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Review

Research on Chaga hypoglycemic functional foods

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Abstract: Chaga, also known as *Inonotus obliquus* (Fr.) Pilát, belongs to the genera *Basidiomycotina*, *Hymenomycetes*, *Hymenochaetales*, *Hymenochaetaceae*, and *Inonotus*. Chaga is a brown polypore fungus that mostly grows under the bark of white birch and silver birch trees. It forms sarcoma-like sclerotia when the bark is damaged. It mainly grows in Northern Europe at the 40° to 50° north latitude, Siberia and the Far East in Russia, Hokkaido in Japan, and the Changbai Mountain area of the Heilongjiang Province and Jilin Province in China. Chaga has various pharmacological activities, such as anti-tumor, hypoglycemic, anti-viral, and anti-inflammatory. *Inonotus obliquus*, an edible fungus with the same origin as medicine and food, has attracted more and more attention. At present, Chaga has become a raw material with great potential for developing functional foods. In this article, Chaga's blood sugar-lowering function, functional ingredients, and blood sugar-lowering mechanism and the development status of Chaga functional foods are reviewed and Chaga's future development is analyzed and forecast.

Keywords: Chaga; blood sugar; functional food; diabetes

1. Introduction

In recent years, the number of patients with diabetes in China has continued to increase. It is expected that from 2020 to 2030, the prevalence of diabetes among adults aged 20 to 79 in China will increase from 8.2% to 9.7%. In addition, the cost of diabetes treatment will increase from US$250.2 billion in 2020 to US$460.4 billion, with an annual growth rate of 6.32%. During this period, the proportion of diabetes costs in China's GDP will also increase from 1.58% to 1.69%, a growth rate that exceeds the economic growth, and the per capita economic burden will increase from US$231 to US$414, with an annual growth rate of 6.02% [1]. Faced with this challenge, the development of innovative foods with blood-sugar-lowering functions has become an urgent need. Dietary intervention is an important component of diabetes management and has a significant impact on the development of diabetes. However, the current dietary intervention methods used to treat diabetes are mainly through a variety of food types, such as cereals and potatoes (whole grains, potatoes, beans, etc.), vegetables and fruits, animal foods (livestock, poultry, fish, eggs, etc.), milk, soybeans, and nuts, as well as the right amount of cooking oil and salt to meet the body's needs while maintaining blood sugar stability. However, there are currently few applications of hypoglycemic substances. Therefore, Chaga, which has good hypoglycemic functional substances, has great potential in dietary intervention to control blood sugar.

Chaga, also known as *Inonotus obliquus* (Fr.) Pilát [2] (**Figure 1**), has an excellent blood-sugar-lowering ability. Using Chaga as a raw material to develop new blood-sugar-lowering functional foods has become a hot topic in current research. The distribution of Chaga resources is mainly in high latitudes [2–5] (**Figure 2**). Studies have shown that Chaga contains high levels of antioxidants, proteins, minerals, fiber, and vitamins [2]. In folk medicine, Chaga is usually consumed as a dietary mushroom. In addition to being consumed directly as a simple food, it also has nutritional benefits, such as anti-cancer, anti-inflammatory, antioxidant, and anti-thrombotic effects [1,6–8]; among them, Chaga's overall impact on the immune system and its improvement of insulin resistance in Type II diabetes show great potential [9]. It can be seen that the development of Chaga-based blood-sugar-lowering functional foods will not only help improve the current situation of Chinese diabetic patients but also reduce the huge social expenditure on diabetes treatment, which is of great significance.

In this paper, the latest progress in the development of Chaga hypoglycemic functional foods is reviewed and the types and effects of its hypoglycemic functional ingredients are discussed. In addition, the types and functions of related products currently on the market are also analyzed.

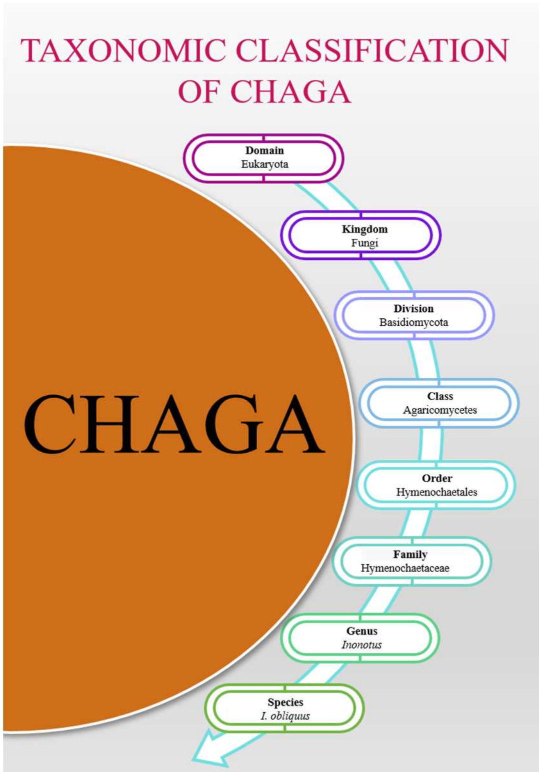

Figure 1. Taxonomic classification of Chaga [2].

