A novel polysaccharide, *Heimioporus retisporus* Polysaccharide (HRP) was extracted from the edible mushroom *Heimioporus retisporus*. HRP had weight-average molecular weight 1,949 kDa and number-average molecular weight 873 kDa, and its major components were arabinose (0.71%), galactose (12.93%), glucose (49.00%), xylose (8.59%), mannose (17.78%), and glucuronic acid (10.99%). Fourier transform infrared spectroscopy and nuclear magnetic resonance spectroscopy revealed that HRP was composed of 1,3-linked β-D-glucose, 1,6-linked β-D-mannose, 1,6-linked β-D-galactose, 1,4-linked β-D-galactose, 1,4-linked β-D-xylose, and 1,5-linked α-L-arabinose. Thermogravimetric analysis indicated that degradation temperature (T_d) of HRP was 200°C. In an STZ-induced diabetic mouse model, oral administration of HRP (40 mg/kg/d) for 28 days significantly reduced blood glucose levels, and reduced heart organ index by decreasing expression of IL-6 and TNF-α. Our findings indicate hypoglycemic effect of HRP, and its potential application as a hypoglycemic agent.

**Keywords:** *Heimioporus retisporus*, polysaccharide, characterization, hypoglycemia, cardioprotective

**KEY POINTS**
1. A polysaccharide HRP was purified from fruiting bodies of *Heimioporus retisporus*.
2. Preliminary structural characterization of HRP was performed.
3. Hypoglycemic activity of HRP was evaluated in a STZ-induced diabetic mouse model.

**INTRODUCTION**
Diabetes is a common metabolic disorder characterized by high blood glucose level resulting from β-cell dysfunction and insulin resistance (1). It may cause damage to various organs (particularly liver, kidney, and brain), and presents increased risk of cardiovascular disease, kidney disease, and partial or complete blindness (2). It is a pro-inflammatory state associated with increased
production of reactive oxygen species (ROS) and expression of inflammatory cytokines (e.g., IL-1β, IL-6, IL-8, TNF-α) that promote apoptosis (3–5). The International Diabetes Federation (IDF) estimates that ∼425 million adults worldwide have diabetes, and that this number will increase to ∼630 million by 2045.

Commonly used diabetes medications have several adverse effects, including hypoglycemia (sulfonylureas) (6), liver damage, cardiovascular disease (thiazolidinedione) (7, 8), and gastrointestinal disorders (flatulence, diarrhea, abdominal pain, nausea, vomiting) (α-glucosidase inhibitors, biguanide) (9, 10). There is an urgent need for effective diabetes medications without such adverse effects. Polysaccharides are naturally occurring compounds present in a wide variety of animals, plants, algae, microorganisms, and fungi, notably medicinal mushroom species. Numerous studies have documented beneficial biological activities of polysaccharides, including hypoglycemic, antioxidant, anticoagulant, antitumor, antimutagenic, anticomplementary, antiviral, and anti-inflammatory activities (11–13, 14). A Hericium erinaceum polysaccharide reduced glucose levels in normal and alloxan-induced diabetic mice without adverse effects (15), and the polysaccharide reduced glucose levels in normal and alloxan-diabetic rats without side effects. Polysaccharides are beneficial biological activities of polysaccharides, including hypoglycemic, antioxidant, anticoagulant, antitumor, antimutagenic, anticomplementary, antiviral, and anti-inflammatory activities. Several studies have documented beneficial biological activities of polysaccharides, including hypoglycemic, antioxidant, anticoagulant, antitumor, antimutagenic, anticomplementary, antiviral, and anti-inflammatory activities (11–13, 14).

