive proteins**

Several bioactive proteins from *G. lucidum* have been reported. One of these is a polypeptide called Lingzhi-8 (LZ-8) which consists of 110 amino acids with a molecular mass of 12 kDa. It has an immunoglobulin-like structure and was the first immunomodulatory protein isolated from the mushroom in 1989 (Hsu and Cheng 2018). Another protein from the fruiting bodies of *G. lucidum* is ganodermin, which has a molecular mass of 15 kDa and has antifungal activity.

**Health benefits of *G. lucidum***

**Antioxidant effects**

Free radicals are unstable and highly reactive chemical entities which contain one or more unpaired electrons and can be uncharged or charged. Free radicals are beneficial to the cell signalling and immune system, as well as maintenance of normal body functioning. However, excessive formation and/or insufficient removal of reactive oxygen species (ROS) and reactive nitrogen species (RNS), known as ‘oxidative stress’, may modulate the blood vessel wall, creating an environment that facilitates the progression of atherosclerosis, and leading to various illnesses, such as heart disease, diabetes and cancer (Johansen et al. 2005; Ullah et al. 2016).

*In vitro* studies demonstrated that several constituents of *G. lucidum*, in particular triterpenoids and polysaccharides, exhibit antioxidant activity, reducing power, scavenging and chelating abilities (Mau et al. 2002; Saltarelli et al. 2009; Wu and Wang 2009; Liu et al. 2010; Sarmadi and Ismail 2010; Kozarski et al. 2011; Ferreira et al. 2015; Krishna et al. 2016). In contrast, polysaccharide extracts of *G. lucidum* have superoxide and hydroxyl radical scavenging activities but do not have antioxidant activity as measured by detecting malondialdehyde (MDA) contents of liver microsomes (Liu et al. 1997). It has been demonstrated that the phenolic compounds from the fresh fruiting bodies of *G. lucidum* exhibit strong 1,1-diphenyl-2-picrylhydrazil (DPPH) radical scavenging activity but low superoxide dismutase (SOD) activity. The study also showed that DPPH radical scavenging activity and SOD activity were positively correlated with phenolic
compounds including caffeic acid, catechin, ferulic acid, gallic acid, myricetin, naringin, pyrogallol, protocatechuic acid, homogentisic acid, and quercetin, as well as total phenolic compounds (Kim et al. 2008). A study comparing the antioxidant activities of four of the most widely known mushrooms, including *G. lucidum*, demonstrated that polysaccharides extracts exhibited a strong correlation between the reducing power and the total amount of phenols and α-glucans, while a correlation between the reducing power and the amount of total polysaccharides and proteins was not found (Kozarski et al. 2012).

In *vivo* studies have shown that *G. lucidum* increases the activity of the antioxidant enzymes SOD and catalase (CAT), which are involved in removing harmful ROS (Cherian et al. 2009; Yurkiv et al. 2015; Vitak et al. 2017; Rahman et al. 2018). A short-term supplementation study over 10 days in healthy subjects showed an improvement in antioxidant status (Wachtel-Galor et al. 2004a), but a longer double-blind, placebo-controlled, cross-over intervention study over 4 weeks with a commercially available encapsulated Lingzhi preparation (1.44 g Lingzhi/day; equivalent to 13.2 g fresh mushroom/day) showed no significant effects in a range of biomarkers for antioxidant status, cardiovascular risk, DNA damage, immune status, and inflammation (Wachtel-Galor et al. 2004b). A placebo-controlled cross-over study in 42 healthy subjects examined the antioxidant and hepatoprotective efficacy of triterpenoids and polysaccharide-enriched *G. lucidum*, which was taken as a 225 mg capsule containing 7% triterpenoid-ganoderic acid (A, B, C, C5, C6, D, E and G), 6% polysaccharide peptides with a few essential amino acids and trace elements, once daily for 6 consecutive months (Chiu et al. 2017). The treatment showed an improvement in total antioxidant capacity, total thiol and glutathione content in plasma, significantly enhanced activities of antioxidant enzymes (SOD, CAT, GPx and glucose-6-phosphate dehydrogenase), and reduced the levels of thiobarbituric acid reactive substances, 8-hydroxy-deoxy-guanosine and hepatic marker enzymes, glutamic-oxaloacetic transaminase and glutamic-pyruvic transaminase. Mild fatty liver detected by abdominal ultrasonic examination was reversed to normal with *G. lucidum* treatment.

### Hypoglycaemic activity

Hyperglycaemia may increase the susceptibility to lipid peroxidation and modulate glucose metabolism in the body, which ultimately contributes to the increased incidence of atherosclerosis or further accelerates its progression (Giugliano et al. 1996; Poznyak et al. 2020). Insulin treatment is essential for people with type 1 diabetes. In type 2 diabetes mellitus (T2DM), lifestyle modification is recommended. If lifestyle modification is not sufficient in achieving glycemic control, patients should be treated initially with metformin (American Diabetes Association 2020). Metformin belongs to the biguanide class of drugs, which originate from the plant goat’s rue or French lilac (*Galega officinalis*, Linnaeus, [Fabaceae]) (Witters 2001). Recently, the glucagon-like peptide 1 (GLP-1) receptor agonists and sodium-glucose cotransporter 2 (SGLT2) inhibitors, which were developed from

| References | Model | Interventions | Findings |
|------------|-------|---------------|----------|
| Zhang et al. 2003 | Alloxan-induced pancreatic islet damage | GI-PS polysaccharides from the fruiting body of *G. lucidum* | GI-PS showed a protective effect |
| Fatmawati et al. 2009 | Human aldose reductase activity | Methanol extracts of 17 medicinal and edible mushrooms | *G. lucidum* showed the highest aldose reductase inhibitory activity |
| Fatmawati et al. 2010 | Human aldose reductase activity | Ganoderic acid Df isolated from the fruiting body of *G. lucidum* | Ganoderic acid Df showed potent human aldose reductase inhibitory activity |
| Fatmawati et al. 2011a | Human α-glucosidase activity | Chloroform extract of the fruiting body of *G. lucidum* | Ganoderol B identified as an active α-glucosidase inhibitor |
| Pan et al. 2015 | PTP1B activity | FYGL proteoglycan isolated from *G. lucidum* | Competitive inhibitor of PTP1B |
| Yang et al. 2018a | Liver tissues of ob/ob mice and HepG2 cells | FYGL proteoglycan isolated from *G. lucidum* | Inhibited PTP1B overexpression, improved IRS1 phosphorylation, activated PI3K/Akt cascades, increased phosphorylation of GSK3β, enhanced insulin-stimulated glycogen synthesis |
| Yang et al. 2018b | Rat myoblast L6 cells | FYGL proteoglycan isolated from *G. lucidum* | Increased insulin-stimulated glucose uptake, inhibited PTP1B expression, increased IRS1 phosphorylation, activated PI3K/Akt, increased phosphorylation of AMPK and up-regulated expression of GLUT4 |

