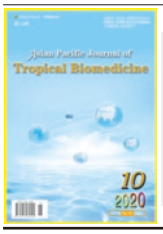

Review Article

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Anti-diabetic properties and bioactive compounds of *Teucrium polium* L.

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ABSTRACT

Diabetes mellitus is a common metabolic disease with considerable morbidity and mortality. Untreated or improperly-treated diabetes can be associated with several long-term complications that necessitate an effective way to manage diabetes. Due to the side effects of synthetic glucose-lowering agents, alternative therapeutic modalities such as medicinal plants have attracted notable attention. *Teucrium polium* L. is a medicinal herb with antioxidant, antinociceptive, anti-inflammatory, hypolipidemic, hepatoprotective, and hypoglycemic properties. *In vitro* and *in vivo* studies have been conducted to characterize the anti-diabetic properties of *Teucrium polium* L. and its bioactive compounds. We conducted a literature study using Scopus, PubMed, and Google Scholar including the keywords "diabetes" and "*Teucrium polium*". We also scanned all the references cited by the retrieved articles. According to this review, *Teucrium polium* administration displayed anti-diabetic effects by targeting different mechanisms and pathways, such as enhancement of insulin secretion and insulin level, improvement of oxidative damage, regeneration of pancreatic β-cells, and promotion of glucose uptake in muscle tissues by increasing GLUT-4 translocation as well as inhibiting α-amylase activity. Although *Teucrium polium* has been widely regarded as a traditional method, the pharmacological studies on anti-diabetic effects are not sufficient, most studies are either *in-vivo* or *in-vitro*. The preclinical and clinical studies are further required to confirm the efficacy of *Teucrium polium*.

KEYWORDS: *Teucrium polium* L.; Diabetes mellitus; Oxidative stress; Inflammation

1. Introduction

Diabetes mellitus (DM) is a typical metabolic disease with conspicuous human morbidity and mortality. Affecting 451 million people globally in 2017, DM is predicted to increase to 693 million by 2045[1]. Untreated or improperly-treated DM can be associated with several acute and chronic problems, including cardiovascular disease, kidney damage, eye problems, foot ulcer, impotence, and even death[2].

DM is characterized by a disturbance of glucose homeostasis and hyperglycemia. Tight control of blood glucose levels is achieved in a relatively small range (80–100 mg/dL) *via* coordinating various peripheral organs, such as the pancreas, adipose tissue, skeletal muscle, liver, and central nervous system in healthy animals and humans[3]. Normal fasting blood glucose levels should be maintained within 80-100 mg/dL. When one or several organs cannot help maintain glucose homeostasis, it will lead to prediabetes (glucose intolerance) and then DM. Common reasons for DM include the malfunctioned insulin secretion from pancreatic β-cells and the resistance to insulin-mediated glucose disposal in peripheral tissues (*e.g.* the muscle, adipose tissue, and liver). The improper treatment of diabetes can lead

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to long-term complications, such as cardiomyopathy, retinopathy, and nephropathy[4]. Thus, effective management of diabetes is important. Given the side effects of many synthetic glucose-lowering agents, natural resources such as medicinal herbs can be more helpful and cost-effective alternative treatments for DM.

Used for hundreds of years for human diseases, medicinal herbs are great sources of various pharmacologically-active compounds. Today, many drugs that are available on the market may originate directly or indirectly from natural products[5]. For instance, galegine is an alkaloid isolated from *Galega officinalis*, which is structurally related to metformin and used as an anti-diabetic before metformin synthesis[6,7].

