Advances in Mechanism Research on Polygonatum in Prevention and Treatment of Diabetes

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Diabetes mellitus is a fast-growing disease with a major influence on people’s quality of life. Oral hypoglycemic drugs and insulin are currently the main effective drugs in the treatment of diabetes, but chronic consumption of these drugs has certain side effects. Polysaccharides, saponins, flavonoids, and phenolics are the primary secondary metabolites isolated from the rhizomes of Polygonatum sibiricum Redouté [Asparagaceae], Polygonatum kingianum Collett & Hemsl [Asparagaceae], or Polygonatum cyrtonema Hua [Asparagaceae], which have attracted much more attention owing to their unique therapeutic role in the treatment and prevention of diabetes. However, the research on the mechanism of these three Polygonatum spp. in diabetes has not been reviewed. This review provides a summary of the research progress of three Polygonatum spp. on diabetes and its complications, reveals the potential antidiabetic mechanism of three Polygonatum spp., and discusses the effect of different processed products of three Polygonatum spp. in treating diabetes, for the sake of a thorough understanding of its effects on the prevention and treatment of diabetes and diabetes complications.

Keywords: Polygonatum, antidiabetic mechanism, hypoglycemic, hypolipidemic, diabetes

INTRODUCTION

Diabetes mellitus (DM) is a comprehensive endocrine and metabolic disease characterized by glucose metabolism disorders, mainly resulting from insulin resistance or insufficient insulin secretion (Xiao et al., 2019). According to the American Diabetes Association, it is divided into four major types: type 1 diabetes (T1DM), type 2 diabetes (T2DM), gestational diabetes (GDM), and diabetes from other causes. T2DM has the highest incidence among these diseases (Skyler and Oddo, 2010). The key factors that cause T2DM are pancreas β-cell failure, insulin resistance, and its complex interrelationships (Thorens, 2011). More importantly, long-term hyperglycemia may cause malfunction and long-term damage in a variety of tissues and organs, particularly the eyes, nerves, kidneys, heart, and blood vessels (Pham et al., 2019; Sloan, 2019).

In recent years, DM has become one of the primary diseases endangering modern people, and the number of patients has been increasing year by year. Almost all patients require oral hypoglycemic agents or injecting insulin. Diabetes is difficult to control in a maintainable long-term lifestyle (Tahrani et al., 2011; Herman et al., 2018). Current oral hypoglycemic agents include the earlier developed metformin and sulfonylureas, as well as some novel hypoglycemic agents targeting the pancreas or liver, such as sodium-dependent glucose transporter 2 (SGLT2) inhibitors, dipeptidyl
According to published reports from 2011 to 2021, "Polygonatum" or "Rhizoma polygonii" combined with "diabetes" or "anti-diabetic," "secondary metabolites," and "processed products" were used as search keywords. The data were collected by various online databases, including PUBMED, Web of Science, Science Direct, SpringerLink, Wiley Online Library, Wanfang, and China Knowledge Network. About 189 papers were found by reading abstracts to exclude repetitive and irrelevant papers. The data were further extracted from the above studies: *P. sibiricum*, *P. kingianum*, and *P. cyrtonema* were used according to the 2020 edition of the Pharmacopoeia of the People’s Republic of China; test design with the control group and functional verification; and dose use strictly in line with the standard (rat dose = human dose g * 0.018/0.02 kg). Eventually, we found that 47 articles met the screening standard and brought into this paper by critically reviewing and analyzing the data, aiming to identify secondary metabolites and processed products of *Polygonatum* involved in the anti-diabetic mechanism.

### SECONDARY METABOLITES OF *POLYGONATUM*

Currently, the secondary metabolites of *Polygonatum* have been reported to include polysaccharides, saponins (steroidal saponins and triterpenoids), flavonoids, phenols, alkaldoids, lignans, phyto-sterols, and volatile oils, of which the first four ones are the major ingredients and have been studied most frequently. Additionally, polysaccharides and saponins were the highest in *P. cyrtonema*, and flavonoids and other phenolics were the highest in *P. sibiricum* (Table 1).

#### Polysaccharides

Polysaccharide is not only an active important component of *Polygonatum* but also an important evaluation index of its quality. It has been reported that polysaccharide is composed of many monosaccharides including fructose (Fru), glucose (Glc), mannose (Man), galactose (Gal), arabino (Ara), and rhamnose (Rha), as well as a handful of glucuronic acid (GlcA) and xylose (Xyl). The molecular weights of polysaccharides from *Polygonatum* plants are estimated to be approximately 2,734~3.6 × 105 Da (Zhao et al., 2018). Two new polysaccharides (PSP50-2-1 and PSP50-2-2) were isolated and purified from the rhizome of *P. sibiricum*, both of which were homogeneous polysaccharides by the analysis of the specific optical rotation. Meanwhile, the result of monosaccharide composition indicated that PSP50-2-1 and PSP50-2-2 were made up of Glc, Gal, and Fru (Liu et al., 2021), with the molecular weight of 7.7 and 7.0 kDa, respectively. More importantly, Wang et al. found that four polysaccharides isolated from *P. sibiricum* (PSP1, PSP2, PSP3, and PSP4) were made up of Gal, Rha, Man, Glu, and Xyl in different proportions, and the immune activity of polysaccharides was closely related to that of Rha residues, with the molecular weight of 4.415, 2.236, 7.743, and 6.467 kDa, respectively (Wang et al., 2020). Zhao et al. found that polysaccharides isoalted from *P. sibiricum*, *P. kingianum*, and *P. cyrtonema* were mainly made up of Fru and pectins, with a molecular weight of more than 4.1 × 105 Da (Zhao et al., 2020).