**Materials and Chemicals**

*Heimioporus retisporus* fruiting bodies were purchased from Kunming, Yunnan Province (China). We previously described inhibition of endogenous oxidative stress and moisturizing effects of crude polysaccharides from *H. retisporus* (19). In the present study, as part of an ongoing search for safe, natural, hypoglycemic agents, we purified a water-soluble polysaccharide, *Heimioporus retisporus* Polysaccharide (HRP) from *H. retisporus*, characterized its chemical structure, assayed its hypoglycemic activity, and examined relationships between its structure and bioactivities. Commonly used diabetes medications have several adverse effects, including hypoglycemia (sulfonylureas) (6), liver damage, cardiovascular disease (thiazolidinedione) (7, 8), and gastrointestinal disorders (flatulence, diarrhea, abdominal pain, nausea, vomiting) (α-glucosidase inhibitors, biguanide) (9, 10). There is an urgent need for effective diabetes medications without such adverse effects. Polysaccharides are naturally occurring compounds present in a wide variety of animals, plants, algae, microorganisms, and fungi, notably medicinal mushroom species. Numerous studies have documented beneficial biological activities of polysaccharides, including hypoglycemic, antioxidant, anticoagulant, antitumor, antimutagenic, anticomplementary, antiviral, and anti-inflammatory activities (11–13, 14). A Hericium erinaceus polysaccharide reduced glucose levels in normal and alloxan-induced diabetic mice without adverse effects (15), and the polysaccharide reduced glucose levels in normal and alloxan-diabetic rats without side effects. Polysaccharides are beneficial biological activities of polysaccharides, including hypoglycemic, antioxidant, anticoagulant, antitumor, antimutagenic, anticomplementary, antiviral, and anti-inflammatory activities (11–13, 14).

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**H. retisporus** fruiting bodies powder

- Hot water extraction
- Supernatant (CHRP)
- Deprotened (seavage method)
- Anion exchange chromatography with DEAE-Sepharose
- DHRP
- Cation exchange chromatography with CM-Sepharose
- CDHRP
- Gel filtration with Superdex G75 16/600
- Dialyzed against distilled water and lyophilized

**FIGURE 1** | Purification of Heimioporus retisporus polysaccharide (HRP) (schematic).

Coupled with pulsed amperometric detector (PAD). Neutral sugars and uronic acids were released by hydrolysis (10% H$_2$SO$_4$, 2.5 h, 105°C). Acid hydrolysates of HRP were diluted and analyzed using HPAEC system (Dionex ISC 3000; United States) with PAD, AS50 autosampler, CarboPac PA20 column (4 x 250 mm, Dionex), and PA-20 guard column (3 x 30 mm). Standard solutions of L-arabinose, D-glucose, D-xylose, D-glucuronic acid, D-mannose, D-galactose, glucuronic acid, and galacturonic acid were used for calibration.

**Fourier Transform Infrared Spectroscopy**

Fourier transform infrared spectroscopy was performed using Optik GmbH Tensor II system (Bruker, Germany). Spectra were recorded from 4,000 to 400 cm$^{-1}$, with resolution 4 cm$^{-1}$ and maximal source aperture (21).

**Nuclear Magnetic Resonance Spectroscopy**

~40 mg HRP was dissolved in 0.55 mL chloroform-d (CDCl$_3$), and solution-state $^1$H and $^{13}$C nuclear magnetic resonance (NMR) spectroscopy (Bruker system) were performed with parameters: spectral width 1,800 Hz for $^1$H dimension and 10,000 Hz for $^{13}$C dimension; delay between transients 2.6 s; delay for polarization transfer corresponding to estimated average $^1$H-$^{13}$C coupling constant 150 Hz. Data were processed using Bruker Topspin-NMR software program (22).

**Thermogravimetric Analysis**

Thermogravimetric analysis (TGA) and derivative thermogravimetry (DTG) were performed using simultaneous thermal analyzer (model STA449F3; Netzsch; Germany). ~8 mg
lyophilized HRP powder was placed in a platinum crucible under nitrogen atmosphere, and heated at rate 10°C/min in temperature range of 30–800°C (23). Data were analyzed using software program Origin 8.0.2.8.

**Scanning Electron Microscopy**
Dried HRP samples were gold-coated by sputter-coater (model IB-3, EiKo, Japan), and morphological features were observed by scanning electron microscopy (model S-3400N, Hitachi, IB-3, EiKo, Japan), and morphological features were observed previously (24).

**Animal Model and Drug Administration**
Male SPF Balb/c mice (weight 20 ± 2 g) from Charles River (Beijing) were maintained in the Experimental Animal Public Service Platform at China Agricultural University (25 ± 2°C, humidity 50 ± 10%, 12 h light/12 h dark cycle), and fed normal chow diet ad lib. After 1 wk acclimation period, mice were i.p. injected with 1% STZ (40 mg/kg) for 5 days (25), and fasting blood glucose (FBG) was measured 24 h after the last injection. A successful model was defined as mice with FBG ≥ 11.0 mmol/L, stable for 1 week (26).