**Table 1. In vitro studies on the hypoglycaemic effects of *G. lucidum*.**

Akt: protein kinase B; AMPK: adenosine monophosphate-activated protein kinase; FYGL: Fudan-Yueyang Ganoderma lucidum; GLUT4: glucose transporter type 4; GSK3β: glycogen synthase kinase-3β; IRS1: insulin receptor substrate 1; PI3K: phosphatidylinositol-3 kinase; PTP1B: protein tyrosine phosphatase 1B.
Table 2. Animal studies on the hypoglycaemic effects of G. lucidum.

| References | Animal model | Interventions | Findings |
|------------|--------------|---------------|----------|
| Hikino et al. 1985 | Normal and alloxan-induced hyperglycaemic mice | Water extracts (10^4 mg/kg crude drug equivalent, i.p.) of the fruiting bodies of G. lucidum for 7 or 27 h | Reduced plasma glucose and 2 glycans, ganoderans A and B, with hypoglycaemic action isolated |
| Hikino et al. 1989 | Normal and glucose-loaded mice | Ganoderan B | Increased insulin and altered enzyme activities |
| Kino et al. 1990 | Autoimmune diabetes model in non-obese mice | Ling Zhi-8 immunomodulatory protein (10.3 – 12.6 mg/kg twice weekly) from 4 weeks of age, followed up to 42 weeks of age | Prevented development of autoimmune diabetes by immunosuppressive mechanism |
| Zhang et al. 2003 | Alloxan-induced diabetic mice | Pre-treatment with intragastric GI-PS (50 – 200 mg/kg) for 10 days | GI-PS partly protected beta cells from necrosis |
| Zhang & Lin 2004 | Normal fasted mice | GI-PS (25 – 100 mg/kg) given by single intraperitoneal injections | Reduced serum glucose and increased insulin levels |
| He et al. 2006 | Streptozotocin-induced diabetic mice | GI-PS (125 and 250 mg/kg) given for 8 weeks | Reduced serum glucose, increased insulin levels and delayed progression of diabetic renal disease |
| Seto et al. 2009 | Genetically obese/diabetic (+/db/+db) and lean (+/db/+m) mice | Water extract of G. lucidum (0.003, 0.03 and 0.3 g/kg) for 4 weeks, oral gavage | Extract reduced serum glucose and liver peptidase expression |
| Li et al. 2011 | Streptozotocin-induced diabetic mice | GI-PS at low (50 mg/kg) and high (150 mg/kg) dose for 28 days | Reduced serum glucose, increased insulin levels and improvements in blood lipids |
| Teng et al. 2011 | Streptozotocin-induced diabetic mice | FYGL proteoglycan from G. lucidum (50 and 150 mg/kg, oral dose) for up to 4 weeks | Reduced plasma glucose with effect comparable with metformin |
| Teng et al. 2012 | Streptozotocin-induced diabetic rats | FYGL proteoglycan from G. lucidum (40 and 120 mg/kg, oral dose) for 30 days | Reduced plasma glucose, increased insulin and inhibited PTP1B |
| Zheng et al. 2012 | Streptozotocin-induced diabetic rats | Low-molecular-weight GI-PS (200 mg/kg) orally for 8 weeks | Reduced serum glucose appeared related to protection of pancreatic β-cells |
| Xiao et al. 2012 | Streptozotocin-induced diabetic mice | Polysaccharides from G. lucidum (50 or 100 mg/kg/day) given for 7 days | Reduced fasting serum glucose and insulin levels |
| Pan et al. 2013 | Obese/diabetic (+/db/+db) mice | FYGL proteoglycan from G. lucidum (75, 250, or 450 mg/kg) for 8 weeks | Reduced HbA1c, increased insulin and C-peptide levels, increased glucokinase and lowered PEPCK activities |
| Sarker 2015 | Rats with alloxan- or corticosteroid-induced diabetes | A petroleum ether extract and a methanol extract of G. lucidum (200, 400, 600 and 800 mg/kg/day) for 7 days | Reduced fasting and postprandial plasma glucose and HbA1c, increased plasma insulin levels and improved lipid profile |
| Xiao et al. 2017 | Streptozotocin-induced diabetic mice | F31 polysaccharide from G. lucidum (50 mg/kg/day) | Decreased fasting serum glucose, fasting serum insulin and liver glucose regulatory enzymes |
| Ratnaningtyas et al. 2018 | Alloxan-induced diabetic rats | Ethanol extract of G. lucidum powdered fruiting bodies (250, 500 and 1000 mg/kg) for 14 days | Dose-dependent reduction in blood glucose, reduction in HbA1c, and increase in insulin |
| Bach et al. 2018 | Streptozotocin-induced diabetic rats | Hydroethanolic extract of G. lucidum (1 mL/kg/day) for 30 days | Reduced plasma glucose and lipid level |

FYGL: Fudan-Yueyang Ganoderma lucidum; HbA1c: Glycosylated Haemoglobin Level; GI-PS: Ganoderma lucidum polysaccharides; PEPCK: phosphoenolpyruvate carboxykinase; PTP1B: protein tyrosine phosphatase.

phlorizin, a natural compound isolated from the bark of apple roots (Tomlinson et al. 2017), have been considered suitable for first-line treatment in some patients with T2DM who have concomitant cardiac or renal disease, in order to improve cardiovascular outcome benefits (Davies et al. 2018).

The hypoglycaemic effects of various extracts from G. lucidum have been studied in different animal models of diabetes and in in vitro experiments to identify mechanisms (Ma et al. 2015; Wang et al. 2016; Winska et al. 2019). The main in vitro, animal and clinical studies investigating the hypoglycaemic effects of G. lucidum are summarised in Tables 1–3, respectively.

**Hypoglycaemic activity of triterpenoids**

A series of in vitro studies by Fatmawati and colleagues have identified that methanol extract from the fruiting bodies of G. lucidum has a strong inhibitory effect on human aldose reductase activity. Ganoderic acid Df (Figure 1), a lanostane-type triterpenoid, exhibited potent aldose reductase inhibitory activity with an IC₅₀ value of 22.8 μM (Fatkawati et al. 2009, 2010). Fatmawati et al. (2011a) subsequently demonstrated that ganoderol B (Figure 2), which was isolated from a chloroform extract of G. lucidum, was effective in inhibiting α-glucosidase activity with an IC₅₀ value of 119.8 μM and the inhibitory effect was stronger than that of acarbose, which is commonly used as a medication to inhibit α-glucosidase in patients with T2DM. Structure-activity studies were performed to identify the structural requirements of lanostane-type triterpenoids from G. lucidum, which were necessary to increase α-glucosidase inhibitory activity (Fatkawati et al. 2013).