#### Saponins

Although saponins are another main active component of *Polygonatum*, their content is relatively low. According to the...
TABLE 1 | Comparison of the major chemical constituents of three Polygonatum spp.

| Species                  | Polysaccharide (mg/g) | Saponin (mg/g) | Flavonoid (mg/g) | Phenol (mg/g) | References             |
|--------------------------|-----------------------|----------------|------------------|---------------|------------------------|
| Polygonatum sibiricum    | 40.68–123.58          | 0.289–2.017    | 0.018–0.035      | 0.013–0.045   | Jiao et al. (2016)     |
| Polygonatum kingianum    | 31.24–140.94          | 1.303–2.845    | 0.015–0.030      | 0.007–0.029   | Jiao et al. (2016)     |
| Polygonatum cyrtonema    | 22.34–140.94          | 0.030–8.820    | 0.004–0.034      | 0.007–0.038   | Jiao et al. (2016)     |

TABLE 2 | Flavonoids isolated from three Polygonatum spp.

| Number | Name                                | Source               | References             |
|--------|-------------------------------------|----------------------|------------------------|
| 1      | 4′,5,7-Trihydroxy-6-methyl-8-methoxy-homoisoavanon | Polygonatum sibiricum | Yu et al. (2016)      |
| 2      | 4′,5,7-Trihydroxy-6-methyl-homoisoavanon          | P. sibiricum         | Yu et al. (2016)      |
| 3      | 4′,5,7-Dihydroxy-8-methyl-homoisoavanon          | P. sibiricum         | Yu et al. (2016)      |
| 4      | 4′,5,7-Tetralydroxy-homoisoavanon               | P. sibiricum         | Yu et al. (2016)      |
| 5      | (3R)-5,7-Dihydroxy-8-methyl-3′-hydroxy-4′-methoxybenzyl-chroman-4-one | Polygonatum cyrtonema | Gan et al. (2013)    |
| 6      | 5,7-Dihydroxy-6,8-dimethyl-3′-hydroxybenzyl-chroman-4-one | P. cyrtonema         | Wang et al. (2019a)   |
| 7      | 5,7-Dihydroxy-6,8-dimethyl-3′-hydroxybenzyl-chroman-4-one | P. cyrtonema         | Wang et al. (2019a)   |
| 8      | 5,7-Dihydroxy-6,8-dimethyl-3′-methoxy-4′-hydroxybenzyl-chroman-4-one | P. cyrtonema         | Wang et al. (2019a)   |
| 9      | 5,7-Dihydroxy-6,8-dimethyl-3′-hydroxybenzyl-chroman-4-one | P. cyrtonema         | Wang et al. (2019a)   |
| 10     | 5,7-Dihydroxy-6,8-dimethyl-3′-methoxybenzyl-chroman-4-one | P. cyrtonema         | Wang et al. (2019a)   |
| 11     | 5,7-Dihydroxy-6,8-dimethyl-3′-methoxybenzyl-chroman-4-one | P. cyrtonema         | Wang et al. (2019a)   |
| 12     | 5,7-Dihydroxy-6,8-dimethyl-3′-methoxybenzyl-chroman-4-one | P. cyrtonema         | Wang et al. (2019a)   |
| 13     | 5,7-Dihydroxy-6,8-dimethyl-3′-methoxybenzyl-chroman-4-one | P. cyrtonema         | Wang et al. (2019a)   |
| 14     | 5,7-Dihydroxy-6,8-dimethyl-3′-methoxybenzyl-chroman-4-one | P. cyrtonema         | Wang et al. (2019a)   |
| 15     | 5,7-Dihydroxy-6,8-dimethyl-3′-methoxybenzyl-chroman-4-one | P. cyrtonema         | Wang et al. (2019a)   |
| 16     | 5,7-Dihydroxy-6,8-dimethyl-3′-methoxybenzyl-chroman-4-one | P. cyrtonema         | Wang et al. (2019a)   |
| 17     | 5,7-Dihydroxy-3′-dimethoxybenzylidene-chroman-4-one | P. cyrtonema         | Wang et al. (2019a)   |
| 18     | Disporopin                           | Polygonatum H        | Wang et al. (2019a)   |
| 19     | Polygonatone H                      | Polygonatum H        | Wang et al. (2019a)   |