Group Blank consisted of five untreated normal mice; 25 diabetic mice were assigned randomly to one control and four experimental groups (intragastric administration; 4-wk feeding period) as follows:

- Group Blank: blank, deionized water.
- Group CK: deionized water; control.
- Group Met: metformin (40 mg/kg); positive control.
- Group HRP-20: HRP 20 mg/kg.
- Group HRP-40: HRP 40 mg/kg.
- Group HRP-80: HRP 80 mg/kg.

Body weight and FBG data were collected for the four experimental groups. At the end of experimental period, mice were sacrificed (cervical dislocation), heart, liver, spleen, and kidney were removed, connective tissue was cleaned and weighed for calculation of organ indices, immediately frozen in liquid nitrogen, and stored at -80°C, for further analysis. All experiments were approved by the Institutional Ethics Committee of China Agricultural University, and performed in accordance with International Standards and Ethical Guidelines for Animal Welfare.

**Fasting Blood Glucose Measurement**
Mice were fasted for 8 h, blood was extracted from tail vein, and the FBG was measured using express glucose meter (On Call).

**Visceral Organ Indices**
For each of various visceral organs, an index was calculated by the formula:

\[
\text{Visceral organ index} = \frac{\text{visceral organ weight}}{\text{body weight}} \times 100\%
\]

**Inflammatory Cytokine mRNA Levels in Heart Tissue**
Total RNA extraction from heart tissue was performed using TRIzol reagent. First-strand cDNA synthesis was performed using a commercial reverse transcription kit as per manufacturer's instructions. Primer sequences used were as follows:

- β-actin forward primer: 5′-AACACCCCAGCCATGACGCTG-3′
- reverse primer: 5′-ATGTCTCGGCTCTGCAAGGAGG-3′
- IL-6 forward primer: 5′-TGCTGGTGACACCTACGGCC-3′
- reverse primer: 5′-GTACTTCCAGAAGCCAGAGG-3′
- INF-α forward primer: 5′-ATGGGCTCCCTCCTCATCGT-3′
- reverse primer: 5′-ATAAGCAATCGCTGACGCTG-3′

PCR procedure was: initial denaturation at 94°C for 4 min, 30 cycles of denaturation at 94°C for 30 s, annealing at 60°C (β-actin) or 62°C (IL-6, TNF-α) for 30 s, extension at 72°C for 30 s, final extension at 72°C for 10 min. Amplification products were confirmed by electrophoresis (1.0% agarose gels) and visualized by Gel Red staining (27).

**Statistical Analysis**
Results were expressed as mean ± SE, and data were analyzed using software program SPSS 20.0 (IBM). Means were compared by one-way analysis of variance (ANOVA), with \( p < 0.05 \) as criterion for significant difference.

**RESULTS**

**Heimioporus retisporus Polysaccharide Molecular Weights and Monosaccharide Components**
\( M_w \) and \( M_n \) of HRP were, respectively, 1,949 and 873.34 kDa, and polydispersity index (PDI, calculated as \( M_w/M_n \)) was 2.232. PDI reflects distribution of molecular weight in each polymer sample, and the low value indicates that chain lengths of HRP vary over a relatively narrow range of molecular weights.

Monosaccharide composition of HRP determined by HPAEC/PAD analysis, is summarized in Table 1. The major component was glucose (49.0%), followed by mannose, galactose, glucuronic acid, and xylose (percentages ranging from 17.8 to 8.6%). Arabinose was a minor component (0.7%).

**Fourier Transform Infrared Spectroscopy Analysis**
In the FT-IR spectrum of HRP (Figure 3), the absorption bands at 3,407 and 2,923 cm\(^{-1}\) represent stretching vibrations of O-H and C-H groups of the sugar ring (28). The 1,652 cm\(^{-1}\) band reflects stretching of \( \alpha-(1,4) \) glycosidic linkages (31), 1,071 cm\(^{-1}\) band indicates that HRP sugar rings are pyranose
rings (32), 855 cm\(^{-1}\) peak represents \(\alpha\)-glycosidic bonds (33), 943 cm\(^{-1}\) band represents \(\beta\)-glycosidic bonds (34), and 530 cm\(^{-1}\) band reflects in-plane C=O bending (35).