Teucrium polium L. (*T. polium*) is a member of the Lamiaceae family and one of the most promising nutraceuticals that exerts a wide range of anti-inflammatory[8], antioxidant[9-11], vasorelaxant[12], memory enhancer[13], anti-diabetic[14,15], and hypolipidemic effects[16]. Also, *T. polium* has anti-carcinogenic[17], anti-hypertensive[18], anti-nociceptive[19], and cardioprotective properties[20]. Moreover, it has anti-diabetic effect *via* several distinct molecular mechanisms, such as enhancing insulin secretion and insulin level, reducing oxidative damage, stimulating regeneration of pancreatic β-cells, promoting glucose uptake in muscle tissues by increasing GLUT-4 translocation and inhibiting α-amylase activity[21]. *T. polium* can be found in Europe, North Africa, and Southwestern Asia. In Iran, it has been used to treat diabetes, heart failure, and gastrointestinal disorders[22]. Previous phytochemical studies of *T. polium* revealed the presence of various compounds in the plant, such as flavonoids, terpenoids, and iridoids[23]. In this study, we discussed the hypoglycemic and anti-diabetic effects of *T. polium* with a specific emphasis on the mechanisms of action.

2. Antihyperglycemic and hypolipidemic effects of *T. polium*

The antihyperglycemic and hypolipidemic properties of *T. polium* have been shown in several studies and the glucose-lowering properties of *T. polium* have been demonstrated by a variety of *in vitro* and *in vivo* studies[15,24,25]. In streptozotocin (STZ)-induced diabetic rats, an aqueous decoction prepared from the aerial parts of *T. polium* displayed a significant reduction in blood glucose level 4 h after intravenous administration and 24 h after intraperitoneal administration. This effect could be attributed to that of *T. polium* in peripheral metabolism of glucose rather than an increase in insulin release; however, no additional information was provided (*e.g.* insulin concentration level and/or histological findings) to support their assumption[25]. In another study, oral administration of *T. polium* aqueous extract in STZ-induced diabetic rats exerted a significant decrease in serum glucose level after 24 h, reaching the level of the normoglycemic animals in 8 days[26]. One study reported that the administration of *T. polium* (0.5 mg/kg) oral powder for 6 weeks significantly reduced the blood glucose levels in STZ-induced diabetic rats[15]. However, in the alloxan-induced diabetic rabbits, intranasal administration of 10% aqueous *T. polium* extract (0.1 mL/kg) did not affect the blood sugar concentration[27]. In another study, the treatment of diabetic rats with *T. polium* aqueous extract (50 mg/kg) for a month could decrease hyperglycemia. However, *T. polium* increased the levels of cholesterol, triglycerides, low-density lipoproteins, alanine transaminase, and aspartate transaminase. These inconsistent results may have been due to the difference in the method of *T. polium* administration[28]. Another study showed the consistently-reduced blood glucose, total cholesterol, very low-density lipoprotein, and triglycerides in diabetic rats treated by hydroalcoholic extract of *T. polium* (300 mg/kg) orally for 14 days[29].

Several studies indicated that the serum levels of cholesterol and triglycerides were typically high in diabetic patients[30]. The hyperlipidemia in DM mainly occurs as a consequence of a deficiency in insulin and dysregulation of metabolic processes such as lipolysis and lipogenesis[31]. The hypolipidemic and hepatoprotective action of *T. polium* has been proposed as one of the major possible mechanisms for the protective actions of the plant against DM. In an experimental study, diabetic animals displayed hypertriglyceridemia, and the treatment with *T. polium* significantly decreased the hyperlipidemia[32,33]. Another study showed that administration of *T. polium* hydroalcoholic extract at 170 mg/kg for 8 weeks effectively reduced the levels of inflammatory serum indices and lipid profile[34]. Therefore, *T. polium* can help prevent the dyslipidemia-related complications of diabetic patients by suppressing hyperlipidemia. However, an overall ranking of antihyperglycemic and hypolipidemic effects of *T. polium* cannot be determined due to the difference in the methods of *T. polium* administration and experimental procedures used in various studies. Further studies are needed to define possible mechanisms and assess the beneficial value of *T. polium* to manage hyperlipidemic conditions.