**Hypoglycaemic activity of proteoglycans/peptidoglycans**

Inhibition of PTP1B activity has been regarded as a potential therapy for T2DM for many years (Johnson et al. 2002). Fudan-Yueyang-G. lucidum (FYGL), which is a water soluble macromolecular proteoglycan extracted from the fruiting bodies of G. lucidum, inhibits PTP1B activity with an IC₅₀ value of
FYGL enhances glycogen synthesis and inhibits the expression of glycogen synthase kinase-3β (GSK3β) in liver tissues of ob/ob mice and HepG2 cells probably via modulating insulin receptor substrate 1 (IRS1)/phosphatidylinositol-3 kinase (PI3K)/protein kinase B (Akt)/AMP-activated protein kinase (AMPK)/GSK3β cascades (Yang et al. 2018a). In rat myoblast PTP1B-transfected L6 cells, FYGL improves insulin resistance by regulating IRS1-glucose transporter type 4 (GLUT4) cascades in the insulin signalling pathway (Yang et al. 2018b). In streptozotocin-induced T2DM mice, FYGL reduces plasma glucose levels with an effect comparable with metformin and rosiglitazone, via inhibiting the PTP1B...
expression and activity, and consequently modulating the tyrosine phosphorylation level of the insulin receptor (IR) 13-subunit (Teng et al. 2011, 2012). In addition, FYGL improves the plasma biochemistry indexes associated with T2DM-accompanied metabolic disorders, including free fatty acids, triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) (Teng et al. 2012). Further mechanistic studies in db/db mice found that the hypoglycaemic effect of FYGL is associated with its ability to enhance insulin secretion, decrease hepatic glucose output, and increase adipose and skeletal muscle glucose disposal (Pan et al. 2013, 2014). In normal and alloxan-induced hyperglycaemic mice, water extraction yielded from the fruiting bodies of *G. lucidum* and the two peptidoglycans, ganoderans A and B, subsequently produced through fractionation have all shown hypoglycaemic activity (Hikino et al. 1985). Administration of ganoderan B increases plasma insulin levels in normal and glucose-loaded mice; it also increases the activities of hepatic glucokinase, phosphofructokinase and glucose-6-phosphate dehydrogenase, decreases hepatic glucose-6-phosphatase (G6Pase) and glycogen synthetase activities and does not affect the activities of hexokinase and glycogen phosphorylase (GP) (Hikino et al. 1989).

### Hypoglycaemic activity of Ganoderma polysaccharides

Hypoglycaemic effects of polysaccharides from *G. lucidum* (Gl-PS) have been demonstrated in several *in vitro* and *in vivo* studies. Gl-PS showed a protective effect against alloxan-induced damage to pancreatic islets *in vitro*. Pre-treatment with intragastric Gl-PS (50-200 mg/kg) for 10 days produced hypoglycaemic effects via its scavenging ability to protect the pancreatic β-cells from alloxan-induced necrosis (Zhang et al. 2003). Gl-PS (25-100 mg/kg) given by single intraperitoneal injections to normal fasted mice reduced serum glucose levels after 3 and 6 h in a dose-dependent manner and increased insulin levels from 1 h after administration via enhancing Ca<sup>2+</sup> influx into pancreatic β cells (Zhang and Lin 2004). Furthermore, administration of Gl-PS produced hypoglycaemic effects and an improvement in lipid profile in streptozotocin-induced diabetic mice (He et al. 2006; Li et al. 2011; Zheng et al. 2012). It has been suggested that the hypoglycaemic effect is mainly through preventing apoptosis of pancreatic β-cells and enhancing β-cells regeneration (Zheng et al. 2012), and a modulation of serum insulin and hepatic mRNA levels of several key enzymes involved in gluconeogenesis and/or glycogenolysis, including GP, fructose-1,6-bisphosphatase (FBPase), phosphoenolpyruvate carboxykinase (PEPCK), and G6Pase (Xiao et al. 2012). Xiao et al. (2017) isolated F31, a β-heteropolysaccharide with a weight-average molecular weight of 15.9 kDa, from Gl-PS. The mechanism of action of Gl-PS F31 may be associated with down-regulation of the hepatic glucose regulated enzyme mRNA levels via AMPK activation, improvement of insulin resistance, and reduction of epididymal fat/body weight ratio (Xiao et al. 2017). An integrative analysis of transcriptomics and proteomics data from the liver from F31-treated diabetic db/db mice found that genes in the glycolysis and gluconeogenesis pathways, insulin pathway, and lipid metabolism pathways showed significantly different expression compared to the untreated mice and that microRNAs probably participated in the regulation of the genes involved in glucose metabolism (Xiao et al. 2018).

### Hypoglycaemic activity of Ganoderma proteins

Ling Zhi-8 (LZ-8), an immunomodulatory protein isolated from the mycelial extract of *G. lucidum*, prevented the development of autoimmune diabetes by reducing antigen-induced antibody formation in non-obese diabetic mice (Kino et al. 1990). In a model of transplanted allogeneic pancreatic rat islets, LZ-8 delayed the rejection process of allografted islets (van der Hem et al. 1995).

### Evidence from clinical studies

Clinical studies of the hypoglycaemic/antidiabetic effects of *G. lucidum* products are very limited. In a placebo-controlled study in 62 patients with T2DM, administration of Ganopoly<sup>TM</sup> at 1800 mg three times daily for 12 weeks reduced fasting and post-prandial plasma glucose levels, as well as HbA1c (Gao et al. 2004b). Administration of a dry extract of *G. lucidum* (3 g) in addition to regular oral hypoglycaemic agents for 12 weeks did not affect fasting glucose or HbA1c; however, the plasma glucose area under the curve during a meal tolerance test was reduced more significantly in patients taking *G. lucidum* (Wang et al. 2008). A randomised, double-blind, placebo-controlled, cross-over study with placebo-controlled run-in and cross-over periods of a Lingzhi product at a dose of 1.44 g daily for 12 weeks was performed in subjects with borderline elevations of blood pressure and/or cholesterol. There were reductions in plasma insulin and homeostasis model assessment-insulin resistance with Lingzhi compared to placebo. The subjects in this study had normal plasma glucose levels and it was speculated that the effects on insulin and insulin resistance would be greater in subjects with impaired glucose tolerance or T2DM (Chu et al. 2012). However, in a more recent study in 84 patients with T2DM and metabolic syndrome, administration of *G. lucidum* alone or combined with Cordyceps sinensis [now called Ophiocordyceps sinensis (Berk.) Sacc. (Ophiocordycepitaceae)], over 16 weeks, did not show any improvement in hyperglycaemia and cardiovascular risk factors (Klupp et al. 2016). It is noteworthy that different extracts of *G. lucidum* will have different components, therefore it may not be appropriate to compare the results from different studies.
Effects on dyslipidaemia

Dyslipidaemia which is characterised by decreased levels of HDL-C and accompanied with increased levels of TG, apo B, and small dense LDL particles, is an important modifiable risk factor for the development of atherosclerosis and CVD. Guidelines for the treatment of lipid disorders recommend initiating treatment with the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors or statins (Grundy et al. 2003). Compounds isolated from fruiting bodies of G. lucidum including ganolucidic acid eta, ganoderic acid K, and the farnesyl hydroquinones (ganomycin J and ganomycin B), showed strong inhibitory activity against HMG-CoA reductase (Figure 3) (Chen et al. 2017).