**Nuclear Magnetic Resonance Analyses**

Structural features of HRP were elucidated by measuring 1-D NMR (\(^1\)H) and 2-D NMR (heteronuclear single quantum coherence; HSQC) spectra. In the \(^1\)H NMR spectrum (Figure 4A), H-1 signals representing six residues were seen at 3.11, 3.17, 3.31, 3.51, 3.73, and 4.06 ppm. The first four (strong signals) indicate presence of \(\beta\)-D-glucose (36), and the latter two reflect \(\beta\)-D-mannose configured residues (37).

In the HSQC spectrum (Figure 4B), six cross-peaks (4.48/102.9, 3.36/72.8, 3.51/85.8, 3.34/68.0, 3.38/76.0, and 3.64, 3.58/60.4 ppm) were assigned, respectively, to H-1/C-1, H-2/C-2, H-3/C-3, H-4/C-4, H-5/C-5, and H-6(a), H-6(b)/C-6 of \(\beta\)-D-Glcp-(1→3)-\(\alpha\)-D-Manp-(1→). \(^1\)H\(^{13}\)C chemical shifts at 3.51/71.2, 73.1/3.62, 68.8/3.95, and 3.78/70.9 ppm were assigned to H-2/C-2, H-3/C-3, H-4/C-4, and H-6/C-6 of \(\beta\)-D-Galp-(1→3)-\(\beta\)-D-Glcp-(1→) residues. Cross-peaks at 3.43/69.8, 3.88/69.3, and 3.41/62.4 were assigned to H-2/C-2, H-4/C-4, and H-6/C-6 of \(\beta\)-D-Galp-(1→3)-\(\beta\)-D-Galp-(1→) residues. Cross-peaks at 4.22/102.2, 3.13/73, 3.46/74.2, and 3.62/75.8 ppm were assigned to H-1/C-1, H-2/C-2, H-3/C-3, H-4/C-4 of \(\beta\)-D-xylan-(1→). Cross-peaks at 4.86/97.2, 3.71/66.2, 3.58/68.0, 4.08/68.2, and 3.72/68.2 were assigned to H-1/C-1, H-3/C-3, H-4/C-4, H-5/C-5, and H-6/C-6 of \(\beta\)-D-Manp-(1→) residues. Cross-peaks at 4.99/102.1 and 3.50/66.30 were assigned to \(\beta\)-D-Manp-(1→5)-\(\alpha\)-L-Araf-(1→) residues (36, 38–40). These findings are consistent with those for monosaccharide composition and \(^1\)H spectra.

**Table 1 | Monosaccharide composition of Heimioporus retisporus Polysaccharide (HRP).**

| Monosaccharide         | Glucose | Mannose | Galactose | Glucuronic acid | Xylose | Arabinose |
|------------------------|---------|---------|-----------|-----------------|--------|----------|
| Molar ratio (%)        | 49.00   | 17.78   | 12.93     | 10.99           | 8.59   | 0.71     |

**DISCUSSION**

Numerous polysaccharides from medicinal mushroom species have been shown to display hypoglycemic activity, but reported structures and activities of such polysaccharides are highly variable depending on extraction and purification methods (42). We used hot water extraction to purify and characterize a novel neutral polysaccharide from the mushroom *H. retisporus* (termed HRP), and demonstrated strong hypoglycemic activity of HRP in an STZ-induced diabetic mouse model.
HRP is composed of glucose (the predominant component), mannose, galactose, glucuronic acid, xylose, and arabinose, in molar ratio 49.00: 17.78: 12.93: 10.99: 8.59: 0.71% (Table 1). The monosaccharides glucose, galactose and mannose are in β-D conformations. The polysaccharides GLP-1 and GLP-2 from *Ganoderma lucidum* are composed of mannose,
FIGURE 6 | Scanning electron microscopy (SEM) imaging of Hemioporus retisporus Polysaccharide (HRP). (a–d) magnifications ×100, ×500, ×1,000, ×2,000.

FIGURE 7 | Antidiabetic effect of Hemioporus retisporus Polysaccharide (HRP). (A) Fasting blood glucose (FBG) level. (B) Weight. (C) Visceral organ index of heart. (D) RT-PCR of TNF-α and IL-6. Values are expressed as mean ± SE. *p < 0.05 for comparison with CK group.
glucose, galactose, and fucose in respective molar ratios 4.9: 63.5: 26.2: 5.4% and 1.6: 90.6: 7.8: 0% (43). The polysaccharide CFP from Pleurotus citrinopileatus is composed of galactose, glucose, glucuronic acid, and glucuronic acid in molar ratio 20.53: 28.75: 5.55: 45.17% (44). Most medicinal fungal polysaccharides have glucose as the major component (45), but there is great variability in identities and proportions of other components.