different structures of saponins in Polygonatum, saponins were divided into steroidal saponins and triterpenoid saponins. Zhao et al. summarized 162 saponins from 18 species of Polygonatum genus, among which 70 steroidal saponins and 12 triterpenoid saponins were isolated from P. sibiricum, P. kingianum, and P. cyrtonema (Zhao et al., 2018). Subsequently, some studies provided novel findings of five novel steroidal saponins isolated from P. sibiricum, 3-O-β-D-glucopyranosyl(1→2)-β-D-glucopyranosyl(1→4)-β-D-fucopyranosyl-(25R/S)-spirost-5-en-3β,17α-diol, 3-O-β-D-glucopyranosyl(1→4)-β-D-fucopyranosyl-(25R/S)-spirost-5-en-3β,17β-diol, 3-O-β-D-glucopyranosyl(1→4)-β-D-fucopyranosyl-(25R)-spirost-5-en-3β,17α-diol, 3-O-β-D-glucopyranosyl(1→4)-β-D-fucopyranosyl-(25R)-spirost-5-en-3β,17β-diol, and kingianoside Z (Zhang et al., 2017; Tang et al., 2019). Two new steroidal saponins were isolated from P. kingianum, named polygakingiaside A and polygakingiaside B, respectively (Ha et al., 2021). A novel steroidal saponin was isolated from P. cyrtonema, named
Huangjingsosterol B (Huang et al., 2020). On the other hand, no new triterpenoid saponins were found in Polygonatum plants because triterpenoid saponins are found principally in the Magnoliopsida class, and steroidal saponins are distributed widely in the Liliopsida class (Faizal and Geelen, 2013).

**Phenolics**

Phenolics include flavonoids, phenolics, and lignins. Flavonoids are ubiquitous in natural plants and have a broad spectrum of biological activities. Until now, 34 flavonoids have been isolated from *P. sibiricum*, *P. kingianum*, and *P. cyrtonema*, which can be divided into six types in accordance with the structure of the parent nucleus: homoisoflavanones, iso flavones, flavones, chalcones, dihydroflavones, and rosandalanes (Table 2). Among them, homoisoflavanones are the most abundant in *Polygonatum*, such as 4’,5,7-trihydroxy-6-methyl-8-methoxy-homoisoflavonan, disporopsin, and polygonatone H.

Phenolics in plants are secondary metabolites synthesized during the normal development of plants. Relatively rare studies have been conducted on the structural properties of the phenolics and lignans from *Polygonatum*. Wang et al. identified two known compounds (narcissoside and nicotifolin) from *P. sibiricum* by 1D/2D NMR and MS data (Wang et al., 2016b). Zhai and Wang isolated syringaresinol-di-O-β-D-glucoside from *P. sibiricum* (Zhai and Wang, 2018). Chen et al. isolated a benzofuran-type lignan (polygonneolignanoside A) from *P. sibiricum* (Chen et al., 2020).

**Other Secondary Metabolites**

The contents of alkaloids, phytosterols, and volatile compounds in *Polygonatum* were extremely low, and their structures were less studied. Polygonatine A and Polygonatine B isolated from *P. sibiricum* were identified as alkaloids (Sun et al., 2005). Four phytosterol compounds have already been identified in *P. sibiricum* and *P. kingianum*, including β-sitosterol, carotenoside, palmitate-3β sitosterol, and (22S)-cholest-5-en-3β,6α,16β,22-tetrol 1-O-α-L-rhamnopyranosyl 16-O-β-D-glucopyranoside (Li et al., 2008; Ahn et al., 2011). Volatile compounds were found in the rhizomes of *P. cyrtonema*, which accounted for 95.97% of the total volatile oils (Yu et al., 2008).

**POTENTIAL ANTIDIABETIC MECHANISM OF Polygonatum ON DIABETES**

Studies have shown that certain active ingredients of traditional Chinese herbal medicines have apparent effects of lowering blood sugar and blood lipids, such as polysaccharides, saponins, flavonoids, phenols, and alkaloids (Xu et al., 2018; Xu et al., 2019; Deng et al., 2020; Hou et al., 2020; Zhuang et al., 2020). *Polygonatum* is rich in these substances and hence is a Chinese herbal medicine with great medicinal value. The number of research papers on secondary metabolites and biological activities of *Polygonatum* is increasing in recent decades.

To date, there are three models to study the antidiabetic mechanism of secondary metabolites from *Polygonatum*: cells, diabetic animal models, and humans (Figure 1). For example, in *in vitro* studies, in which the IR-3T3-L1 adipocytes and IR-HepG2 cells were cultured, it was found that *Polygonatum* could increase glucose intake by alleviating oxidative stress and inflammation (Cai et al., 2019; Luo et al., 2020). In animal models of diabetes, for the sake of identifying the metabolic impact of the *Polygonatum* rhizome extract, high-fat diet (HFD)-, streptozotocin (STZ)-, or alloxan-induced rats were administered *Polygonatum* orally at a certain dose for a period. It is suggested that *Polygonatum* could decrease high blood glucose by analyzing various factors related to metabolic syndrome (Pang et al., 2018; Gu et al., 2020; Li et al., 2020). In addition, *Polygonatum* also improves homeostasis model assessment of insulin sensitivity (HOMA-IS) and homeostasis model assessment of insulin resistance (HOMA-IR) of patients with diabetes in clinical studies (Ping, 2021).