3. Anti-diabetic mechanisms of *T. polium*

3.1. Stimulation of pancreatic insulin secretion

Loss of β-cells in the pancreas is a pathologic feature observed in diabetic patients. Oxidative stress has been implicated in β-cell destruction[35]. Compounds with anti-oxidative effects may contribute to the regeneration of β-cells and the restoration of insulin levels. The published data suggest that *T. polium* may lower blood glucose by increasing insulin secretion and regenerating the β-cells[36,37]. The antihyperglycemic and anti-diabetic actions of *T. polium* extract have been shown in *in vitro* studies. In a rat insulinoma

cell line, freeze-dried extract of *T. polium* containing flavonoids showed insulinotropic effects at a dose of 500 μg/mL. However, no difference has been found in the cholesterol and triglyceride levels following the administration of *T. polium* extract in diabetic animals[38]. Monfared and Pournourmohammadi reported that *T. polium* (0.01 mg/mL), sodium molybdate and sodium orthovanadate, alone or in combination with each other, improved insulin-secretory function of the cultured islet cells, which compared to the matched control, increased the insulin secretion significantly at high glucose concentration (16.7 mM)[39]. Furthermore, the results from other studies showed that in STZ-induced diabetic rats, the administration of ethanol extract of aerial parts of *T. polium* at a dose of 0.5 g/kg body weight for 6 weeks decreased the blood glucose levels significantly. Also, the treatment at a concentration of 0.1 mg/mL increased the rate of insulin release[15]. The stimulation of insulin secretion by rutin and apigenin (major flavonoids from *T. polium*) has been reported[14], in which the administration of rutin and apigenin increased insulin release due to their antioxidant activity. Furthermore, these flavonoids had free radical scavenging and antiglycation activity, as well as inhibitory effects on the advanced glycation end product production[14]. In another study, rutin and apigenin (0.5 mM to 8 mM) had no effects on insulin secretion in rat-isolated pancreatic islets in the presence of either 5 or 11.1 mM of the glucose. However, in pancreatic islets treated with STZ, insulin secretion was increased in the presence of the same amounts of glucose[40].

Pancreas regeneration is facilitated by *T. polium*[37]. Given the effects of *T. polium* on pancreatic regeneration, the administration of *T. polium* aerial parts extract twice a day during 14 days could enhance the regeneration of the STZ-destructed islets. To evaluate this capacity and histopathologic examination, the pancreatic tissue was stained with hematoxylin and eosin. This effect is probably due to the fact that the pancreas contains stable cells, which are capable of regeneration[37]. Yazdanparast *et al.*[41] conducted a series of studies on the hypoglycemic effects of *T. polium* on isolated rat islets. Accordingly, the regeneration of the β-cells and insulin release is increased by *T. polium* extract (0.1 mg/mL). This study could provide evidence for the effectiveness of *T. polium* on the pancreatic islets regeneration in diabetic rats[41]. Also, oral administration of aqueous extract of *T. polium* to healthy and STZ-induced diabetic rats for several days showed that the aqueous extract reduced the level of serum glucose during oral glucose tolerance tests in diabetic animals. As a result, the number of pancreatic islets per unit area was increased, while the glucokinase activity was elevated in diabetic animals treated with the *T. polium* extract[42]. A former study by Tabatabaie *et al.* showed that the treatment of the STZ-induced DM rats with *T. polium* extract (0.5 g/kg) for six consecutive weeks relieved dyslipidemia and oxidative stress-associated diabetes. Here, glucose tolerance showed a remarkable improvement among the treatment groups, suggesting the presence of elevated insulin levels in blood[33].

Glucokinase, an insulin sensor in the pancreatic beta cells, is a novel target for anti-diabetic therapy[43]. In this regard, the beneficial effect of *T. polium* on the regeneration of pancreatic islets and glucokinase activity was previously reported[42]. Taken together, these results suggest that *T. polium* can potentiate the rate of insulin secretion from islets and regeneration of the pancreas, implying that *T. polium* may be useful for the development of novel insulin secretagogues (insulin secretion) agent for DM treatment. Although the results of these studies have shown that *T. polium* extracts have protective effects in all doses, more significant protection was observed in special doses. These findings needed to be confirmed by additional studies.

3.2. Enhancement of glucose uptake in the skeletal muscle

As a prominent feature of DM, any defect in GLUT4 transport or trafficking pathway may lead to insulin resistance. Thus, special attention is being paid to compounds that can enhance this translocation process in the absence of insulin. Insulin stimulates the transport of glucose in target tissues by recruiting intracellular membrane vesicles and containing the glucose transporter GLUT4 to the plasma membrane, which results in increased glucose uptake[44].