The cholesterol-lowering properties of G. lucidum have been demonstrated in a series of in vitro and ex vivo studies, and in hamsters and minipigs (Berger et al. 2004). The organic fractions containing oxygenated lanosterol derivatives inhibited cholesterol synthesis in T9A4 hepatocytes. The investigators found that both 2.5 and 5% dried G. lucidum reduced hepatic microsomal ex-vivo HMG-CoA reductase activity. In hamsters, administration of 5.0% dried G. lucidum decreased TC and HDL-C but not LDL-C, whereas in minipigs, 2.5% dried G. lucidum reduced all these parameters.

The improvements in the lipid profile in some diabetic animal models and in patients with T2DM treated with G. lucidum products may be related to the improvement in glycemic control, rather than a direct effect on lipid metabolism as hyperglycemia is often associated with elevated TG and reduced HDL-C (Taskinen and Borén 2015). In a randomised, double-blind, cross-over study in 26 patients with borderline elevations of blood pressure and/or cholesterol, administration of Lingzhi (1.44 g extract/d) for 12 weeks produced a non-significant trend for reduction in TG and increase in HDL-C (Chu et al. 2012). Those changes could have been related to improvements in insulin resistance as these lipid abnormalities, hypertension, central obesity and insulin resistance cluster together in the metabolic syndrome.

Antihypertensive effects

The most recent guidelines for the management of hypertension recommend initiating antihypertensive drug therapy in most patients with a combination of two different drugs from the classes of thiazide diuretics, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, or angiotensin receptor blocker (ARBs) (Whelton et al. 2018; Williams et al. 2018). Triterpenes and G. lucidum proteins have been demonstrated to possess potent ACE-inhibitory properties in vitro (Abdullah et al. 2012; Mohamad Anser et al. 2013). Mohamad Anser et al. (2013) reported that the protein fractions from the mycelia of G. lucidum contain highly potent anti-ACE proteins with IC_{50} values below 200 µg/mL. Furthermore, three small peptides with ACE-inhibitory activity, including Gln-Leu-Val-Pro (QLVP), Gln-Asp-Val-Leu (QDV1), and Gln-Leu-Asp-Leu (QLDL), were recently isolated from G. lucidum mycelia (Wu et al. 2019). Notably, QLVP worked in a mixed-type manner against ACE and has an IC_{50} value of 127.9 µmol/L.

A transverse aortic constriction (TAC) mouse model of pressure overload-induced cardiomyopathy and heart failure revealed that administration of oral G. lucidum spore oil every other day for 14 days normalised ejection fraction, corrected the fractional shortening and reduced left ventricular hypertrophy. The cardioprotective effect is associated with reduced expression of circular RNA circ-Foxo3, which plays a role in the pathogenesis of heart failure (Xie et al. 2016).

An early uncontrolled trial in Japanese showed that supplementation with G. lucidum extract (240 mg daily) for 6 months reduced blood pressure in hypertensive patients but not borderline hypertensive or normotensive patients (Kanmatsuse et al. 1985). In a double-blind, randomised, placebo-controlled study in 160 patients with confirmed coronary heart disease (CHD), treatment with G. lucidum polysaccharides (Ganopoly™) for 12 weeks improved the symptoms of CHD and reduced average blood pressure from 142.5/96.4 mmHg to 135.1/92.8 mmHg, whereas there was no significant blood pressure reduction in the control group (Gao et al. 2004a). Serum TC also decreased significantly with Ganopoly™ therapy, but not in the control group.

Anti-inflammatory effects

Inflammation is a physiological response to harmful stimuli that are physical, chemical, or biological in nature. A number of inflammatory markers, such as high-sensitivity C-reactive protein (hsCRP), interleukin (IL)-6, IL-1, and tumour necrosis factor (TNF)-α, have been shown to be associated with obesity, metabolic syndrome, and an elevated risk of chronic diseases (Pravenec et al. 2011; Dallmeier et al. 2012). Elevated circulating levels of hsCRP and IL-6 predict the development of T2DM through diminishing insulin sensitivity (Guarner & Rubio-Ruiz 2015). Obesity-induced inflammation has been implicated as a risk factor in the pathogenesis of T2DM, insulin resistance, CVD, and metabolic syndrome (Kumar et al. 2019).

There are several in vitro studies showing the anti-inflammatory effect of G. lucidum extracts. The triterpene extract from G. lucidum contains highly potent anti-ACE proteins with IC_{50} values below 200 µg/mL. Furthermore, three small peptides with ACE-inhibitory activity, including Gln-Leu-Val-Pro (QLVP), Gln-Asp-Val-Leu (QDV1), and Gln-Leu-Asp-Leu (QLDL), were recently isolated from G. lucidum mycelia (Wu et al. 2019). Notably, QLVP worked in a mixed-type manner against ACE and has an IC_{50} value of 127.9 µmol/L.

A transverse aortic constriction (TAC) mouse model of pressure overload-induced cardiomyopathy and heart failure revealed that administration of oral G. lucidum spore oil every other day for 14 days normalised ejection fraction, corrected the fractional shortening and reduced left ventricular hypertrophy. The cardioprotective effect is associated with reduced expression of circular RNA circ-Foxo3, which plays a role in the pathogenesis of heart failure (Xie et al. 2016).

An early uncontrolled trial in Japanese showed that supplementation with G. lucidum extract (240 mg daily) for 6 months reduced blood pressure in hypertensive patients but not borderline hypertensive or normotensive patients (Kanmatsuse et al. 1985). In a double-blind, randomised, placebo-controlled study in 160 patients with confirmed coronary heart disease (CHD), treatment with G. lucidum polysaccharides (Ganopoly™) for 12 weeks improved the symptoms of CHD and reduced average blood pressure from 142.5/96.4 mmHg to 135.1/92.8 mmHg, whereas there was no significant blood pressure reduction in the control group (Gao et al. 2004a). Serum TC also decreased significantly with Ganopoly™ therapy, but not in the control group.