**In Vitro Models**

The nuclear factor erythroid 2-related factor 2/heme oxygenase-1 (Nrf2/HO-1) signaling pathway is closely related to pancreatic β-cell injury, obesity, glucose metabolism disorders, and insulin resistance. Polysaccharides of *P. sibiricum* (PSP) (50, 100, and 250 μg/ml) can alleviate IR and proliferation of IR-3T3-L1 adipocytes by activating Nrf2/HO-1 signaling pathway in IR-3T3-L1 adipocytes, they promoted the expression of Nrf2 and HO-1 and lessened the expression levels of inflammatory cytokines [interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α)], and subsequently enhanced...
glucose intake by stimulating the expression of transporter subtype-4 (GLUT4). When the Nr2 gene was silenced, the expressions of inflammatory cytokines, HO-1, GLUT4, and glucose intake were elevated, thereby reversing the therapeutic effect of PSP in IR-3T3-L1 adipocytes (Cai et al., 2019).

In IR-HepG2 cells, polysaccharides from *P. kingianum* (PKP) enhanced the levels of glucose utilization efficiency at doses of 6.25, 12.5, and 25 mg/L (Li et al., 2020); saponins from *P. sibiricum* (PSS) could significantly inhibit insulin resistance in a dose-dependent manner in HepG2 cells, but it was noteworthy that when the concentration of PSS was above 500 μg/ml, it affected cell viability. Moreover, PSS also could markedly attenuated the activities of α-glucosidase and α-amylase in vitro (Luo et al., 2020).

### Animal Models

Polysaccharides of *P. cyrtonema* (PCP) (450–900 mg/kg) significantly improved the survival rate of STZ-induced T1DM female rats by inhibiting weight loss, suppressing inflammatory cytokine expression in the liver, and increasing insulin receptor substrate (IRS) expression, thereby improving the hepatic immune response (Wang et al., 2019b). More importantly, both low (120 mg/kg) and high (480 mg/kg) doses of PKP improved diabetic symptoms by increasing short-chain fatty acid (SCFA) levels, modulating gut microbiota composition, and reducing inflammation in HFD rats (Gu et al., 2020).

Saponins from *P. kingianum* (TSPK) also have antidiabetic effects. STZ-induced diabetic rats were given TSPK for 8 weeks at 0.025 and 0.1 g/kg. TSPK could alleviate hyperlipidemia and hyperglycemia in diabetic rats, and the genome-wide expression indicated that expression of GLUT4 was significantly upregulated. In contrast, the expression of G6P was downregulated in the insulin signal pathway (Lu et al., 2016). The structure and number of gut microbiota of rats treated with TSPK were significantly changed, so TSPK may prevent T2DM by regulating gut microbiota and the secretion of SCFAs (Yan et al., 2017). Furthermore, PSS can activate hexokinase and then converts glucose to glucose-6-phosphatase (G6P), which promotes glycogen synthesis and ultimately reduces insulin resistance. Interestingly, the number of bacteria changed in the dung of the T2DM rats treated with PSS (1, 1.5, and 2 g/kg), with the result that the number of probiotics increased and the number of harmful bacteria decreased (Luo et al., 2020).

Shu et al. found that total flavonoids of *P. sibiricum* (TFP) have significant hypoglycemic effects on both T1DM and T2DM. Compared to those of the control group, the hypoglycemic effects of 100 and 200 mg/kg of TFP were similar to those of 20 mg/kg of acarbose in STZ-induced T1DM rats. In HFD- and alloxaan-induced T2DM rats, 200 mg/kg of TFP had a similar hypoglycemic effect to 15 mg/kg of glitazone. After 9 days of treatment with 100 and 200 mg/kg of TFP, the fasting blood glucose (FBG) of rats decreased in a dose-dependent manner. Besides, TFP significantly inhibited α-amylase activity in a dose-dependent manner in vitro (Shu et al., 2012). Overall, TFP may have multiple beneficial effects on lessening hyperglycemia induced by alloxaan, STZ, and HFD in diabetic rats, respectively.

However, there is another class of phenolic compound (syringaresinol-di-O-β-D-glucoside (SOG)) isolated from *P. sibiricum* that exerts an antidiabetic effect. Treatment with SOG (25, 50, and 75 mg/kg) facilitated insulin secretion and reduced the levels of lipid metabolism and oxidative stress in the STZ-induced diabetic rats, as well as downregulated the expression of nitrotyrosine (NT) and TGF-β1 in kidneys (Zhai and Wang, 2018). Thus, SOG showed a significant antidiabetic effect by suppressing oxidative stress.

In summary, polysaccharides, saponins, flavonoids, and other phenolics of *Polygonatum* have a prominent role in lowering blood sugar and blood lipids in DM (Table 3). The minimum dose of *Polygonatum* secondary metabolites is 25 mg/kg, and the maximum dose is 2 g/kg.