Intragastric administration of 40 mg/kg HRP in an STZ-induced diabetic mouse model caused significant reduction of blood glucose level, but had no notable effect on body weight. HRP was found to decrease visceral organ index for heart, and we therefore used RT-PCR assay to evaluate expression levels of inflammatory cytokines IL-6 and TNF-α in heart. IL-6 expression level was reduced by HRP treatment. Previous investigations of elevated tissue concentrations of inflammatory cytokines in mouse diabetes models indicate that inflammatory processes promote development of diabetic cardiomyopathy. For example, intramyocardial inflammation (including increased expression of IL-6 or TNF-α) contributed to diabetic cardiomyopathy (3). Activated macrophages enhance the production of IL-6, but excessive activation of macrophages can cause damage to living organisms (46). HRP may protect the heart by preventing excessive activation of macrophages.

Many recent studies have revealed hypoglycemic effects of certain polysaccharides (45, 47, 48). One example is a polysaccharide (SERP1) from the herb Sarcandra glabra (family Chloranthaceae) composed of 1,4-linked α-D-galacturonic acid, methyl esterified 1,4-linked α-D-galacturonic acid, 1,4-linked α-D-glucuronic acid, 1,5-linked α-L-arabinose, 1,3-linked β-D-galactose, 1,4-linked β-D-glucose, 1,4,6-linked β-D-glucose, 1,6-linked β-D-glucose, and 1,2-linked rhamnose (49). HRP in this study was composed of 1,3-linked β-D-glucose, 1,6-linked β-D-mannose, 1,6-linked β-D-galactose, 1,4-linked β-D-galactose, 1,4-linked β-D-xylene, and 1,5-linked α-L-arabinose. HRP and SERP1 thus have similar monosaccharide compositions, but different linkages. More generally, there are numerous naturally occurring polysaccharides that display hypoglycemic activity, but none of them have the same compositions, linkages, or conformations (34, 49–55). There is no direct evidence that polysaccharide components control hypoglycemic activity based on ratios of specific monosaccharides. On the other hand, several studies suggest that mannogalactoglucan domain plays a role in suppressing hyperglycemia, consistent with our findings (45, 56, 57). Yang et al. (45) analyzed hypoglycemic activity of 18 polysaccharides extracted from fruiting bodies of various mushroom species. In a db/db mouse model, neutral polysaccharide AAMP-N, which has a large mannogalactoglucan domain, strongly enhanced insulin sensitivity in vitro, reduced FBG, and modulated lipid metabolism. Future studies by our group and others will elucidate the link between structural characteristics of polysaccharides and their hypoglycemic activities.

Therefore, we characterized HRP, a water-soluble neutral polysaccharide extracted from H. retisporus, as a heteropolysaccharide composed of 1,3-linked β-D-glucose, 1,6-linked β-D-mannose, 1,6-linked β-D-galactose, 1,4-linked β-D-galactose, 1,4-linked β-D-xylene, and 1,5-linked α-L-arabinose. In an STZ-induced diabetic mouse model, HRP significantly reduced blood glucose level and heart visceral organ index by downregulating IL-6 expression. HRP has strong potential for application as a hypoglycemic, cardioprotective dietary supplement in diabetes treatment.

COMPLIANCE WITH ETHICAL STANDARDS

Consent for publication: All authors listed on this manuscript have read and agreed to the publication of this research.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The animal study was reviewed and approved by the Institutional Ethics Committee of the China Agricultural University (No: CAU20180420-5).

AUTHOR CONTRIBUTIONS

QL conceived and designed the study. QL, XF, PW, YL, and ZZ performed the purification, characterization, bioactivity assay, and analyzed data. CY, GT, and QL identified and collected Heimioporus retisporus fruiting bodies. QL, XF, and PW wrote the manuscript. All authors read and approved the manuscript in its finalized form.