Anti-inflammatory effects

Inflammation is a physiological response to harmful stimuli that are physical, chemical, or biological in nature. A number of inflammatory markers, such as high-sensitivity C-reactive protein (hsCRP), interleukin (IL)-6, IL-1, and tumour necrosis factor (TNF)-α, have been shown to be associated with obesity, metabolic syndrome, and an elevated risk of chronic diseases (Pravenec et al. 2011; Dallmeier et al. 2012). Elevated circulating levels of hsCRP and IL-6 predict the development of T2DM through diminishing insulin sensitivity (Guarner & Rubio-Ruiz 2015). Obesity-induced inflammation has been implicated as a risk factor in the pathogenesis of T2DM, insulin resistance, CVD, and metabolic syndrome (Kumar et al. 2019).

There are several in vitro studies showing the anti-inflammatory effect of G. lucidum extracts. The triterpene extract from G.
G. lucidum reduced the secretion of TNF-α and IL-6, and inflammatory mediator nitric oxide (NO) and prostaglandin E(2) (PGE2) from lipopolysaccharide (LPS)-activated murine macrophages via inhibition of nuclear factor-kB (NF-kB) and activator protein 1 (AP-1) signalling (Dudhgaonkar et al. 2009). G. lucidum sterols downregulated the mRNA expressions of NO, TNF-α, IL-1β, and IL-6, and attenuated LPS-induced cell polarisation by modulating mitogen-activated protein kinase (MAPK) and NF-kB pathways (Xu et al. 2021). Furthermore, G. lucidum ethanol extract reduced the excessive production of NO, PGE2, and pro-inflammatory cytokines, IL-1β, and TNF-α via inhibition of the NF-kB and toll-like receptor signalling pathways in LPS-stimulated BV2 microglial cells (Yoon et al. 2013).

In an in vivo study, administration of water extract of G. lucidum (2 g/kg, s.c.) 1 h prior to applying carrageenan reduced both the first and second phases of carrageenan-induced inflammation (Lin et al. 1993). It has been demonstrated that both ethyl acetate and 70% methanol extracts of G. lucidum (500 and 1000 mg/kg) produced anti-inflammatory effects against carrageenan-induced acute and formalin-induced chronic inflammation in mice and the effect was comparable to that of the standard reference drug, diclofenac (10 mg/kg) (Sheena et al. 2003).

The anti-inflammatory effect of G. lucidum supplementation has been investigated in several small scale trials. In a clinical trial involving 45 ST-elevation myocardial infarction (STEMI) and non-STEMI patients, the polysaccharides of G. lucidum (750 mg/day in 3 divided doses for 90 days) decreased the levels of IL-1 and TNF-α, as well as the MDA levels (Sargowo et al. 2019). In a recent randomised closed-label clinical trial involving 38 patients with atrial fibrillation, consumption of polysaccharides of G. lucidum (PT Sahabat Lingkungan Hidup, Surabaya, Indonesia), 3 times a day for 90 days, reduced significantly the systolic and diastolic blood pressure, heart rate, LDL-C, IL-1β, IL-6, hsCRP, and TNF-α, compared to placebo-treated patients (Rizal et al. 2020). These data suggest that G. lucidum polysaccharide peptides may have beneficial effects against factors involved in the pathogenesis of atherosclerosis and atrial fibrillation. The main active compounds which have been shown to influence some of the major risk factors for CVD are shown in Figure 4.

Adverse effects

G. lucidum is generally regarded as safe and is listed in the safest drug class (Class 1 Drug) in the American Herbal Products Association Botanical Safety Handbook with no known herb-drug interactions (McGuffin et al. 1997). Recent human clinical trials with G. lucidum have included laboratory safety parameters such as hepatic, renal, and hematological biomarkers and no pathological abnormality or serious adverse event has been reported (Klupp et al. 2015, 2016). Mild symptomatic adverse effects such as dry mouth, sore throat, and nausea have been reported occasionally. A case of hepatotoxicity related to G. lucidum mushroom powder was reported from Hong Kong in 2004, but this was thought to be due to the excipient ingredients (Yuen et al. 2004). Another case of fatal fulminant hepatitis in a patient taking Lingzhi in powder form was reported from Thailand in 2007 (Wannuang et al. 2007). Such cases do need careful assessment before attributing the effects to G. lucidum components, but they also illustrate the need to be vigilant with herbal treatments.

It is important to be cautious when taking herbal supplements in combination with conventional medications, particularly those that are very sensitive to herb or drug interactions such as warfarin. Most herbal supplements are contraindicated in patients taking warfarin. G. lucidum may have a mild antithrombotic effect itself in high doses and this could increase the effect of other anticoagulant or antiplatelet medications, including aspirin (Kumaran et al. 2011), resulting in an increased risk of bruising or bleeding. In patients taking other prescription medications, it is generally better to separate the intake of those medications and G. lucidum products by at least two hours in case there is any interference with drug absorption.

Conclusions

G. lucidum has a reputation for many beneficial effects from a historical perspective and its safety has largely been established by empirical observation. The beneficial effects are supported by several in vitro studies and studies in animals, but clinical trials in humans in the cardiovascular field are limited. Secondly, the use of different products in the clinical trials makes it difficult to

Figure 4. Potential mechanisms for cardiovascular disease prevention and therapy with constituents of Ganoderma lucidum.
compare the results. In the prevention and treatment of CVD, the hypoglycaemic effects of *G. lucidum* are the best established properties from the *in vitro* and animal studies, but these benefits have not been confirmed in recent clinical trials. Components from *G. lucidum* herbal materials have been identified with lipid-lowering and antihypertensive effects and compounds with specific mechanisms of action have been isolated. Nevertheless, the content of these components and their bioavailability in different *G. lucidum* formulations are uncertain and clinical trials in these areas have been inadequate. Further studies are needed to isolate all the active ingredients with known biological activity, and to characterise their bioavailability for specific indications before clinical trials pertaining to the use of *G. lucidum* products for relevant clinical benefits are conducted. Clinical trials should be performed in subjects with abnormal baseline levels of cardiovascular risk factors that are being targeted so that improvements can be seen more readily.

**Acknowledgments**

We are grateful for the support from the Faculty of Medicine, Macau University of Science and Technology.

**Author contributions**

Conceptualisation - S.W.C. and B.T.; Writing - Original draft preparation – S.W.C., B.T. and P.C.; Writing - Review and editing S.W.C., B.T., P.C. and C.W.K.L.

**Disclosure statement**

No potential conflict of interest was reported by the author(s).

**Funding**

This work was funded by the Institutional Development Grant of Caritas Institute of Higher Education, grant number IDG200114.