### Clinical Application

To date, clinical studies verified that a few Chinese patent medicines containing *Polygonatum* have a beneficial effect on diabetes, such as Tangwei capsules, Jinlida granules, Tangmaikang granules, Jiangtangjia tablets, and Qizhi Jiangtang capsules (Tables 4, 5). Jinlida granules could significantly decrease the level of hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) in the 2-h postprandial blood glucose (2hPG) in the individuals who received Jinlida granules (9 g) compared to the control groups (Lian et al., 2019). Jiangtang Tongmait capsules (1.05 g) combined with glibenclamide can reduce the blood glucose level, improve HOMA-IR and HOMA-IS of patients with T2DM, and reduce the severity of clinical symptoms of T2DM (Ping, 2021). HbA1c and HOMA-IR were significantly decreased after treatment with Jiangtangshu tablets (1.5 g) combined with repaglinide, while GLP-1 and fasting serum insulin (FINS) levels were significantly increased (Li and Li, 2019). After treatment with Qizhi Jiangtang capsules (2.5 g), NO serum content was increased, and endothelin-1 (ET-1), thromboxane B2 (TXB2), blood urea nitrogen (BUN), serum creatinine (Scr) contents were lower than those in the control group, which eventually improved renal microcirculation and dysfunction (Si and Xue, 2021). In conclusion, these Chinese patent medicines could effectively control blood glucose and inhibit insulin resistance without significant adverse effects and could be used as an adjuvant drug for the treatment of T2DM and its complications.

### POTENTIAL ANTIDIABETIC MECHANISM OF POLYGONATUM ON DIABETES COMPLICATIONS

Diabetes can also lead to complications of other diseases, such as acute kidney injury (AKI), diabetic retinopathy (DR), and diabetic nephropathy (DN). The p38 MAPK is the most critical and common signaling pathway in protecting against inflammatory kidney injury (Ahmed and Mohamed, 2018). Gentamicin (GM) can stimulate the secretion of inflammatory cytokines via activation of p38 mitogen-activated protein kinase (MAPK)/activation transcription factor 2 (p38 MAPK/ATF2) pathway, triggering a set of inflammatory cascade reactions that result in kidney injury. However, PSP could markedly...
TABLE 3 | Antidiabetic properties of three Polygonatum spp. in cells and animal models.

| Species          | Part of plant | Compounds         | Concentration       | Treatment duration | Model                                      | Index                                          | References                     |
|------------------|---------------|-------------------|---------------------|--------------------|--------------------------------------------|------------------------------------------------|-----------------------------------|
| Polygonatum sibiricum | Rhizome      | Polysaccharide    | 50, 100, and 250 µg/ml | 12, 24, and 48 h   | IR-3T3-L1 adipocytes                       | IL-1β, IL-6, and TNF-α; NF2 and HO-1†           | Cai et al. (2019)                |
| Polygonatum kingianum | Rhizome      | Polysaccharide    | 100 mg/L            | 24 h               | iNOS/G/PI3K/Akt†                            |                                                | Li et al. (2020)                 |
| P. sibiricum     | Rhizome      | Saponin           | 10, 5, 1, 0.5, and 0.1 mg/ml | 36 h               | iNOS/G/PI3K/Akt†                           | Glucose consumption, HK, and PK†                | Luo et al. (2020)               |
| P. sibiricum     | Rhizome      | Polysaccharide    | 200, 400, and 800 mg/kg | 12 weeks           | STZ-induced diabetic rats                   | Bax, EGF, p38, VEGF and TGF-β; Bcl-2†         | Wang et al. (2019c)             |
| P. kingianum     | Rhizome      | Polysaccharide    | 120, 240, and 480 mg/kg | 14 weeks           | HFD rats                                   | FBG, HDL-C, harmful bacteria; TC, TG, LDL-C, FINS, beneficial bacteria† | Li et al. (2020)               |
| P. kingianum     | Rhizome      | Polysaccharide    | 1,190 mg/kg         | 4 weeks            | STZ-induced diabetic rats                   | FBG, HDL-C; TC, TG, LDL-C and TC/HDL-C         | Li et al. (2020)               |
| P. kingianum     | Rhizome      | Polysaccharide    | 0.1 g/kg            | 8 weeks            | HFD rats                                   | FBG, harmful bacteria; FINS, beneficial bacteria† | Yan et al. (2017)              |
| Polygonatum cyrtonema | Rhizome      | Polysaccharide    | 450 and 900 mg/kg   | 4 weeks            | STZ-induced diabetic rats                   | IL-6, IL-1α; IRS-1†                           | Wang et al. (2019b)            |
| P. sibiricum     | Rhizome      | Saponin           | 1, 1.5, or 2 g/kg   | 11 weeks           | STZ-induced diabetic rats                   | Water consumption, food intake, blood glucose, body weight† | Luo et al. (2020)              |
| P. sibiricum     | Rhizome      | Saponin           | 100, 200, and 300 mg/kg | 2 weeks           | Aloxan-induced diabetic rats                | G6P; GLUT4, PPAR-γ†                           | Pang et al. (2018)             |
| P. kingianum     | Rhizome      | Saponin           | 0.025 g/kg and 0.1 mg/kg | 8 weeks            | STZ-induced diabetic rats                   | G6P; GLUT4, PPAR-γ†                           | Lu et al. (2016)               |
| P. kingianum     | Rhizome      | Saponin           | 0.025 and 0.1 g/kg  | 8 weeks            | HFD rats                                   | FBG, harmful bacteria; FINS, beneficial bacteria† | Yan et al. (2017)              |
| P. sibiricum     | Rhizome      | Flavonoid         | 50, 100, and 200 mg/kg | 10 days            | Aloxan-induced diabetic rats                | Alpha-amylase; insulin†                       | Shu et al. (2012)             |
| P. sibiricum     | Rhizome      | Phenolic          | 25, 50, and 75 mg/kg | 8 weeks            | STZ-induced diabetic rats                   | TC, TG, LDL-C, FFA, MDA, SOD, CAT, AST, ALT, ALP, and TGF-β1; HDL-C, T-AOC† | Zhai and Wang (2018)          |
| P. sibiricum     | Rhizome      | Polysaccharide    | 200, 400, and 800 mg/kg | 12 weeks           | STZ-induced DR rats                         | FBG, HbA1c, SOD†; insulin, C-peptide, MDA 1; NGAL, KIM-1, IL-1α, IL-6, TNF-α, and p38 MAPK† | Wang et al. (2017)            |
| P. sibiricum     | Rhizome      | Polysaccharide    | 0.25, 0.5, and 1 g/kg | 2 weeks            | GM-induced AKI rats                         | Urea nitrogen, serum creatinine, Wnt4, β-catenin | Han et al. (2020)             |
| P. sibiricum     | Saponin      | Saponin           | 35 and 70 mg/kg     | 16 weeks           | STZ-induced DN rats                         | HFD rats                                      | Jing (2019)                    |