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### REFERENCES

1. Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. *Lancet.* (2017) 389:229–51. doi: 10.1016/S0140-6736(17)30588-2

2. Mazzone T, Chat A, Plutzky J. Cardiovascular disease risk in type 2 diabetes mellitus: insights from mechanic studies. *Lancet.* (2008) 371:1800–9. doi: 10.1016/S0140-6736(08)60768-0

3. Bugger H, Abel ED. Molecular mechanisms of diabetic cardiomyopathy. *Diabetologia.* (2014) 57:660–71. doi: 10.1007/s00125-014-3171-6

4. Diamant M, Lamb DI, Smit JWA, de Roos A, Heine RJ. Diabetic cardiomyopathy in uncomplicated type 2 diabetes is associated with the metabolic syndrome and systemic inflammation. *Diabetologia.* (2005) 48:1669–70. doi: 10.1007/s00125-005-1821-4

5. Teng J, Dwyer KM, Hill P, See E, Ekinci EI, Jerums G, et al. Spectrum of renal disease in diabetes. *Nephrol. (2014)* 19:528–36. doi: 10.1111/nep.12288

6. Chang HJ, Tseng CF, Wang JY. Hypoglycemia-induced myocardial infarction: an unusual adverse effect of sulfonylureas. *Int J Cardiol.* (2007) 115:414–6. doi: 10.1016/j.ijcard.2006.01.062

7. Chang CY, Schiano TD. Review article: drug hepatotoxicity. *Aliment Pharmacol Ther.* (2007) 25:1153–51. doi: 10.1111/j.1365-2036.2007.03307.x

8. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA.* 298:1189–95. doi: 10.1001/jama.298.11.1189

9. Guiffrid M, Latinnovic R. Mortality in type 2 diabetic subjects prescribed metformin and sulphonylurea drugs in combination: cohort study. *Diabetes Metab Res Rev.* (2004) 20:239–45. doi: 10.1002/dmr.457

10. van der Laar FA, Lucassen PL, Akkermans RP, van de Lisdonk EH, Rutten GE, van Weel C. Alpha-glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and meta-analysis. *Diabetes Care.* (2005) 28:154–63. doi: 10.2337/diacare.28.1.154

11. Sudharsan S, Subhapradha N, Seediya P, Shannugam V, Madeswaran P, Shannugam A, et al. Antioxidant and anticoagulant activity of sulfated polysaccharide from *Gracilaria delichopensis* (Forsskal). *Int J Biol Macromol.* (2015) 81:228–37. doi: 10.1016/j.ijbiomac.2017.01.040

12. Wang DD, Wu QX, Pan WJ, Hussain S, Mehmood S, Chen Y. A novel polysaccharide from *Hohenbuehelia serotina* and bioactivity of a polysaccharide from *H. serotina* and *H. versicolor* combined with *L. versicolor* in C57BL/KsJ db/db mice. *Pharmacol Ther.* (2014) 132:393–405. doi: 10.1016/j.phaco.2013.09.030

13. Li F, Cui SH, Zha XQ, Bansal V, Jiang YL, Asghar MN, et al. Structure and characteristics of polysaccharide from *Amorphophallus corrogatus* in Vietnam. *Carbohydr Polym.* (2011) 84:64–8. doi: 10.1016/j.carbpol.2010.10.074

14. Yin Z, Sun-Waterhouse D, Wang J, Ma C, Waterhouse GIN, Kang W. Anti-inflammatory and immunomodulating polysaccharides from *Coriolus versicolor* and bioactivity of a polysaccharide extracted from protocorm-like bodies of *Morus alba* L. Int J Biol Macromol. (2012) 58:5743–50. doi: 10.1016/j.ijbiomac.2019.03.230

15. Liu W, Lv X, Huang W, Yao W, Gao X. Characterization and hypoglycemic effect of a neutral polysaccharide extracted from the residue of *Codonopsis pilosula*. *Carbohydr Polym.* (2018) 197:215–26. doi: 10.1016/j.carbpol.2018.05.067

16. Wu J, Chen M, Shi S, Wang H, Li N, Su J, et al. Hypoglycemic effect and mechanism of a pectic polysaccharide with hexenuronic acid from the fruits of *Ficus pumila* L. in C57BL/KsJ db/db mice. *Carbohydr Polym.* (2017) 178:209–20. doi: 10.1016/j.carbpol.2017.09.050