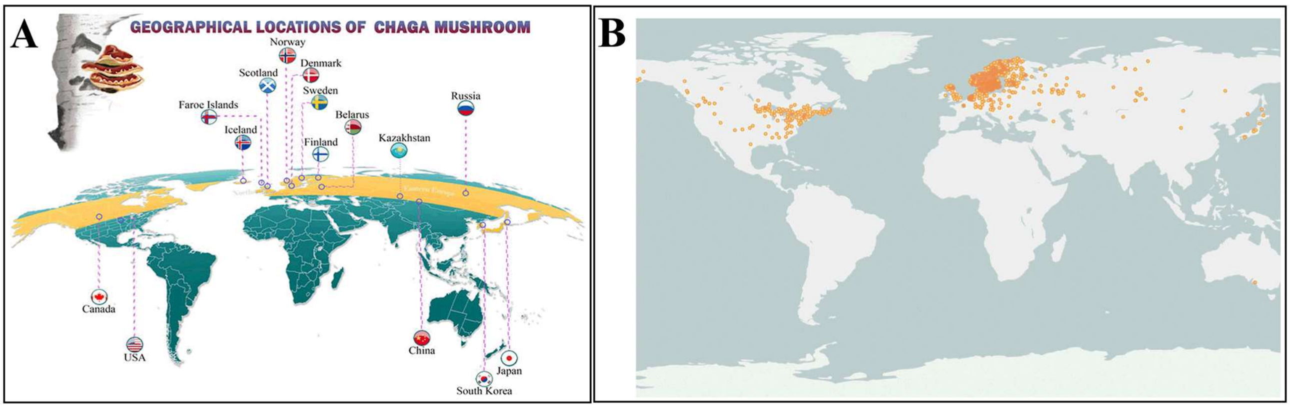

Figure 2. Distribution of Chaga resources around the world [2,5].

2. Pharmacological functions of Chaga in lowering blood sugar

Long-term high blood sugar can cause lesions in multiple tissues and organs throughout the body, increasing the risk of acute and chronic complications. Diabetes has become the third-largest health threat in the world, and China is a country with a large number of patients [6]. In recent years, relevant studies have shown that Chaga has the function of lowering blood sugar [10]. Zhu et al. used Type II diabetic mice as a model to explore the hypoglycemic effects of compound Chaga tablets. They found that after treatment with the compound Chaga tablets, the weight loss symptoms caused by Type II diabetes in mice were alleviated and their blood sugar was reduced [11]. Zhou et al. inferred through research that Chaga has a certain function of repairing damaged pancreatic B cells and promoting insulin secretion [12]. Zhao et al. pointed out that Chaga can enhance the glucose tolerance and insulin sensitivity of mice and quickly promote the recovery of disordered glucose metabolism in mice, thus inhibiting the deterioration of diabetes [13]. In Xu et al.'s study, a Chaga extract was fed to diabetic mice and found to reduce the activity of maleic dialdehyde. After a histomorphological examination, it was found that the Chaga extract significantly reduced the damage of damaged pancreatic tissue [14]. In addition, the study found that the chemical components extracted from Chaga had a hypoglycemic effect and revealed its hypoglycemic and anti-lipid peroxidation mechanism in alloxan-induced diabetic mice [15]. Related studies have also shown that Chaga has the function of protecting diabetic kidneys. Liu et al. found through mouse experiments that the protection of Chaga extract against diabetic nephropathy is related to its antioxidant damage [16]. In the study of Feng et al., it was found that Chaga improved HFD/STZ-induced lipid metabolism and renal function disorders by regulating NOS-cGMP-PDE5 signaling, and Chaga could repair HFD/STZ-induced renal podocyte damage and HFD/STZ-induced renal dysfunction (**Figure 3**) [17].