The study performed by Kadan *et al.* indicated that both hexane and methanol extract of *T. polium* showed *in vitro* insulin-independent, as well as the insulin-dependent translocation of GLUT4 to the plasma membrane of skeletal muscle, leading to *in vivo* improvement of glycemia. These results indicate the synergistic effects between insulin and extract on the active GLUT4 translocation through insulin-independent signaling cascades[45]. Furthermore, gas-chromatography mass spectrometry was used for phytochemical screening of the active ingredients of *T. polium*. A mixture of a wide range of phytochemicals was extracted. Methanolic extracts contained (5E,8E,11E)-methyl heptadeca-5,8,11-trienoate (5.6%); (9Z,12Z)-octadeca-9,12-dienoic acid (4.5%); 3,7,11-trimethyldodeca-1,6,10-trien-3-ol (4.4%), and palmitic acid (4.2%) as the major compound. Cisvaccenic acid (20%), butyl (2-ethylhexyl) phthalate (12.2%), and palmitic acid (7.2%) are the main components in the hexane extract. Alternately, the active components of *T. polium* facilitated GLUT4 translocation in insulin-independent mechanisms. It is possible that active components of *T. polium* possess insulin-sensitizing activity. It is needful to separate these compounds to show its cellular molecular pathways and to identify its specific anti-diabetic mechanisms.

3.3. Inhibition of glucose absorption

The inhibition of the digestion and absorption of dietary

carbohydrates represents an important target in the management of diabetes[46]. Thus, finding α-glucosidase and α-amylase inhibitors from natural resources can be a milestone in drug discovery research associated with DM.

One of the possible mechanisms in the anti-diabetic effect of *T. polium* is the inhibition of carbohydrate-hydrolyzing enzymes, pancreatic α-amylase, and intestinal α-glucosidase. According to Salehi *et al*., *T. polium* methanolic extract [(10.2 ± 0.4) μg/mL] exhibited α-glucosidase inhibitory properties that can be considered as the first-line treatment for type 2 diabetes[47]. In starch-fed animals, oral administration of aqueous liquid extract in the aerial parts of *T. polium* at a dose of 125 mg/kg diminished peak hyperglycemia at 45 minutes from about 6.5 to 5 mM. In an oral glucose tolerance test, the extract at a dosage of 500 mg/kg effectively reduced glycemia[47].

Furthermore, the extract at 125 mg/kg had no effects on improving glucose tolerance in an oral glucose tolerance test. However, at 500 mg/kg, it decreased glycemia from about 6.5 to 5.5 mM. The extract at 10 g/100 mL demonstrated no appreciable anti-α-amylase or anti-glucosidase efficacy *in vitro*[48]. In another study, weak α-amylase inhibitory activity (5%) was observed with the 50% methanolic extract of *T. polium*[49]. Despite several studies have shown *T. polium* extracts possess anti-α-glucosidase and anti-α-amylase effectiveness, some indicated weak inhibition effect on α-glucosidase and α-amylase. This fact may arise from the difference in administration methods and polarities of the solvents.

3.4. Inhibition of oxidative damage

Oxidative stress occurs as a result of an imbalance between the production and scavenging of free radical species[20,50,51]. The increased oxidative stress plays an important role in the initiation and progression of numerous chronic disorders[52,53]. Several studies have shown that the development of DM complications is attributed to the uncontrolled production of reactive oxygen species[54,55]. Thus, effective antioxidant therapy is required to prevent or ameliorate the complications of diabetes caused by oxidative damage. Medicinal plants contain bioactive antioxidant compounds.

