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Pharmacological evaluation of medicinal plants with antidiabetic activities in Ethiopia: A review

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ABSTRACT

Diabetes mellitus is a serious, chronic disease that occurs either when the pancreas does not produce enough insulin, or when the body can't effectively use insulin. Herbal medicines have been commonly used by diabetic patients for the treatment of diabetes mellitus. To include findings from different studies, publications related to *in vivo* and invitro antidiabetic activities of medicinal plants in Ethiopia were searched from different databases, such as Web of Science, Google Scholar, Medline, Scopus, and PubMed, using English key terms. Different medicinal plant parts were used experimentally for antidiabetic effects in Ethiopia. Among these, leaves (69%) were the most commonly investigated medicinal plant parts followed by roots (14%) and seeds (7%). Most of the investigations were completed with hydro-methanolic extracts to obtain a higher percentage of yield. Medicinal plants such as *Thymus schemperi* R, *Thymus vulgaris* L, *Hagenia abyssinica, Aloe megalacantha baker, Aloe moticola* Reyonolds, *Aloe pulecherrima* Gilbert & sebseb, *Bersama abyssinica* fresen, *and Rubus Erlangeri* Engl have shown *in vitro* α-amylase inhibitory activity. However, only *Hagenia abyssinica, Thymus schemperi* R, and *Thymus vulgaris* L have exhibited α-glucosidase inhibitory activity. Likewise, only the extract of *Aloe pulecherrima* Gilbert & sebseb posses' maltase and sucrose inhibitory activity. *In vivo* antidiabetic activity were conducted for the extract of medicinal plants such as *A. remota, S. rebaudiani, T. schemperi, T. vulgaris, H. abyssinica, C. aurea, D. stramonium, A. megalacantha, A. moticola, A.integrifolia, A. pulecherrima, B. grandiflorum, B. abyssinica, P. schimperiana, M. stenopetala, C. aure, J. schimperiana, T. brownie, C. macrostachys, I. spicata, O. integrifolia, C. abyssinica, R. Erlangeri, L. culinaris, A. camperi, A. polystachyus, A. ilicifalius, C. tomentosa,* and *C. Edulis.* This review gives collective evidence on the potential antidiabetic activities of medicinal plants in Ethiopia. Moreover, further studies are recommended to substantiate the use of these medicinal plants as an antidiabetic agent.

1. Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin action, insulin secretion, or both. Diabetic complications could be linked to alteration in the body's antioxidant defense system, increased oxidative stress, and dyslipidemia [1].

According to the International Diabetes Federation (IDF) report, there are 451 million (age 18–99 years) people with diabetes worldwide. These figures were expected to increase to 693 million) by 2045. It was estimated that almost half of all people (49.7%) living with diabetes are undiagnosed. Moreover, there were an estimated 374 million people with impaired glucose tolerance (IGT) and it was projected that almost 21.3 million live births to women were affected by some form of hyperglycemia in pregnancy. In 2017, approximately 5 million deaths worldwide were attributable to diabetes in the 20–99 years age range [2]. Several studies reported the prevalence of diabetes mellitus complications varying from 20 to 90.5% [3–7]. Previous studies in Ethiopia revealed that hypertension, visual disturbance, nephropathy, and neuropathy were the highest four chronic complications diagnosed in diabetic patients [8–11].

Generally, there are four classifications of diabetes mellitus such as Type I DM, Type II DM, gestational GDM, and specific types of DM (drug-induced diabetes, latent autoimmune diabetes in adults, cystic fibrosis diabetes, monogenic diabetes [12]. Oxidative stress is believed to be the basic cause of tissue damage, organ dysfunctions, and cellular injury

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usually linked to diabetic complications. Oxidative stress refers to elevated intracellular levels of reactive oxygen species that cause impairment to biological molecules like DNA, lipids, and proteins [13]. Oxidative stress could be decreased to a significant level by the action of numerous antioxidant enzymes including glutathione peroxidase, catalase, glutathione reductase, and superoxide dismutase [14].