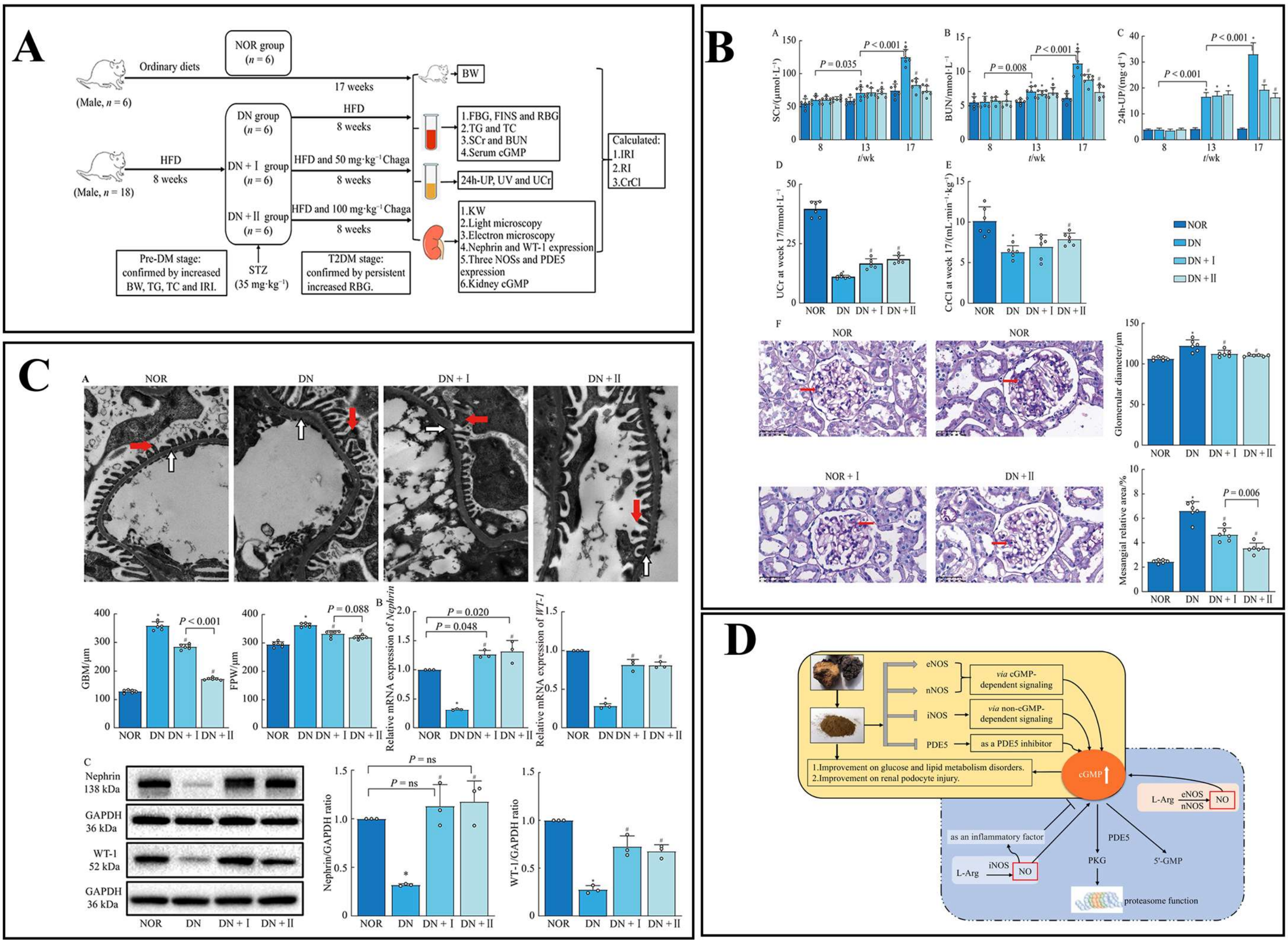

Figure 3. Research on the role of Chaga in counteracting HFD/STZ-induced lipid metabolism disorders and renal dysfunction by regulating NOS-cGMP-PDE5 signaling pathway: **A**: experimental method; **B:** detection of renal function indicators and histological examination of renal tissue sections; **C**: effects of Chaga on HFD/STZ-induced podocyte injury; **D**: mechanism of Chaga in regulating lipid metabolism disorders and renal injury (eNOS: endothelial nitric oxide synthase; nNOS: neural nitric oxide synthase; iNOS: inducible nitric oxide synthase; cGMP: cyclic guanosine monophosphate; PDE5: phosphodiesterase type 5; L-Arg: L-arginine; NO: nitric oxide; and PKG: activated protein kinase G) [17].