**ORCID**

Sze Wa Chan [http://orcid.org/0000-0002-2979-3855](http://orcid.org/0000-0002-2979-3855)  
Brian Tomlinson [http://orcid.org/0000-0001-6717-5444](http://orcid.org/0000-0001-6717-5444)  
Paul Chan [http://orcid.org/0000-0003-4958-5487](http://orcid.org/0000-0003-4958-5487)  
Christopher Wai Kei Lam [http://orcid.org/0000-0003-3994-2030](http://orcid.org/0000-0003-3994-2030)

**References**

Abdullah N, Ismail SM, Aminuddin N, Shuib AS, Lau BF. 2012. Evaluation of selected culinary-medicinal mushrooms for antioxidant and ACE inhibitory activities. Evid Based Complement Alternat Med. 2012:46238.  
Ahmad MF. 2018. *Ganoderma lucidum*: persuasive biologically active constituents and their health endorsement. Biomed Pharmacother. 107:507–519.  
Ahmad MF, Ahmad FA, Azad ZAA, Alam MI, Ansari JA, Panda BP. 2013. Edible mushrooms as health promoting agent. Adv Sci Focus. 1(3):189–196.  
American Diabetes Association. 2020. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes—2020. Diabetes Care. 43(Supplement 1):S98–S110.  
Baby S, Johnson AJ, Govindan B. 2015. Secondary metabolites from *Ganoderma*. Phytochemistry. 114:86–101.  
Bach EE, Hi EMB, Martins AMC, Nascimento PAM, Wadt NSY. 2018. Hypoglycemic and hypolipidemic effects of *Ganoderma lucidum* in streptozotocin-induced diabetic rats. Medicines (Basel). 5(3):78.

Berger A, Drait A, Kranky E, Monnard I, Hajjaj H, Meirim I, Piguet-Welsch C, Hauser J, Mace K, Niederberger P. 2004. Cholesterol-lowering properties of *Ganoderma lucidum* in vitro, ex vivo, and in hamsters and minipigs. Lipids Health Dis. 3:2.  
Bishop KS, Kao CH, Xu Y, Glucina MP, Paterson RR, Ferguson LR. 2015. From 2000 years of *Ganoderma lucidum* to recent developments in nutraceuticals. Phytochemistry. 114:56–65.  
Chen DH, Shiou WY, Wang KC, Huang SY, Shie YT, Tsai CM, Shie JF, Chen KD. 1999. Chemotaxonomy of triterpene pattern of HPLC of *Ganoderma lucidum* and *Ganoderma tsugae*. Inl Chinese Chemical Soc. 46(1):47–51.  
Chen B, Tian J, Zhang J, Wang K, Liu L, Yang B, Bao L, Liu H. 2017. Triterpenes and meroterpenes from *Ganoderma lucidum* with inhibitory activity against HMGs reductase, aldose reductase and α-glucosidase. Fitoterapia. 120:6–16.  
Cherian E, Patani G, Sudheep NS, Janardhanan KK. 2009. Free-radical scavenging and mitochondrial antioxidant activities of Reishi-*Ganoderma lucidum* (Curt: Fr) P. Karst and Arroyagapa-Chichiyanzus zeylanicus Gaertns extracts. J Basic Clin Physiol Pharmacol. 20(4):289–308.  
Chiu HF, Fu HY, Lu YY, Han YC, Shen YC, Venkatakrishnan K, Golovinskaia O, Wang CK. 2017. Triterpenoids and polysaccharide peptides-enriched *Ganoderma lucidum*: a randomized, double-blind placebo-controlled crossover study of its antioxidant and hepatoprotective efficacy in healthy volunteers. Pharm Biol. 55(1):1041–1046.  
Chu TT, Tomlinson BW, Fok BS, Lee KK, Tomlinson B. 2012. Study of potential cardioprotective effects of *Ganoderma lucidum* (Lingzhi): results of a controlled human intervention trial. Br J Nutr. 107(7):1017–1027.  
Curtis W. 1781. Flora Londinensis, or, Plates and descriptions of such plants as grow wild in the environs of London. London: for the author and B. White. [1775]-1779.  
Dallmeier D, Larson MG, Vasan RS, Meigs JB, Fox CS. 2012. Metabolic syndrome and inflammatory biomarkers: a community-based cross-sectional study at the Framingham Heart Study. Diabetol Metab Syndr. 4(1):28.  
Davies MJ, D’Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingle G, Rossing P, Tsapas A, Wexler DJ, Buse JB. 2018. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 41(12):2669–2701.  
Dudhgaonkar S, Thyagarajan A, Sliva D. 2009. Suppression of the inflammatory response by triterpenes isolated from the mushroom *Ganoderma lucidum*. Int Immunopharmacol. 9(11):1272–1280.  
Eckel RH, Grundy SM, Zimmet PZ. 2005. The metabolic syndrome. Lancet. 365(9486):1415–1428.  
Endo A. 2004. The origin of the statins. 2004. Atheroscler Suppl. 5(3):125–130.  
Fatmawati S, Kondo R, Shimizu K. 2013. Structure-activity relationships of lanostane-type triterpenoids from *Ganoderma Lingzhi* as α-glucosidase inhibitors. Bioorg Med Chem Lett. 23(21):5900–5903.  
Fatmawati S, Kurashiki K, Takeda S, Nishio S, Shimizu K, Sato M, Imaiizumi K, Takahashi K, Kamiya S, Kaneko S, et al. 2009. The inhibitory effect on aldose reductase by an extract of *Ganoderma lucidum*. Phytother Res. 23(1):28–32.  
Fatmawati S, Shimizu K, Kondo R. 2010. Ganoderic acid Df, a new triterpenoid with aldose reductase inhibitory activity from the fruiting body of *Ganoderma lucidum*. Fitoterapia. 81(8):1033–1036.  
Fatmawati S, Shimizu K, Kondo R. 2011a. Ganoderol B: a potent alpha-glucosidase inhibitor isolated from the fruiting body of *Ganoderma lucidum*. Phytochemistry. 81(12):1053–1055.  
Fatmawati S, Shimizu K, Kondo R. 2011b. Structure-activity relationships of ganoderic acids from *Ganoderma lucidum* as aldose reductase inhibitors. Bioorg Med Chem Lett. 21(24):7295–7297.  
Ferreira IC, Heleno SA, Reis FS, Stojkovic D, Queiroz MJ, Vasconcelos MH, Sokovic M. 2015. Chemical features of *Ganoderma* polysaccharides with antioxidant, antitumor and antimicrobial activities. Phytochemistry. 114:38–55.  
Gao Y, Chen G, Dai X, Ye J, Zhou S. 2004a. A phase II/III study of Ling Zhi mushroom *Ganoderma lucidum* (W.Curt.:Fr.) Lloyd (*Aphyllophoromycetideae*) extract in patients with coronary heart disease. Int J Med Mushr. 6(4):327–334.  
Gao Y, Lan J, Dai X, Ye J, Zhou S. 2004b. A phase II/III study of Ling Zhi mushroom *Ganoderma lucidum* (W.Curt.:Fr.) Lloyd (*Aphyllophoromycetideae*) extract in patients with type II diabetes mellitus. Int J Med Mushrooms. 6(1):33–39.  
Giugliano D, Ceriello A, Paolillo G. 1996. Oxidative stress and diabetic vascular complications. Diabetes Care. 19(3):257–267.
Guarner V, Rubio-Ruiz ME. 2015. Low-grade systemic inflammation connects aging, metabolic syndrome and cardiovascular disease. In: Yashin AI, Jazwinski SM, editors. Aging and health - a systems biology perspective. Based: Karger; p. 99–106.