Note. IRS, insulin receptor substrate; HK, hexokinase; PK, pyruvate kinase; PPAR-γ, peroxisome proliferator-activated receptor-gamma; FFA, fatty acid; CAT, catalase; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; T-AOC, total antioxidant capacity.

TABLE 4 | Chinese patent medicines containing Polygonatum with hypoglycemic effect in human studies.

| Drug name                  | Dosage/ times (g) | Cases | Adverse reactions | Index                          | References               |
|----------------------------|-------------------|-------|-------------------|--------------------------------|--------------------------|
| Jiangtang Tongmai capsule  | 1.05              | 60    | —                 | HOMA-IS†; HOMA-IR†             | Ping (2021)              |
| Tangwei capsule            | 2.5               | 80    | Nausea and dizziness | FBG, 2hPG, HbA1c†             | Chen and Zhang (2019)    |
| Tangmai kang granule        | 5                 | 102   | No                | FPG, 2hPG, HbA1c, TG, TC, LDL-C, IL-6†; HDL-C† | Yong et al. (2019)       |
| Qizhi Jiangtang capsule     | 2.5               | 80    | No                | ET-1, TXB2, BUN, SQR†; NO†    | Si and Xue (2021)        |
| Jinlia granule              | 9                 | 128   | Nausea, rash, and heart palpitations | FPG, 2hPG, HbA1c, TC, TG, LDL-C, IL-6, MDA, HOMA-IR†; HDL-C, SOD, HOMA-β† | Fan et al. (2021)        |
| Jiangtangshu tablet         | 1.5               | 165   | Diarrhea, constipation, and abdominal pain | HbA1c, FBG, HOMA-IR†; GLP-1 and FINS† | Li and Li (2019)         |
| Jiangtangjia tablet         | 1.83              | 38    | —                 | FBG†                           | Fan (2012)               |

decrease the expression levels of neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule-1 (KIM-1), preventing the p38 MAPK/ATF2 pathway to suppress the secretion of inflammatory cytokines in the kidney (Han et al., 2020). As a result, PSP has a potential pharmacotherapy on GM-induced AKI rats.
TABLE 5 | Chinese patent medicine prescription containing Polygonatum with hypoglycemic effect (data from db.yaozh.com).

