Antidiabetic activity of the lingzhi or reishi medicinal mushroom *Ganoderma lucidum*: A review

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Abstract

Non-communicable diseases are the leading cause of death and some of the serious problems currently facing developed countries. A novel nutraceutical or drugs for both curing and preventing diabetes mellitus, one of the non-communicable diseases, has to be identified because the existing synthetic drugs have several limitations. For more than a century medicinal plants, including medicinal mushrooms, have traditionally been used in the treatment of diabetes mellitus, but only a few have been tested for their safety and efficacy. This article is focused on *Ganoderma lucidum* (known as lingzhi or reishi) mushrooms, one of the well-known medicinal mushrooms which is used for promoting health and longevity in traditional Chinese medicine. The reishi mushroom contains several important phytochemical substances including terpenoid, steroids, phenols, nucleotides, glycoproteins, and polysaccharides. Many researchers have reported the major impact of these phytochemical substances on patients with diabetes mellitus. The antidiabetic activity of the *Ganoderma lucidum* mushroom, and the potential to be considered as a candidate for a new treatment of diabetes mellitus, will be reviewed.

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Introduction

The American Diabetes Association[1] estimated the total costs of diagnosed diabetes mellitus (DM) rose to $245 billion in 2012 from $174 billion in 2007, a 41 percent increase over a five-year period. The average cost of illness per diabetic patient was $1,576 in Singapore,[2] $1,502 in China,[3] $882 in Thailand,[4] $847 in Colombia,[5] $526 in India,[6] and $126 in Ethiopia.[7] Ethnomedicinal resources like ethnobotany, ethnomycology and ethnozoology in different areas of the world have been used in the management of DM due to their costs and effectiveness.[8] Many Asian countries use traditional wild edible mushrooms as a delicacy and also as nutritional foods and medicines.[9,10] Most mushrooms are composed of around 90% water by weight. The remaining 10% consists of 10–40% protein, 2–8% fat, 3–28% carbohydrate, 3–32% fibre, 8–10% ash, and some vitamins and minerals, with potassium, calcium, phosphorus, magnesium, selenium, iron, zinc, and copper accounting for most of the mineral contents.[11,12] An example of medicinal mushrooms, *Tremella fuciformis*, known as snow fungus or silver ear fungus, is widespread and one of the most popular fungi in the cuisine and medicine of China. The glucuronoxylomannan from the fruiting bodies exhibits a significant dose-dependent hypoglycaemic activity,[13] and exopolysaccharides that improve insulin sensitivity possibly through regulating peroxisome proliferator-activated receptor gamma-mediated lipid metabolism.[14] In the West, *Auricularia auricular-judae* known as the Jew's ear or jelly ear, is used for complaints including sore throats, sore eyes and jaundice. The polysaccharide extracted from the mushroom fruiting bodies exhibits hypoglycaemic activity.[15] *Agrocybe aegerita* is known as "yanagi matsutake" in Japan, "pioppino" in Italy or "samthaube" in Germany.[16] The glucan and heteroglycan from fruiting bodies also show hypoglycaemic activity.[17] The nutritious *Phellinus baumii* with its delicious taste was studied for antihyperglycaemic activities of exopolysaccharides in Taiwan.[18]

Ganoderma lucidum, popularly known as the "mushroom of immortality", is one of the ethnomycological medicines in China, Japan, Korea and other Asian countries.[19] It has been widely used for more than two thousand years as "traditional medicinal mushrooms and fungi" or "mushroom nutraceuticals" to relieve symptoms of various diseases.[20,21,22] This mushroom has been classified into Fungi (Kingdom), Basidiomycota (Phylum), Agaricomycetes (Class), Polyporales (Order), Ganodermataceae (Family), and Ganoderma (Genus). There are around 80 species belonging to the genus Ganoderma which are popularly referred to as shelf mushrooms or bracket fungi. Characteristically, they produce shelf- or bracket-shaped, or occasionally circular fruiting bodies called conks that lie in a close planar grouping of separate or interconnected horizontal rows.[23]

Nomenclature

The name *Ganoderma* comes from the Greek words *Ganos* meaning "brightness" and *derma* meaning "skin". The Latin word *lucidum* means "shiny" or "brilliant". The common name for *G. lucidum* is "língzhī" meaning "supernatural mushroom" in Chinese. The other names are reishi, mannentake (Japanese), yeong ji, yung gee (Korean), hed lin juer (Thai), and linh chi (Vietnamese).[24]

Morphological characteristics

G. lucidum is a large, dark mushroom with a glossy exterior and a woody texture. Glaeser and Smith[23] explained the morphological

structure of the fruiting body in more detail, 2.5–3.5 cm wide, semi-circular to fan-shaped or kidney-shaped, surface with concentric zones and furrows, shiny, dark red, reddish-brown to orange-brown becoming ochre or yellow toward the margin.