A number of *in vitro* and *in vivo* studies have shown that the extract of the *T. polium* has potent antioxidant properties[56-60]. Antioxidant activity of *T. polium* can be attributed to its constituents, especially phenolic compounds. Phenolic compounds include such compounds as flavonoids, tannins, and phenolic acids[61-63]. In an *in vitro* study, Kadifkova *et al*. investigated the effect of the chemical composition and antioxidant activity of various extracts obtained from *Teucrium* species. The obtained results showed that *Teucrium* species possess free radical and hydroxyl radical scavenging as well as antioxidant activity[64]. In the same study, the results indicated that ethyl acetate fraction of *T. polium* possessed the highest antioxidant capacity, which was similar to Trolox (water-soluble vitamin E analogue)[65]. In another study, it was reported that *T. polium* extracts could attenuate oxidative damage leading to β-cell dysfunction, significantly enhance insulin release and peripheral metabolism of glucose, and ameliorate glycemic control[33,36,66]. In STZ-induced diabetic rats, oral administration of hydroethanolic extract of aerial parts of *T. polium* at a dose equivalent to 0.5 g plant powder/kg/day for 30 days decreased blood glucose level from 294 to 98 mg/dL. Also, this regimen lowered the lipid peroxidation of the pancreas by 64%, elevated activities of superoxide dismutase, catalase, and increased contents of glutathione by 45%, 52%, and 105%, respectively. In addition, nitric oxide levels were also restored to the level of the nondiabetic group by treatment with the extract[24].

T. polium is known to contain the flavones eupatorin, cirsimaritin, apigenin-4',7-dimethylether, cirsiliol[67] as well as rutin, apigenin, and 3,6-dimethoxy-apigenin, 4,7-dimethoxy apigenin, which are antioxidant *in vitro*[68]. Rutin (quercetin-3-*O*-rutinoside) along with flavone apigenin was isolated from *T. polium* and identified as *in vitro* free radical scavenging and antiglycation agents. Moreover, these two flavonoids showed inhibitory effects on the formation of advanced glycation end products from bovine serum albumin in the presence of glucose. These two flavonoids also prevented oxidative stress conditions produced by STZ, which could increase insulin secretion[66]. These findings suggest the existence of sterols and flavonoids in *T. polium* extract and its antioxidant effect is a possible mechanism of action underlying the anti-diabetic effects of *T. polium*.

3.5. Increased activation of adenosine monophosphate-activated protein kinase (AMPK)

AMPK has been considered to be a potential therapeutic target to treat numerous diseases such as DM[69,70]. It is a central metabolic sensor and senses the ratio of ATP to AMP, which helps maintain cellular energy homeostasis. AMPK becomes activated when the ATP/AMP ratio is decreased[71]. Moreover, AMPK activity is reduced in response to chronic low-grade inflammation associated with diabetes and insulin resistance[72]. *T. polium* activates the energy metabolism and insulin secretion by stimulating AMPK. Qujeq *et al*. demonstrated that the *T. polium* leaf extract enhanced the insulin content and AMPK level compared to the untreated group in isolated pancreases[73]. These results suggest that *T. polium* leaf extract stimulates AMPK level that could play an important role in insulin release, but the biochemical relevance of these findings is unclear. Therefore, further studies are necessary to confirm this potential.

Table 1. Summary of experimental studies on antidiabetic activities of *Teucrium polium* (*T. polium*).