Hapuarachchi KK, Wen TC, Jeevona R, Wu XL, Kang JC. 2016. Mycosphere essays 15. *Ganoderma lucidum* - are the beneficial medical properties substantiated? Mycosphere. 7(6):687–715.

Hsu PL, Lin YC, Ni H, Mo FE. 2018. Protein tyrosine phosphatase 1B and diabetes mellitus. Oxid Med Cell Longev. 2018:3491703.

Johnson TO, Ermolieff J, Jirousek MR. 2002. Protein tyrosine phosphatase 1B and reperfusion of isolated heart. Bull Exp Biol Med. 158(6):739–741.

Kozarski M, Klaus A, Niksi M, Jakovlevic D, Helser J, Van Griesven L. 2011. Antioxidative and immunomodulating activities of polysaccharide extracts of the widely used mushrooms *Ganoderma lucidum* and *Phellinus linteus*. Food Chem. 129(4):715–720.

Liu Z, Liu J, Zhao Y. 2005. Possible mechanism underlying the antitherapeutic activity of a proteoglycan isolated from the mycelia of *Ganoderma lucidum* in rats. J Biochem Mol Biol. 38(1):34–40.

Li F, Zhang Y, Zhong Z. 2011. Antihyperglycemic effect of *Ganoderma lucidum* polysaccharides on streptozotocin-induced diabetic mice. Int J Mol Sci. 12(9):6135–6145.

Lin JM, Lin CC, Chiu HF, Yang JJ, Lee SG. 1993. Evaluation of the antiinflammatory and liver-protective effects of *Aneochitulaa formosanus, Ganoderma lucidum* and *Gynostemma pentaphyllum* in rats. Am J Chin Med. 21(1):59–69.

Liperoti R, Vetraio DL, Bernabei R, Onder G. 2017. Herbal medications in cardiovascular disease. J Am Coll Cardiol. 69(9):1188–1199.

Liu C, Huang Y. 2016. Chinese Herbal medicine on cardiovascular diseases and the mechanisms of action. Front Pharmacol. 7:469.

Liu F, Ooi VEC, Chang ST. 1997. Free radical scavenging activities of mushroom polysaccharides extracts. Life Sci. 60(10):763–771.

Liu Q, Tie L. 2019. Preventive and therapeutic effect of *Ganoderma* (Lingzhi) on diabetes. Adv Exp Med Biol. 1182:201–215.

Liu W, Wang H, Pang X, Yao W, Gao X. 2010. Characterization and antioxidant activity of two low-molecular-weight polysaccharides purified from the fruiting bodies of *Ganoderma lucidum*. Int J Macromol. 46(4): 451–457.

Ma H-T, Hsieh J-F, Chen S-T. 2015. Anti-diabetic effects of *Ganoderma lucidum*. Phytochemistry. 114:109–113.

Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Fereira BA, et al. 2020. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 41(11):111–188.

Mau JL, Lin HC, Chen CC. 2002. Anti-angiotensin converting enzyme (ACE) proteins from mycelia of *Ganoderma lucidum* (Curtis) P. Karst. BMC Complement Alter Med. 13:256. doi: 10.1186/1471-2474-2-24.

Pan D, Wang L, Chen C, Hu B, Zhou P. 2015. Isolation and characterization of a hyperbranched proteoglycan from *Ganoderma lucidum* for anti-diabetics. Carbohydr Polym. 117:106–114.

Pan D, Zhang D, Wu J, Chen C, Xu Z, Yang H, Zhou P. 2013. Antidiabetic, antiheparinemic and antioxidant activities of a novel proteoglycan from *Ganoderma lucidum* fruiting bodies on db/db mice and the possible mechanism. PLoS One. 8(7):e68332.

Pan D, Zhang D, Wu J, Chen C, Xu Z, Yang H, Zhou P. 2014. A novel proteoglycan from *Ganoderma lucidum* fruiting bodies protects kidney function and ameliorates diabetic nephropathy via its antioxidant activity in db/db mice. Food Chem Toxicol. 63:111–118.

Poznyak A, Grechko AV, Poggyo P, Maiovedova VA, Alfieri V, Orekhov AN. 2020. The diabetes mellitus-atherosclerosis connection: the role of lipid and glucose metabolism and chronic inflammation. Int J Mol Sci. 21(5): 1835.

Pravenec M, Kajtai T, Zidek V, Vanda V, Mljenic P, Simakova M, Silhavy J, Malinska H, Oliyarny O, Kazdova L, et al. 2011. Effects of human C-reactive protein on pathogenesis of features of the metabolic syndrome. Nutr Diabetes. 1(4):718.

Pravenec M, Kajtai T, Zidek V, Vanda V, Mljenic P, Silhavy J, Malinska H, Oliyarny O, Kazdova L, et al. 2011. Effects of human C-reactive protein on pathogenesis of features of the metabolic syndrome. Nutr Diabetes. 1(4):718.

Pravenec M, Kajtai T, Zidek V, Vanda V, Mljenic P, Silhavy J, Malinska H, Oliyarny O, Kazdova L, et al. 2011. Effects of human C-reactive protein on pathogenesis of features of the metabolic syndrome. Nutr Diabetes. 1(4):718.
endothelial cell, anti-inflammation, and antioxidant in STEMI and NSTEMI patients. In: Khottimah H, Budianto WY, editors. International conference on bioinformatics and nanomedicine from natural resources for biomedical research. Melville (NY): Amer Inst Phys.

Sarker MMR. 2015. Antihyperglycemic, insulin-sensitivity and anti-hyperlipidemic potential of Ganoderma lucidum, a dietary mushroom, on alloxan-and glucocorticoid-induced diabetic Long-Evans rats. FFHD. 5(12):450–466.