3. Functional ingredients in Chaga for blood sugar regulation

3.1. Polysaccharides

Inonotus obliquus polysaccharides are composed of monosaccharides, such as L-rhamnose, D-arabinose, D-xylose, D-mannose, D-glucose, and D-galactose. The molar ratios of monosaccharides in polysaccharides with different ionic strengths are different [18]. Studies have found that the β-glucan contained in Chaga has a variety of properties that promote human health, including immunomodulation, anti-inflammatory effects, and antioxidant activity [19]. Polysaccharides contained in Chaga play an important role in controlling blood sugar. Existing research results show that the hypoglycemic mechanism of polysaccharides mainly includes regulating enzyme activity, liver glucose metabolism, and intestinal flora, as well as protecting and regulating blood sugar, repairing pancreatic cells, and improving insulin sensitivity [20–24]. Xia found that the crude polysaccharides of *Inonotus obliquus* and its graded alcohol polysaccharides have good glucosidase inhibition and can reduce the in-vitro hydrolysis rate and degree of potato starch [25]. Other studies have found that compound polysaccharides based on Chaga polysaccharides can alleviate symptoms, such as polydipsia, polyphagia, and polyuria, in Type II diabetic mice to a certain extent and, especially at low doses, can also increase thymus and spleen indexes, protect the liver and kidneys, increase liver glycogen levels, and lower blood sugar [26]. Results have also shown that Chaga polysaccharides can significantly restore the body weight and fat weight of laboratory mice, as well as reduce fasting blood sugar levels, improve glucose tolerance, increase liver glycogen levels, and improve insulin resistance [10,27] (**Figure 4**). Some studies have found that Chaga polysaccharides play a role in controlling blood sugar by protecting the kidneys. Chaga polysaccharides can improve the process of oxidative stress response in mouse kidney tissue, protect kidney tissue damage and swelling, alleviate pathological changes in kidney tissue, improve symptoms such as glomerular deformation and empty nuclei caused by inflammation, and relieve symptoms of glycosuria and proteinuria, thereby improving and enhancing renal function [16]. Wang et al. found that Chaga polysaccharide and its chromium complex can effectively inhibit the formation of non-enzymatic glycosylation end products and inhibit the activities of α-amylase, α-glucosidase, and pancreatic lipase, thus showing a certain ability to regulate blood sugar after meals and a lipid-lowering potential. In addition, Chaga polysaccharide and its chromium complex can significantly protect liver L02 cells from hydrogen peroxide-induced oxidative damage by improving cell viability, inhibiting morphological changes, and maintaining mitochondrial integrity. In particular, its chromium complex can significantly alleviate liver, kidney, and pancreatic tissue damages caused by oxidative stress and hypoglycemia. In latest studies, it was found that Chaga and its polysaccharide products have a protective effect on the kidney of mice with diabetic kidney disease (DKD) [28–30] (**Figure 5**). These results indicate that the potential anti-diabetic mechanisms of Chaga polysaccharides and its chromium complex may be related to the homeostasis of blood sugar and the restoration of the endogenous antioxidant system [31,32] (**Figure 6**). More importantly, Chaga polysaccharides had no significant effect on the blood sugar and glucose tolerance of normal mice ($p > 0.05$), which shows a certain safety [33]. In addition, Chaga polysaccharides have significant anti-diabetic effects and are expected to become a potential candidate drug in the clinical treatment of diabetes [34].

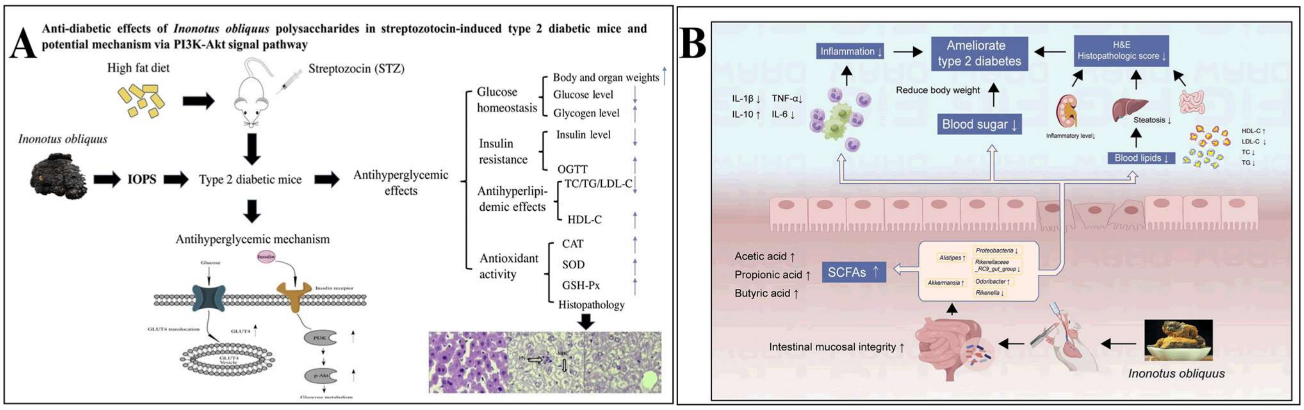

Figure 4. A: Potential mechanism of Chaga polysaccharide's hypoglycemic effect on Type II diabetic mice via PI3K-Akt signaling pathway [10]. **B**: Chaga's effects on reducing body weight and fasting blood glucose in diabetic mice and its mechanism of alleviating the degree of pathological changes in the intestine, liver, kidney, and pancreas of diabetic mice [27].