Phytochemical substances

Mau et al.[25] reported that the non-volatile components in *G. lucidum* in Taiwan were 1.8% ash, 26–28% carbohydrate, 3–5% fat, 59% fibre, and 7–8% protein, as also reported in Japan,[26] North America,[27] and Korea.[28] Major phytochemical constituents of *G. lucidum* are terpenoid, steroids, phenols, nucleotides and their derivatives, glycoproteins, and polysaccharides. In addition, the major phytochemical constituents of *G. lucidum* are (i) terpenoid compounds: ganoderic acids, ganosporeric acid A, ganoderals, ganoderiols, and lucidenic acids;[29,30,31] (ii) proteins and amino acids: glutamic acid, aspartic acid, cysteine, methionine, lysine and leucine;[32] (iii) polysaccharides and peptidoglycans: xylose, mannose, galactose and fructose in different configuration, including 1–3, 1–4, and 1–6 linked β and α-D or L-substitutions, and chitin;[33,34,35] (iv) nitrogenous compounds: nucleosides including adenosine and 5-deoxy-5′ methylsulfinyl adenosine; (v) other components: phosphorus, silica, sulphur, potassium, calcium, and magnesium.[36]

Traditional uses

G. lucidum is traditionally used for its anti-inflammatory,[30,37] antimicrobial,[35,38] antidiabetic,[39,40] antitumor,[41,42] antimetastatic activities,[36,43] as well as antigenotoxicity,[44] immunomodulatory,[45] and antioxidant activities,[46,47] and associated diseases such as hepatic diseases,[48,49] gastrointestinal diseases,[50,51] and chronic kidney diseases.[52,53]

Antihyperglycaemic activity

Medicinal mushrooms have gained huge interest from researchers around the world because of their positive bioactivity effects.[10] However, there is still not much data available regarding the antidiabetic activity of these medicinal mushrooms. Hikino et al.[54] from Japan reported the hypoglycaemic effect of ganoderans A and B, two polysaccharides isolated from the fruiting body of *G. lucidum* when tested on alloxan-induced diabetic mice. It was also reported that the ganoderan B substance increased the plasma insulin level in normal and glucose-loaded mice. Moreover, it showed significant increase in the activities of hepatic glucokinase, phosphofructokinase and glucose-6-phosphate dehydrogenase, and also decreased the hepatic glucose-6-phosphate and glycogen synthetase activities, thus reducing the glycogen content in the liver.[55] Moreover, a third polysaccharide, ganoderan C isolated from this mushroom also showed a significant hypoglycaemic effect in mice.[55,56] Zhang and Lin[57] from China investigated the hypoglycaemic effect of *G. lucidum* polysaccharides by using intraperitoneal injection with single doses of 25, 50, and 100 mg/kg extract in fasted mice. These polysaccharides lowered the serum glucose levels at three hours and six hours after administration in a dose-dependent manner. They also raised the circulating insulin levels and intensity of [Ca^{2+}] at one hour after administration. Xiao et al.[58] from China investigated the hypoglycaemic effect of 50 and 100 mg/kg/day *G. lucidum* polysaccharides administered for seven days in streptozotocin-induced diabetic mice. The parameters fasting serum glucose, insulin, and epididymal white adipose tissue weight were significantly decreased. The hepatic mRNA levels of glycogen phosphorylase, fructose-1,6-bisphosphatase, phosphoenolpyruvate carboxykinase and glucose-6-phosphatase genes were also significantly lower. Seto et al.[39] from Hong Kong investigated the hypoglycaemic effect of 0.03 and 0.3 g of *G. lucidum* per kg body weight of mice for four weeks oral consumption. The extract markedly reduced levels of phosphoenol-pyruvate carboxykinase, which are usually high in diabetic mice. Jia et al.[46] from China investigated the hypoglycaemic effect of polysaccharides in *G. lucidum* extract in streptozotocin-induced diabetic rats for 30 days. The results showed serum insulin levels increased and glucose levels decreased. Treatment with streptozotocin also elevated levels of lipid peroxidation markers (thiobarbituric acid reactive substances, lipid hydroperoxides), decreased levels of non-enzyme antioxidants (vitamin C, reduced glutathione, vitamin E), and decreased activities of the antioxidant enzymes (SOD, catalase, and glutathione peroxidase). After treatment with these polysaccharides, levels of non-enzyme and enzyme antioxidants increased and lipid peroxidation levels decreased.

In addition to the animal experimental studies, a clinical study by Gao et al.,[59] with 71 patients with confirmed type 2 DM were supplemented with polysaccharide extracted from *G. lucidum* (Ganopoly) in 1800 mg doses, three times daily for 12 weeks. Glycosylated haemoglobin and plasma glucose decreased significantly, indicating a hypoglycaemic effect of this extract.

G. lucidum possesses the antidiabetic effect using multiple pathways. One is through its insulin-releasing activity due to a facilitation of Ca^{2+} inflow to the pancreatic β cells.[57] The decrease in fasting serum glucose levels by *G. lucidum* polysaccharides may be associated with decreased mRNA expression levels of several key enzymes involved in gluconeogenesis and/or glycogenolysis.[58] Recently, Ma et al.[60] summarised the antidiabetic effects of *G. lucidum* as (i) polysaccharides by increasing glucose-6-phosphate dehydrogenase, phosphofructokinase and glucokinase, but inhibiting glycogen synthetase, manganese superoxide dismutase and glutathione peroxidase; (ii) proteoglycan by inhibiting protein tyrosine phosphatase 1B; (iii) triterpenoids namely ganoderic acid Df inhibiting aldose reductase, while ganoderol B inhibiting α-glucosidase; (iv) protein namely Ling Zhi-8 by decreasing lymphocyte infiltration and increasing the antibody detection of insulin.

Conclusion

In conclusion, it has been suggested that polysaccharide constituents in medicinal mushrooms appear to be effective for both the controlling of blood glucose and the modification of the

course of diabetic complications without side-effects. This review particularly explores *G. lucidum* that has demonstrated clinical and experimental antihyperglycaemic properties by preventing or reducingthe development of DM.

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