| Drug name          | Sources of prescription                                                                 | Prescription                                                                 |
|--------------------|----------------------------------------------------------------------------------------|------------------------------------------------------------------------------|
| Jiangtang Tongmai  | National Chinese patent medicine standard assembly Internal medicine Qi blood body fluid subvolume | *Pseudostellaria heterophylla* (Miq.) Pax [Caryophyllaceae; Pseudostellaria Radix], *Astragalus mongholicus* Bunge [Fabaceae; *Astragalus mongholicus* radix], *Polygonatum sibiricum* Redouté [Asparagaceae; Polygonati rhizoma], *Asparagus cochinchinensis* (Lour.) Merr [Asparagaceae; Asparagi radix], *Ophiopogon japonicus* (Thunb.) Ker Gawl [Asparagaceae; *Ophiopogon* radix], *Scrophularia ningpoensis* Hemsl [Scrophulariaceae; Scrophulariae radix], *Trichosanthes kirilowii* Maxim [Cucurbitaceae; Trichosanthis radix], *Atractylodes lancea* (Thunb.) DC [Asteraceae; Atractylodis rhizoma], *Anemarrhena asphodeloidea* Bunge [Asparagaceae; *Anemarrhena rhizoma*], *Pueraria lobata* (Willd.) Ohwi [Fabaceae; *Puerariae lobatae* radix], *Coptis chinensis* Franch [Ranunculaceae; *Coptidis* rhizoma], *Salvia miltiorrhiza* Bunge (Lamiaceae; *Salviae miltiorrhiza* radix et rhizoma), *Leonurus japonicus* Houtt [Lamiaceae; *Leonuri herba*], *Paeonia tetchi* Lynch [Paeoniaceae; *Paeoniae rubra* radix], *Hirudo niponica* Whitman [Hirudinidae; Hirudo], *Clematis chinensis* Osbeck [Ranunculaceae; *Clematidis* radix et rhizoma], *Litchi chinensis* Sonn [Sapindaceae; *Litchi* fructus], *Pheretima aspergillum* (E. Perrier) [Megascolecidae; Pheretima], *Conioselinum anthrisoides* Chuanxiong [Apiaceae; *Chuanxiong* rhizoma], *Starch* |
TABLE 5 | (Continued) Chinese patent medicine prescription containing Polygonatum with hypoglycemic effect [data from db.yaozh.com].

| Drug name      | Sources of prescription                                      | Prescription                                                                 |
|---------------|---------------------------------------------------------------|------------------------------------------------------------------------------|
| Jiangtang jia Tablet | Pharmacopoeia of the People's Republic of China 2020 edition | [Dioscoreaceae; Dioscorea rhizoma], S. ningpoensis Hemsl [Scrophulariaceae; Scrophulariae radix], Schisandra chinensis (Turcz.) Baill [Schisandraceae; Chinese magnolia fruit], O. japonicus (Thunb.) Ker Gawl [Asparagaceae; Ophiopogonis radix], L. aggregata (Sims) Kosterm [Laureaceae; Linderae radix], T. kirilowii Maxim [Cucurbitaceae; Trichosanthis radix], C.auranti. L. [Rutaceae; Auranti fructus], A. mongholicus Bunge [Fabaceae; Astragal mongholici radix], R. glutinosa (Gaertn.) DC [Orobanchaceae; Rehmanniae radix], P. sibiricum Redoute [Asparagaceae; Polygonati rhizoma], P. heterophylla (Mcq.) Pax [Caryophyllaceae; Pseudostellaria Radix], T. kirilowii Maxim [Cucurbitaceae; Trichosanthis radix] |

VEGF is a crucial angiogenic growth factor that facilitates the migration, proliferation, and angiogenesis of vascular endothelial cells (Hu et al., 2015). Moreover, some growth factors can promote retinal cell proliferation, such as transforming growth factor-β (TGF-β), which can contribute to cell proliferation and differentiation and suppress DNA synthesis of vascular endothelial cells (Sharma et al., 2015). Epidermal growth factor (EGF) works on the proliferation of retinal capillary endothelial (Sugimoto et al., 2013). However, the treatment of PSP notably reduced the expression of VEGF, TGF-β, and EGF in the DR retina (Wang et al., 2019c). In STZ-induced DR rats, the expression of apoptotic protein B-cell lymphoma-2 factor (Bcl-2) was enhanced, while the expression of Bcl2-associated X protein (Bax) and p38 was reduced in PSP-treated rats. p38 MAPK is pivotal in the regulation of apoptosis. In addition, PSP can also reduce the activity of the superoxide dismutase (SOD) enzyme and increase the content of malondialdehyde (MDA), thus reducing oxidative stress of DM rats (Wang et al., 2017).

Wnt/β-catenin pathway (Wnt) signaling is involved in pancreas development and islet function (Liu and Habener, 2008; Wang et al., 2015; Palsgaard et al., 2016) and plays a vital role in modulating GLP-1 through regulating the transcription of the proglucagon gene in T2DM (Welzel et al., 2009). Zou et al. proved that Shen’an granules could regulate urinary protein, renal function, and dyslipidemia in DN rats, and such effects are achieved by suppressing the activation of the Wnt/β-catenin signaling pathway (Zou et al., 2016). Furthermore, the hypoglycemic effect of PSS on T2DM was also related to the Wnt/β-catenin signaling pathway. There is evidence that the expression of Wnt4 and β-catenin in the DN model group has been notably enhanced compared with that of the control group. In contrast, the expression of Wnt4 and β-catenin in the high-dose and low-dose PSS groups notably decreased (Jing, 2019). Therefore, PSS can suppress the process of tubulointerstitial fibrosis by blocking the activation of the Wnt/β-catenin signaling pathway and finally plays a vital role in kidney protection.