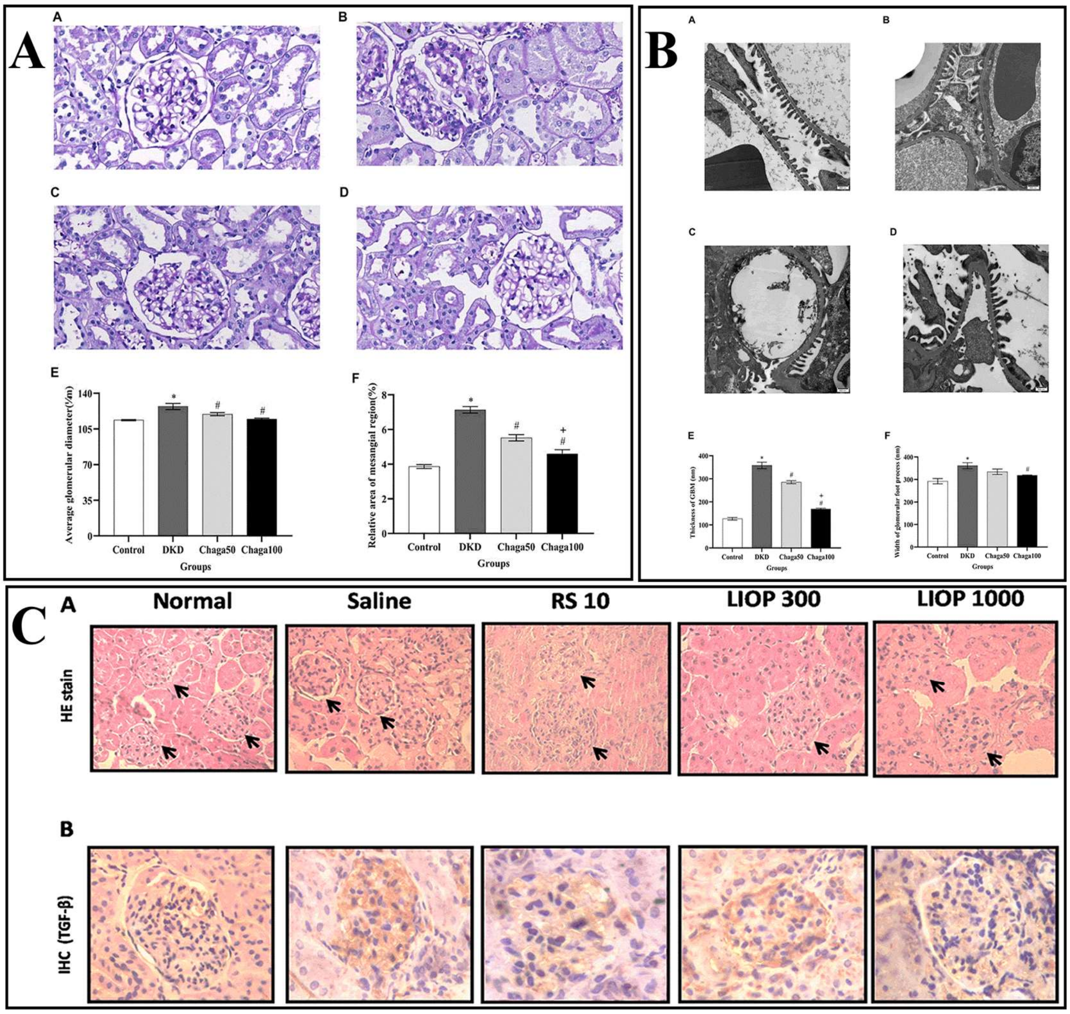

Figure 5. A: Effects of Chaga on pathological parameters of DKD rat model under light microscopy. **B**: Effects of Chaga on pathological parameters of DKD rat model under electron microscope. **C**: Histopathological study of renal cortex of C57BL/6 mice with HFD+STZ-induced diabetic nephropathy examined after treatment with LIOP (300 and 1000 mg/kg) and rosiglitazone (10 mg/kg), compared with the effect of saline group, alternating at eight weeks [29,30].

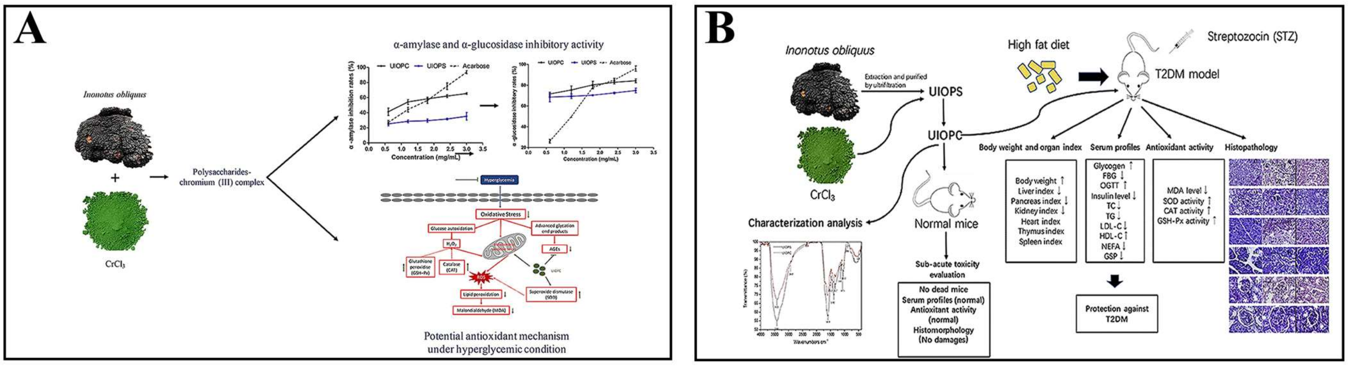

Figure 6. A: Effects of Chaga polysaccharides and its chromium complex on formation of advanced glycation end products, α-amylase activities, α-glucosidase activities, and hydrogen-peroxide-induced cell oxidative damage in liver L02 cells [31]. **B**: Effects of Chaga polysaccharides and chromium complex on anti-diabetic ability of STZ-induced T2DM mice [32].