Sarmadi BH, Ismail A. 2010. Antioxidative peptides from food proteins: a review. Peptides. 31(10):1949–1956.

Seo HW, Hwang TM, No M, Jung HJ, Kim JC, Choi JS, Kim JH, Lee HK, Lee I, Bae K, et al. 2009. Steroids and terpenes from the fruit bodies of Ganoderma lucidum and their anti-complement activity. Arch Pharm Res. 32(11):1573–1579.

Seth SW, Lam TY, Tam HL, Au AL, Chan SW, Wu JH, Yu PH, Leung GP, Ngai SM, Yeung JH, et al. 2009. Novel hypoglycemic effects of Ganoderma lucidum water-extract in obese/diabetic (+/d+b+d) mice. Phytomedicine. 16(5):426–436.

Sheena N, Ajith TA, Janardhanan KK. 2003. Anti-inflammatory and anti-nociceptive activities of Ganoderma lucidum occurring in South India. Pharm Biol. 41(4):301–304.

Shiao MS. 2003. Natural products of the medicinal fungus Ganoderma lucidum: occurrence, biological activities, and pharmacological functions. Chem Rec. 3(3):172–180.

Taskinen M-R, Borén J. 2015. New insights into the pathophysiology of dyslipidemia in type 2 diabetes. Atherosclerosis. 239(2):483–495.

Teng BS, Wang CD, Yang JH, Wu JS, Zhang D, Zheng M, Fan ZH, Pan D, Zhou P. 2011. A protein tyrosine phosphatase 1B activity inhibitor from the fruiting bodies of Ganoderma lucidum (Fr.) Karst and its hypoglycemic potency on streptozotocin-induced type 2 diabetic mice. J Agric Food Chem. 59(12):6492–6497.

Teng BS, Wang CD, Zhang D, Wu JS, Pan D, Pan LF, Yang JH, Zhou P. 2012. Hypoglycemic effect and mechanism of a proteoglycan from Ganoderma lucidum on streptozotocin-induced type 2 diabetic rats. Eur Rev Med Pharmacol Sci. 16(2):166–175.

Tomlinson B, Hu M, Zhang Y, Chan P, Liu ZM. 2017. A comprehensive review of the structure elucidation and biological activity of triterpenoids from Ganoderma spp. Molecules. 19(11):17478–17535.

Xiao C, Wu QP, Cai W, Tan JB, Yang XB, Zhang JM. 2012. Hypoglycemic effects of Ganoderma lucidum polysaccharides in type 2 diabetic mice. Arch Pharm Res. 35(10):1793–1801.

Xiao C, Wu Q, Xie Y, Tan J, Zhang Y, Bai L. 2018. Hypoglycemic mechanisms of Ganoderma lucidum polysaccharides F31 in db/db mice via RNA-seq and iTRAQ. Food Funct. 9(12):6495–6507.

Xiao C, Wu Q, Zhang J, Xie Y, Cai W, Tan J. 2017. Antidiabetic activity of Ganoderma lucidum polysaccharides F31 down-regulated hepatic glucose regulatory enzymes in diabetic mice. J Ethnopharmacol. 196:47–57.

Xie YZ, Yang F, Tan W, Li X, Jiao C, Huang R, Yang BB. 2016. The anti-cancer components of Ganoderma lucidum possesses cardiovascular protective effect by regulating circular RNA expression. Oncoscience. 3(7–8):203–207.

Xu Z, Chen X, Zhong Z, Chen L, Wang Y. 2011. Ganoderma lucidum polysaccharides: Immunomodulation and potential anti-tumor activities. Am J Chin Med. 39(1):15–27.

Xu J, Xiao C, Xu H, Yang S, Chen Z, Wang H, Zheng B, Mao B, Wu X. 2021. Anti-inflammatory effects of Ganoderma lucidum sterols via attenuation of the p38 MAPK and NF-kB pathways in LPS-induced RAW 264.7 macrophages. Food Chem Toxicol. 150:112073.

Yang Z, Chen C, Zhao J, Xu W, He Y, Yang H, Zhou P. 2018a. Hypoglycemic mechanism of a novel proteoglycan, extracted from Ganoderma lucidum, in hepatocytes. Eur J Pharmacol. 820:77–85.

Yang Z, Wu F, He Y, Zhang Q, Zhang Y, Zhou G, Yang H, Zhou P. 2018b. A novel FPT1P18 inhibitor extracted from Ganoderma lucidum ameliorates insulin resistance by regulating IRS1-GLUT4 cascades in the insulin signaling pathway. Food Funct. 9(1):397–406.

Yoon HM, Jang KI, Han MS, Jeong JW, Kim GY, Lee JH, Choi HY. 2013. Ganoderma lucidum ethanolic extract inhibits the inflammatory response by suppressing the NF-kB and toll-like receptor pathways in lipopolysaccharide-stimulated BV2 microglial cells. Exp Ther Med. 5(3):957–963.

Yuen MF, Ip PP, Ng WK, Lai CL. 2004. Hepatotoxicity due to a formulation of Ganoderma lucidum (Lingzhi). J Hepatol. 41(4):686–687.

Yurkiv B, Wasser SP, Nevo E, Sybirna NO. 2015. Antioxidant effects of medicinal mushrooms Agaricus brasiliensis and Ganoderma lucidum (high Basidimycetes): evidence from animal studies. Int J Med Mushrooms. 17(10):493–555.

Zeng P, Guo Z, Zeng X, Hao C, Zhang Y, Zhang L, Liu Y, Li H, Li J, Zhang L. 2018. Chemical, biochemical, preclinical and clinical studies of Ganoderma lucidum polysaccharide as an approved drug for treating myopathy and other diseases in China. J Cell Mol Med. 22(7):3278–3297.

Zheng HN, He JH, Yuan L, Lin ZB, Huang R, Xiao C. 2016. In vitro and in vivo protective effect of Ganoderma lucidum polysaccharides on alloxan-induced pancreatic islets damage. Life Sci. 73(18):2307–2319.

Zhang HN, Lin ZB. 2004. Hypoglycemic effect of Ganoderma lucidum polysaccharides. Acta Pharmacol Sin. 25(2):191–195.

Zhang S, Pang G, Chen C, Qin J, Yu H, Liu Y, Zhang X, Song Z, Zhao J, Wang L, et al. 2019. Effective cancer immunotherapy by Ganoderma lucidum polysaccharide-gold nanocomposites through dendritic cell activation and memory T cell response. Carbohydr Polym. 205:192–202.

Zheng J, Yang B, Yu Y, Chen Q, Huang T, Li D. 2012. Ganoderma lucidum polysaccharides exert anti-hyperglycemic effect on streptozotocin-induced diabetic rats through affecting β-cells. Comb Chem High Throughput Screen. 15(7):342–350.