17. Rabinovitch A, Sorensen O, Suarez-Pinzon WL, Power RE, Rajotte RV, Bleakley RC. Analysis of cytokine mRNA expression in syngeneic islet grafts of NOD mice: interleukin 2 and interferon gamma mRNA expression correlate with graft rejection and interleukin 10 with graft survival. *Diabetologia.* (1994) 37:833–7. doi: 10.1007/BF00404341

18. Wang D, Sun SQ, Wu WZ, Yang SL, Tan JM. Characterization of a water-soluble polysaccharide from *Boletus edulis* and its antimutagenic and immunomodulatory activities in renal cancer in mice. *Carbohydr Polym.* (2014) 105:127–34. doi: 10.1016/j.carbpol.2013.12.085

19. Wang H, Gao T, Du Y, Yang H, Wei L, Bi H, et al. Anticancer and immunostimulating activities of a novel homogalacturonan from *Hippophae rhamnoides* L. berry. *Carbohydr Polym.* (2015) 131:288–96. doi: 10.1016/j.carbpol.2015.06.021

20. Bociek SM, Welti D. The quantitative analysis of uronic acid polymers by infrared spectroscopy. *Carbohydr Res.* (1975) 42:217–26. doi: 10.1016/0008-6215(75)82423-9

21. Yang JP, Hsu T, Lin F, Hsu W, Chen Y. Potential anti diabetic activity of extracellular polysaccharides in submerged fermentation culture of *Coriolus versicolor* LHL. *Carbohydr Polym.* (2012) 90:174–80. doi: 10.1016/j.carbpol.2012.05.011

22. Kan YJ, Chen TQ, Wu YB, Wu JG, Wu JZ. Antioxidant activity of polysaccharide extracted from *Ganoderma lucidum* using response surface methodology. *Int J Biol Macromol.* (2015) 72:151–7. doi: 10.1016/j.ijbiomac.2014.07.036

23. Jiang L, Kong F, Li N, Zhang D, Yan C, Lv H. Purification, structural characterization and in vitro antioxidant activity of a novel polysaccharide from *Rhizopogon roseus*. *Carbohydr Polym.* (2016) 147:365–71. doi: 10.1016/j.carbpol.2016.04.001

24. Ru Y, Chen X, Wang J, Guo L, Lin Z, Peng X, et al. Structural characterization, hypoglycemic effects and mechanism of a novel polysaccharide from *Tetrastigma hemsleyanum*. *Int J Biol Macromol.* (2019) 123:757–83. doi: 10.1016/j.ijbiomac.2018.11.085

25. Wang WF, Stevenson A, Reuter DC, Sirota JM. Absolute band intensities and bioactivity of a polysaccharide extracted from *Protocorm-like body of Heimioporus retisporus*. *J Carbohydr Polym.* (2016) 147:390–5. doi: 10.1016/j.jcarbpol.2014.08.026

26. Bociek SM, Welti D. The quantitative analysis of uronic acid polymers by infrared spectroscopy. *Carbohydr Res.* (2017) 436:162–72. doi: 10.1016/j.carres.2017.04.001
39. Li MF, Fan YM, Xu F, Sun RC. Structure and thermal stability of polysaccharide fractions extracted from the ultrasonic irradiated and cold alkali pretreated bamboo. J Appl Polym Sci. (2011) 121:176–85. doi: 10.1002/app.33491

40. Liu X, Liu D, Chen Y, Zhong R, Gao L, Yang C, et al. Physicochemical characterization of a polysaccharide from *Agrocybe aegerita* and its anti-ageing activity. Carbohydr Polym. (2020) 236:116056. doi: 10.1016/j.carbpol.2020.116056

41. Varma CAK, Jayaram Kumar K. Characterization and evaluation of smart releasing polysaccharide from yellow poinciana seed of Jharkhand. Int J Biol Macromol. (2018) 118:215–62. doi: 10.1016/j.ijbiomac.2018.07.057

42. Prashanth KVH, Tharanathan RN. Chitin/chitosan: modifications and their unlimited application potential - an overview. Trends Food Sci Tech. (2007) 18:117–31. doi: 10.1016/j.tifs.2006.10.022

43. Li J, Gu F, Cai C, Hu M, Fan L, Hao J, et al. Purification, structural characterization, and immunomodulatory activity of the polysaccharides from *Glycyrrhiza inflata*. J Biol Macromol. (2020) 143:806–13. doi: 10.1016/j.ijbiomac.2019.09.141