3.2. Polyphenols

Mushroom polyphenols have a variety of beneficial effects on the human body: anti-cancer, anti-oxidation, hypoglycemic, anti-aging, and prevention of neurodegenerative diseases and cardiovascular diseases [35]. The polyphenol content of Chaga generally exceeds those of other fungi. Among them, the total phenol content of Chaga was found to be 97 μmol GAE/mg [36], which was the fungus with the highest polyphenol content and the best antioxidant effect among the many studied medicinal mushrooms. *Inonotus obliquus* polyphenols are secondary metabolites with a polyphenol structure and have good antioxidant activity [18] and hypoglycemic ability [37]. Dong et al. separated nine polyphenols using a macroporous resin, namely, colorless anthocyanidin, pyranoside, curculigoside, flavin-3-O-hexoside, 7-xyloside catechol, scutellarin B, tangerin, catechins, and rutin [38]. Further research results have shown that Chaga fruiting bodies also contain polyphenols, such as coumaric acid, ferulic acid, scutellarin, and isoscutellarin [39]. According to other studies, Chaga also contains polyphenols such as 4-hydroxy-3,5-dimethoxybenzoic acid, 2-hydroxy-1-hydroxymethylethyl ester, protocatechuic acid, caffeic acid, 3,4-dihydroxybenzaldehyde, 2,5-dihydroxyterephthalic acid, syringic acid, and 3,4-dihydroxyphenylacetone [40]. Peng and Shahidi detected 111 different phenolic compounds, including phenolic acids, flavonoids, coumarins, quinones, and styrylpyranone, by analyzing the ethanol extract of Chaga [41]. In general, the polyphenols contained in Chaga can be divided into four categories: flavonoids, phenolic acids, flavonoid isomers, and other polyphenols. Among them, the main mechanism of the hypoglycemic action of flavonoids and phenolic acids is to inhibit α-glucosidase and α-amylase activities because α-glucosidase and α-amylase are key enzymes for digesting dietary carbohydrates into glucose [42,43]. Therefore, once the activities of these two enzymes are inhibited, the glucose content in the blood decreases; in addition, there are also studies showing that the effect of phenolic acids in stimulating glucose uptake is comparable to those of metformin and thiazolidinediones (the main common oral hypoglycemic drugs) [44], indicating that the phenolic acids' ability to lower blood sugar is very significant. It can be seen that the polyphenols contained in Chaga can effectively inhibit the increase of blood sugar.

3.3. Triterpenoids

Triterpenoids have a positive effect on controlling blood sugar. Studies have found that the various triterpenoids contained in *Inonotus obliquus* are mainly of three types: lanolinane, oleanane, and lupine [45,46]. According to other studies, the active products of *Inonotus obliquus* fermentation are mainly *Inonotus obliquus* terpenes and betulinic acid. Lanosterol, *Inonotus obliquus* alcohol, and trametinic acid are obtained from the fruiting bodies of *Inonotus obliquus* after extraction, separation, purification, and identification. Lanosterol, *Inonotus obliquus* alcohol, and trametinic acid in the fruiting bodies of *Inonotus obliquus* and *Inonotus obliquus* terpenes in the mycelium have a certain inhibitory effect on α-glucosidase and α-amylase [47]. The mechanism of action is that the triterpenoids of *Inonotus obliquus* produce a competitive inhibition on α-glucosidase and a mixed inhibition of non-competitive and competitive inhibitions on α-amylase [47]. In addition, Chaga also contains triterpenoids such as tramadol acid (TA), indolediol, and betulinic acid (BA). Based on the current extensive research results, BA has been shown to have hypoglycemic effects and multiple immunomodulatory activities, and BA can also promote the secretion of leptin and insulin [48]. Based on the hypoglycemic principle of the commercial hypoglycemic drug Acarbose, a study found that inhibiting the activity of α-glucosidase and α-amylase prolonged the time for carbohydrates to be broken down into glucose [49]. Researchers have also measured the α-glucosidase inhibition rate and α-amylase inhibition rate of the triterpenoids of Chaga. The experiments found that Chaga triterpenoids had certain inhibitory activity against both α-glucosidase and α-amylase. The IC_{50} value of betulinic acid on α-glucosidase was 0.26 mg/mL, which was significantly lower than the IC_{50} value of Acarbose (0.37 mg/mL). The IC_{50} value of inonotus terpenoid D on α-amylase was 7.86 mg/mL, which was significantly lower than the IC_{50} value of Acarbose (10.51 mg/mL) [47].