In brief, the studies of molecular mechanisms suggest that Polygonatum influences the development of diabetic complications by regulating MAPK, adenosine monophosphate-activated protein kinase (AMPK), and Wnt/β-catenin signaling pathway (Figure 2).

EFFECTS OF DIFFERENT PROCESSED PRODUCTS OF POLYGONATUM ON DIABETES

TCMs need to be processed to have a better therapeutic effect, unlike Western medicine. Processed TCMs have an apparent therapeutic effect, low toxicity, and convenience for storability. Moreover, different processing methods of the same drug show different efficacy.

An effort was made to compare the effect of hypoglycemic and hypolipidemic among ninefold-processed P. kingianum and four products of P. kingianum processed with different auxiliary materials (wine, black beans, Rehmannia glutinosa (Gaertn.) DC [Orobanchaceae] and L. barbarum L. [Solanaceae]). All five processed P. kingianum products were administered in high-glucose rats and high-fat rats at doses of 1.95 and 1.35 mg/l, respectively. The results confirmed that the hypoglycemic effect of ninefold-processed P. kingianum and P. kingianum processed with R. glutinosa (Gaertn.) DC had markedly enhanced effects, while L. barbarum L. processed P. kingianum shows no significant effect. Additionally, ninefold-processed P. kingianum has the best hypolipidemic effect, and L. barbarum L. processed P. kingianum has the lowest effect through detecting the content of four factors related to lipid metabolism [total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDLC), and low-density lipoprotein cholesterol (LDLC)] (Zhang, 2019). Other studies revealed that water extracts from each processed product of P. sibiricum (10 g/kg) were given by intragastric administration for 6 weeks; fourfold processing of P. sibiricum can better improve Qi and Yin deficiency syndrome by increasing the body weight and tail diameter of rats and regulating the glucose and lipid metabolism, compared to ninefold-processed P. sibiricum (Ma et al., 2019). Li et al. found that fermented P. sibiricum (FPS) could lower insulin, FBG, and lipid metabolism than P. sibiricum. FPS showed greater efficacy than P. sibiricum in decreasing insulin resistance by increasing the p-AKT/AKT ratio, and FPS had a hypolipidemic effect on liver and fat in STZ-induced diabetic rats by improving lipolysis and inhibiting adipogenesis (Li et al., 2021).
FUTURE PROSPECTS

The beneficial effects of antidiabetes may be related to the metabolites of natural products in the human body. For instance, conjugated (glucuronidated and sulfated) metabolites of hydroxytyrosol and oleuropein are detected in plasma and urine following oleuropein consumption at a single dose of 76.6 mg per person. The concentration of oleuropein metabolites was significantly increased compared with oleuropein (149 vs. 3.55 ng/ml) in plasma (Bock et al., 2013). However, there are no studies on the beneficial effects of chemical components of Polygonatum against diabetes, and this may be related to metabolites in humans, and the specific mechanism needs to be further studied. Beyond that, it also is worth further exploring whether different active components of Polygonatum work alone or in a particular proportion with better curative effect against diabetes.

CONCLUSION

Diabetes mellitus, known as thirst dissipation in ancient China, was characterized by polydipsia, polyuria, polyphagia, emaciation, fatigue, and frequent urination. Now, it is common knowledge that DM is a group of metabolic diseases characterized by hyperglycemia, which is a chronic disease that cannot be cured by pharmaceutical means, but treatments can alleviate the development and symptoms of diabetes. With the increasing number of diabetic patients, natural products of Polygonatum (polysaccharides, saponins, flavonoids, and phenols) have attracted wide attention on account of their efficacy in lowering blood sugar and blood lipids. However, there are more studies on the hypoglycemic effect of polysaccharides and saponins than that of flavonoids and phenols. However, flavonoids and other phenolics are worthy of being studied. In addition, this review also summarizes the three insulin signaling pathways—p38MAPK, AMPK, and Wnt/β-catenin signaling pathways—that might be involved in the treatment of diabetes with Polygonatum, whereas these signaling pathways could result in a variety of biological activities to change, such as glucose uptake and glycogen synthesis, cell survival, oxidative stress, inflammation, and lipid metabolism. Consequently, the mechanism of action and targets of Polygonatum have been studied from the perspective of its unique chemical components, which is crucial to lay the foundation for clinical research.

Preclinical and clinical studies have shown that Polygonon has a positive therapeutic effect on diabetes. However, there is still a lack of research on Polygonon intake in humans. It is worth noting that the minimum effective dose of Polygonon must be determined in clinical studies due to individual differences.

Overall, the antidiabetic efficacy of Polygonon is well-known, and the antidiabetic benefits of bioactive components, especially polysaccharides and saponins, have widely been reported. Meanwhile, the combination use of Polygonon and other clinical hypoglycemic drugs could enhance the therapeutic effect of hypoglycemic drugs, giving Polygonon a broader
application prospect in the treatment of diabetes and its complications.

**AUTHOR CONTRIBUTIONS**

SL and Q-JJ: conceptualization, writing-original draft. Y-QP, TF, and SH: collected the literatures. JD and Z-SL: writing-review and editing.

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