44. Hao YL, Sun HQ, Zhang XJ, Wu LR, Zhu ZY. A novel acid polysaccharide from *Leleba oldhami* shells. Carbohydr Polym. (2016) 144:438–46. doi: 10.1016/j.carbpol.2016.02.073

45. Wang Z, Zhao X, Liu X, Chen Z, Zhou S, Wang J, Yao W, et al. Characterization and hypoglycemic effect of a polysaccharide extracted from the fruit of *Lycium barbarum*. Carbohydr Polym. (2013) 98:8–16. doi: 10.1016/j.carbpol.2013.04.057

46. Yin Z, Liang Z, Li C, Wang J, Ma C, Kang W. Immunomodulatory effects of polysaccharides from edible fungus: a review. Food Sci Hum Wellness. (2021) 10:393–400. doi: 10.1016/j.fswh.2021.04.001

47. Wang Z, Zhao X, Liu X, Lu W, Jia S, Hong T, et al. Anti-diabetic activity evaluation of a polysaccharide extracted from fermented broth of *Pleurotus citrinopileatus*: hypoglycemic activity in vitro and chemical structure. J Mol Struct. (2020) 1220:128717. doi: 10.1016/j.molstruc.2020.128717

48. Yin C, Noratto GD, Fan X, Chen Z, Yao F, Shi D, et al. The impact of mushroom polysaccharides on gut microbiota and its beneficial effects to host: a review. Carbohydr Polym. (2020) 250:116942. doi: 10.1016/j.carbpol.2020.116942

49. Liu W, Lu W, Chai Y, Liu Y, Yao W, Gao X. Preliminary structural characterization and hypoglycemic effects of an acidic polysaccharide SERP1 from the residue of *Sarcandra glabra*. Carbohydr Polym. (2017) 176:340–51. doi: 10.1016/j.carbpol.2017.08.071

50. Gong Y, Zhang J, Gao F, Zhou J, Xiang Z, Zhou C, et al. Structure features and in vitro hypoglycemic activities of polysaccharides from different species of Maidong. Carbohydr Polym. (2017) 173:215–22. doi: 10.1016/j.carbpol.2017.05.076

51. He X, Fang J, Ruan Y, Wang X, Sun Y, Wu N, et al. Structures, bioactivities and future prospective of polysaccharides from *Morus alba* (white mulberry): a review. Food Chem. (2018) 245:899–910. doi: 10.1016/j.foodchem.2017.11.084

52. Liu J, Zhao Y, Wu Q, John A, Jiang Y, Yang J, et al. Structure characterisation of polysaccharides in vegetable "okra" and evaluation of hypoglycemic activity. Food Chem. (2018) 242:211–6. doi: 10.1016/j.foodchem.2017.09.051

53. Zhao H, Lai Q, Zhang J, Huang C, Iia L. Antioxidant and hypoglycemic effects of acidic-extractable polysaccharides from *Cordyceps militaris* on type 2 diabetes mice. Oxid Med Cell Longev. (2018) 2018:9150807. doi: 10.1155/2018/9150807

54. Yin C, Noratto GD, Fan X, Chen Z, Yao F, Shi D, et al. Characterization and hypoglycemic activity of a beta-pyran polysaccharides from bamboo shoot (Leleba oldhami Nakal) shells. Carbohydr Polym. (2016) 144:438–46. doi: 10.1016/j.carbpol.2016.02.073

55. Zhu J, Liu W, Yu J, Zou S, Wang J, Yao W, et al. Characterization and hypoglycemic effect of a polysaccharide extracted from the fruit of *Lycium barbarum*. Carbohydr Polym. (2013) 98:8–16. doi: 10.1016/j.carbpol.2013.04.057

56. Jiang X, Meng W, Li L, Meng Z, Wang D. Adjuvant therapy with mushroom polysaccharides for diabetic complications. Front Pharmacol. (2020) 11:168. doi: 10.3389/fphar.2020.00168

57. Wu J, Shi S, Wang H, Wang S. Mechanisms underlying the effect of polysaccharides in the treatment of type 2 diabetes: a review. Carbohydr Polym. (2016) 144:474–94. doi: 10.1016/j.carbpol.2016.02.040

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