4. Development of Chaga-based foods that lower blood sugar levels

4.1. Current status of Chaga resources

The mycelium of *Inonotus obliquus* has cold-resistant and frost-resistant properties and can survive in highly cold areas at −40 °C [50]. In China, *Inonotus obliquus* is mainly distributed in cold areas, such as the Changbai Mountains in Jilin, the Greater Khingan Mountains in Inner Mongolia, and the Lesser Khingan Mountains in Heilongjiang [51]. It is also found in North China, Northwest China, and South China. The Shanxi Academy of Agricultural Sciences has discovered *Inonotus obliquus* in the middle and southern sections of the Luliang Mountains in Shanxi. Through a comprehensive analysis of its morphological characteristics, growth environment, and quality, it was found that the *Inonotus obliquus* in these areas is morphologically similar to similar fungi in the Greater Khingan Mountains. Although there are significant differences in the growth environment, the quality is comparable [52].

Chaga grows very slowly in nature, generally taking 10–15 years to form pharmacologically active sclerotia, and the host species and the culture medium type of the mycelium will affect the content of bioactive substances in the obtained biomass

[53]. It has been found that wild *Inonotus obliquus* is not a reliable natural drug resource [54]. However, *Inonotus obliquus* strains have strong adaptability and can grow on conventional culture media, thereby obtaining a large amount of mycelium and fermentation products [55,56]. At present, submerged fermentation is widely used in China to obtain Chaga and its products. Submerged fermentation technology is an important part of modern biotechnology. Submerged fermentation technology, designed by Gaden et al. in the 1940s, uses a bioreactor for cultivating microorganisms [57]. The technology has many advantages, including a short production time, a large product volume, convenience, fewer restrictions on conditions (season and temperature), and reduced contamination by foreign bacteria. Related studies have shown that the polysaccharides in the fermentation broth and mycelium produced by deep liquid fermentation are higher or equal to those in wild fruiting bodies in terms of content and biological activity, which is consistent with the results for many medicinal fungal polysaccharides obtained via deep fermentation [58]. Yan and Guo found that under this fermentation method, the optimal condition for the fermentation broth of *Inonotus obliquus* was at 30 g/L of glucose, 4 g/L of peptone, and 8 g/L of beef extract. Under this condition, the biomass and polysaccharide yield of *Inonotus obliquus* were the highest [59]. In recent years, simply optimizing fermentation conditions or improving culture media has had difficulty in meeting future development needs, and the addition of exogenous inducers to stimulate the growth of mycelium and the accumulation of secondary metabolites has attracted more and more attention [60]. For example, Yang and Meng compared the mycelium and polysaccharide yield of *Inonotus obliquus* in culture media containing different vitamins (VB-6 and VB-1). The results showed that the culture medium containing VB-6 had a higher mycelium and polysaccharide yield (4 μg/mL) [50]. Lou et al. found that oleic acid and fungal elicitors can increase the production of betulinic acid in submerged cultures and promote the growth of mycelium [61]. Other studies have found that adding crushed straw and corn to a culture medium of *Inonotus obliquus* greatly increased the yield of the low-molecular-weight polysaccharides (29 kDa) of *Inonotus obliquus* and that the polysaccharides had high antioxidant activity [62]. The latest research showed that under a high-pH and 100 ℃ condition, the Swiss water process is a potentially effective method for extracting fungal nutrients and functional components from Chaga [63]. In addition, according to Huynh et al., the extraction of triterpenoids using the Folch method can obtain a higher total yield [64].

4.2. Current status of development of Chaga-related foods that lower blood sugar levels

Due to its multiple pharmacological effects, *Inonotus obliquus* has been widely used in clinical treatment and medicine [42]. However, there are few reports on the preparation process of *Inonotus obliquus* for food and health products, and there are no mature *Inonotus obliquus* food and related health products in China [65]. However, with the in-depth research and the improvement of scientific and technological levels in recent years, many companies or researchers have tried to develop related functional foods [66] (see **Figure 7** for the development process of Chaga functional food). In Japan, consumers prefer tea made from *Inonotus obliquus* powder because this drinking method is not only simple but also can effectively lower blood sugar levels and enhance immunity, which is very suitable for the health and wellness needs of modern fast-paced life [50]. In South Korea, by incorporating *Inonotus obliquus* extract into daily foods, such as biscuits and candies, consumers are provided with a healthy and convenient way of eating [67]. In China, Wang et al. developed a Chaga lactic acid bacteria beverage through optimization experiments [68]. Due to their wide range of pharmacological activities, such as lowering blood sugar, improving immunity, and resisting fatigue, the polysaccharide compounds produced by *Inonotus obliquus* are used in the development of functional foods and health products in Russia, China, and the United States. After reviewing Chaga-related products on major e-commerce platforms, such as Amazon and Taobao, we noticed that the most popular product types on the market include health supplements, teas, tinctures, etc. Among them, some health foods called natural insulin, such as Sorlife Chaga capsules, IOPS tea, tablets, etc., have been successfully launched on e-commerce platforms. In order to meet consumers' expectations for product quality and enhance manufacturers' brand reputation, manufacturers should consider adopting internationally recognized quality control standards, such as ISO22000:2018 Food Safety Management System and Hazard Analysis and Critical Control Points (HACCP) [69].