Study type	Dosage, route, and duration of exposure	Parameters/results	References
STZ-induced DM; rat	5 mL 20% w/v, *i.p.* 5 mL 20% w/v, *i.v.*	↓BG	[11]
STZ-induced DM; rat	Aqueous-extract for 12 days	↓BG	[27]
STZ-induced DM; rat	Aqueous extract 4.5 g/mL for 12 days	↓BG ↑Number of pancreatic islets per unit area; ↑Glucokinase activity	[43]
STZ-induced DM; rat *In vitro*: isolated pancreatic rat islets	Powder 0.5 g/kg oral for 6 weeks	↓BG; ↑Serum insulin ↑Insulin release	[20]
In vitro	Methanol extract 50%	↓α-amylase activity	[50]
STZ-induced DM; rat	Oral extract dose of 1 mL/rat (equivalent to 0.5 g plant powder/kg body weight) for 6 weeks	↓BG;↑Insulin level; Regeneration of β-cell	[42]
STZ-induced DM; rat	Extract 100 and 200 mg/kg/day for 2 weeks	↑BW; ↓BG; ↓Hyperalgesia	[24]
Alloxan-induced hyperglycemic rabbit	Extract 10%, intranasal	No significant difference observed between the extract-treated and non-treated control animals	[28]
STZ-induced DM; rat	Aqueous extract 50 mg/kg for 4 weeks	↓BG; ↑Cho, TG, LDL, AST, ALT	[29]
In vitro	Extract-ethyl acetate fraction	Suppression of the formation of AGEs and protein oxidation	[66]
STZ-induced DM; rat	Powder 0.5 g/kg for 30 days; gavage	↓BG; ↓MDA; ↑GSH, CAT, SOD; ↓NO	[26]
In vitro	Apigenin and rutin isolated from *T. polium*	Inhibitory effects on the production of AGEs from bovine serum albumin in the presence of glucose; ↓Oxidative stress condition; ↑Insulin release in rat islets	[20]
In vitro/isolated rat pancreas	Aqueous extract and methanolic extract	↑Insulin release	[37]
In vitro/rat pancreatic islets	0.01 mg/mL Extract	↑Insulin release	[40]
STZ-induced DM; rat	Oral aqueous and ethanol extract 1 g/L for 8 weeks	↓BG; ↓VLDL, TG	[21]
STZ-induced DM; rat	Oral hydroalcoholic extract 300 mg/kg for 14 days	↓BG; ↓Total cholesterol, HDL, VLDL, and triglycerides; ↑Serum insulin levels	[30]
In vitro/rat pancreatic islets	500 μg/L of the *T. polium* leaf extract	↑Insulin release; ↑AMPK level	[74]
Starch induced hyperglycemia, rat	Aqueous extracts 125, 250 and 500 mg/kg, intragastric	↓BG 45 min post starch intragastric administration	[49]
In vitro	Aqueous extracts 1, 5, 10, 12.5, 25, 50 and 100 mg/mL	No change in α-amylase and α-amyloglucosidase	
STZ-induced DM; rat INS-1E cells *in vitro*	Aqueous extracts 125 mg/kg for 10 days	↓BG (*i.g.* better than *i.p.*); ↑Insulin release; No change in lipid profile	[39]
STZ-induced DM; rat	Oral, 200 mg/kg hydro-alcoholic extracts for 6 weeks	↓BG, triglyceride, cholesterol	[33]
STZ-induced DM; rat	Oral, 0.5 g/kg hydroalcoholic extract for 6 weeks	↓BG, ↓TC, TG, LDL-C, VLDL-C, ↑HDL-C; ↓MDA, ↑SOD, CAT, GSH; ↑Expression of Pdx1, ↓p-JNK	[34]
STZ-induced DM; rat	Oral, aerial parts extract twice a day for 14 days	↑Pancreatic regeneration	[38]

STZ, streptozotocin; DM, diabetes mellitus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; AGEs, advanced glycation end products; AMPK, AMP-activated protein kinase; BG, blood glucose; BW, body weight; CAT, catalase; Cho, cholesterol; GSH, glutathione; HDL, high-density lipoprotein; *i.p.*, intraperitoneal injection; *i.v.*, intravenous injection; *i.g.*, intragastric administration; LDL, low-density lipoprotein; MDA, malondialdehyde; NO, nitric oxide; PDX1, pancreatic and duodenal homeobox 1; p-JNK, phosphorylated c-Jun NH_2-terminal kinase; SOD, superoxide dismutase; TG, triglycerides; VLDL, very low-density lipoproteins.

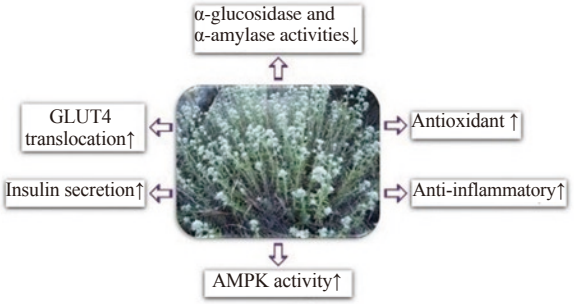

Figure 1. Antidiabetic properties of *Teucrium polium* extract which seems to mediate, at least partially, through improving insulin secretion, promoting AMPK activity, increasing antioxidant parameters, decreasing α-amylase and α-glucosidase activity, and stimulating GLUT4 translocation.