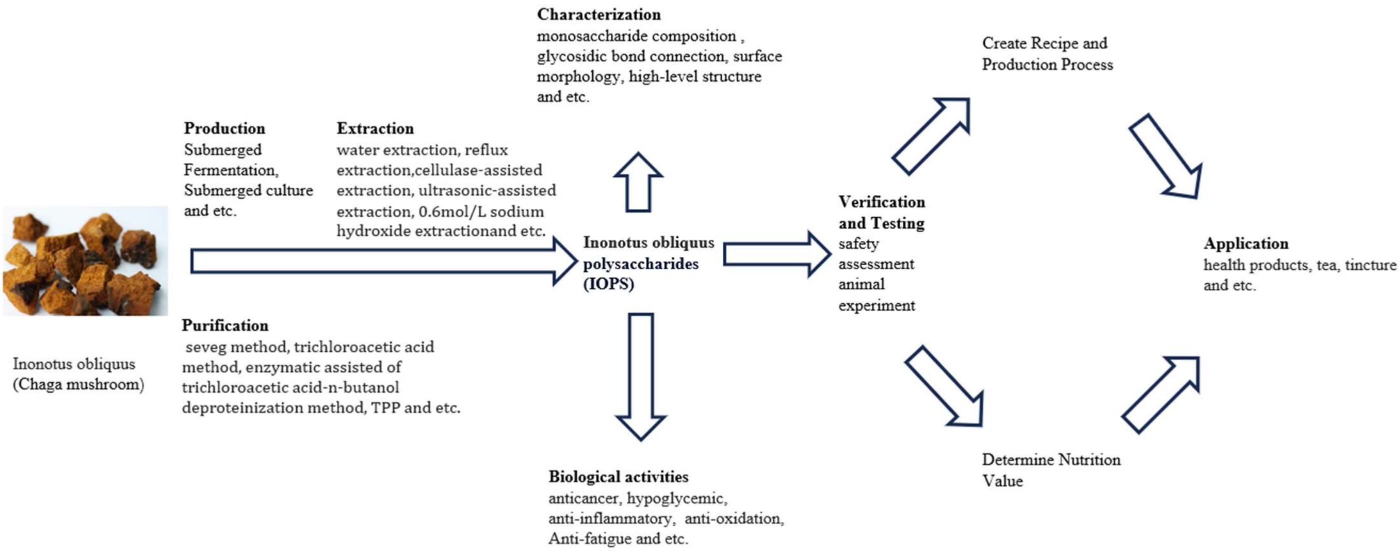

Figure 7. Process of developing Chaga polysaccharide functional foods [66].

4.3. Development prospects of Chaga functional foods for lowering blood sugar

The hypoglycemic pharmacological function of Chaga has been widely confirmed. Given the increasing incidence of diabetes in the world today, the development of Chaga functional foods for hypoglycemic purposes will certainly receive more attention. As people's demand for a healthy diet increases, the development of Chaga functional foods will also bring greater business opportunities. At present in China, there are many Chaga functional foods on the market, and many of them are labeled with the function of regulating blood sugar. However, most of these products are foreign brands, which means that the channels for obtaining Chaga functional foods in China are limited and expensive. The large market gap will inevitably attract domestic functional food developers to develop corresponding products. Regarding the development of domestic Chaga foods, in order to provide consumers with more effective Chaga functional foods for hypoglycemia, its hypoglycemic active ingredients should be studied in more detail and its related bioactive substance extraction process also needs to be further optimized and innovated. In addition, the safety of Chaga extracts needs further research and certification. Finally, as part of a lifestyle of preventing diabetes, it is also important to use personalized tools to promote behavioral changes [70–72]. In the future, the development of Chaga functional foods should be combined with more scientific fields to fully explore and develop Chaga's physiological potential. Given the diversity of consumer needs and expectations, the design of functional foods, the technology development, and the formulation of marketing strategies have become particularly critical [73]. In the future, the development of Chaga functional foods will also pay more attention to the specific needs of individual consumers. Based on many current reports, it can be foreseen that Chaga functional foods have broad market prospects.

5. Conclusion

This article reviewed the physiological function of Chaga in lowering blood sugar and its active substances that are beneficial to blood sugar regulation, summarized the current status of Chaga resources and the progress of related functional food development, and finally looked to its future development. It should be noted that all hypoglycemic active substances contained in Chaga have not been fully studied and hence further research is needed. The optimization of the extraction process of Chaga active substances will also be an important direction for future research. At present, several types of Chaga functional foods have been industrialized, but there are still many technical problems to be overcome for the industrial production of Chaga functional foods specifically used for lowering blood sugar.

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Conflict of interest: The authors declare no conflict of interest.

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