The anti-diabetic activities of *T. polium* in both *in vivo* and *in vitro* reports are summarized in Table 1. Our review of literature data indicated that *T. polium* treatment affects DM *via* several mechanisms, including antioxidant activity, increasing insulin secretion and insulin level, regeneration of pancreatic β-cells, promotion of glucose uptake through stimulation of GLUT-4 translocation, and inhibiting α-amylase activity (Figure 1).

4. Toxicity and adverse effects

Despite anti-diabetic properties of *T. polium* extract (*e.g.* stimulation of pancreatic insulin secretion, enhanced glucose uptake in the skeletal muscle, and B cells) in diabetic rats, there are a few reports about toxic effects. For instance, intra-esophageal administration of 1 g/mL *T. polium* extract in diabetic rats twice daily or 10 days resulted in hepatic necrosis that was widespread in periventricular and midzonal areas of the liver lobules[26]. A similar study showed an increase in enzyme activities of alanine aminotransferase and aspartate aminotransferase in female rats receiving 300 mg/kg *T. polium*. On the other hand, a significant increase was observed in the liver weight of diabetic male rats receiving 600 mg/kg[74]. A recent report also indicated at 200 mg/kg, *T. polium* extract provoked liver and kidney tissue damages with a significant rise in biochemical markers of tissue injury[75]. Moreover, *T. polium* has shown toxic effects on embryogenesis at the early stage[76] in a dose-dependent manner, in which the liver could be as a target organ. This may be due to the presence of several neoclerodane diterpenoids in *T. polium* extract. So, despite the great effects of *T. polium* extracts in ameliorating diabetes, high dose usage should be limited due to hepatic effects in subchronic cases.

5. Conclusion

T. polium treatment displayed anti-diabetic effects by targeting different mechanisms and pathways, such as enhancing insulin secretion and insulin level, improving oxidative damage, regenerating the pancreatic β-cells, and promoting the glucose uptake in muscle tissues by increasing of GLUT-4 translocation, as well as inhibiting α-amylase activity. *T. polium* extracts suppress pathophysiologic pathways associated with insulin resistance and improve glycemic control. It is to a great safe in low doses and might serve as an effective adjunct with other anti-diabetic medications to lower the side effects and increase the efficacy. Moreover, it could be used to palliate insulin resistance as a nutritional supplement in prediabetes. Therefore, *T. polium* and its bioactive compounds have great potential for managing diabetes. There have been no studies regarding the effects of *T. polium* on long-term microvascular implications of diabetes, such as retinopathy, cardiomyopathy, nephropathy, and endothelial dysfunction. Thus, to evaluate the effects of *T. polium* on these complications, the following assessments are recommended: evaluating the biomarkers and mediators of diabetic retinopathy such as those related to inflammation and angiogenesis *(e.g.* vascular endothelial growth factor), cardiac enzymes, pathways involved in apoptosis and fibrosis of the heart and kidney, cardiac and kidney function, factors involved in vascular dysfunction, such as endothelial adhesion molecules and nitric oxide level.

Despite all the endeavors, some studies in the future should focus on the fine molecular targets and its bioactive compounds. Also, extended clinical studies with *T. polium* should also be designed, conducted, and evaluated critically to explore the detailed health benefits of this medicinal herb. All the above-collected data show that *T. polium* extracts have a broad range of pharmacological attributes, such as antioxidant, antinociceptive, anti-inflammatory, hypolipidemic, hepatoprotective, and hypoglycemic effects. Results of studies on the chemical, toxicity, and pharmacological properties of *T. polium* support the opinion that this plant possesses useful therapeutic characteristics. On the other hand, further studies should be conducted to categorize the active constituents and confirm their related pharmacological components.

Conflict of interest statement

We declare that there is no conflict of interest.

Authors' contributions

AAA and MM conceived and organized the review; AMZ, SN and KME contributed to the writing and editing of the manuscript.

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