Diabetes mellitus may cause acute complications like hyperosmolarity and ketoacidosis [15]. Its cause is obscure but appears to be precipitated by the same factors as ketoacidosis, especially those resulting in dehydration [16]. Diabetes mellitus also causes chronic complications like renal impairment, retinopathy, cardiovascular disorder, and foot ulcer. Patients with diabetes have an increased occurrence of arterial, cerebrovascular, peripheral, and atherosclerotic cardiovascular diseases [17].

No successful cure for diabetes mellitus has yet been found but can be managed using oral anti-diabetic agents, insulin, and diet modification. Medicinal plants may provide alternative management [18]. Affordability, accessibility, cost, tolerability, and Compromised effectiveness are some of the limitations of current conventional anti-diabetic drugs. African medicinal plants are frequently used in the treatment of diabetes mellitus and deliver an alternative therapy [19].

In Ethiopia, there are several medicinal plants used for the treatment of diabetes mellitus and a number of these were examined for their antihyperglycemic effect. About 80–90% of Ethiopians use medicinal plants as a primary form of health care [20,21]. The uses of plant-based medicine have continued to be a good foundation of natural products for the management of different illnesses. Several plant species were investigated and the majority of them have important phytoconstituents and the use of novel compounds from plants for pharmaceutical purposes has been steadily increasing [22]. There are preliminary studies on the scientific evidence of commonly used medicinal plants in Ethiopia though the evidence was not synthesized and research is required on different herbal formulations and indigenous plants. Thus, this study aimed to review the *in vivo* and *in vitro* antidiabetic activity of medicinal plants used for diabetic management in Ethiopia.

2. Pharmacological management of diabetes mellitus

Insulin replacement therapy is the mainstay for patients with type I DM, Insulin is also important in type II DM when blood glucose levels cannot be controlled by exercise, weight loss, diet, and oral medications [23].

The most common treatment strategy has been the combination of once or twice-daily injections of long-acting insulin-like glargine or insulin detemir and short-acting insulin-like lispro, aspart, glulisine, and neutral insulin. Detemir and glargine insulin are usually favored over neutral protamine hagedorn insulin since their use is linked to lower rates of nocturnal and severe hypoglycemia [24]. Novel ultra-long-acting insulin analogs are being developed. Insulin degludec delivers basal insulin coverage for more than 40 h and attains comparable glycemic control with less overnight hypoglycemia than glargine [25].

Oral hypoglycemic agents include drugs that decrease hepatic glucose production like biguanides, drugs that stimulate insulin secretion from the β-cells like sulphonylureas, drugs targeting the Glucagon-Like Peptide-1 axis like GLP-1 receptor agonists, drugs that delay carbohydrate uptake in the gut like a-glucosidase inhibitors, drugs that improve insulin action like thiazolidinediones, sodium-glucose cotransporter 2 inhibitors, bile acid sequestrants, and dopamine agonists [26,27]. Clinically, there are also untoward side effects, enormous cost, and noticeable treatment failures associated with conventional antidiabetic drugs. Thus, generating an urgent need and desire for alternative treatments is required [28].

3. Medicinal plants in diabetes mellitus management

Herbal medicines have been used by a large number of diabetic patients (80–85%) for the treatment of diabetes mellitus [29,30]. Ethnobotanical studies revealed that more than 1200 medicinal plants have been used for the management of diabetes mellitus [31]. The plant-derived medicines may correct metabolic abnormalities and delay the development of diabetic complications [32]. In the previous studies, the new bioactive drugs isolated from plants with hypoglycemic effects revealed antidiabetic effects with more efficacy than conventional medication used for the management of diabetes mellitus [33,34].

The world health organization suggested that plant-based medicines be further studied as they are frequently considered to be less toxic and side effects [35]. Globally, several extracts of medicinal plants have been used for the management of diabetes mellitus, and these are considered relatively less toxic, side effects, and are inexpensive [36]. Numerous bioactive compounds were isolated from plant extracts for direct use, or as a lead compound [37]. For instance, Metformin is an oral hypoglycemic agent synthesized from *Galega officinalis* that was used traditionally for the management of diabetes mellitus [37].

Different medicinal plant parts were used experimentally for antidiabetic effects in Ethiopia. Among these, leaves were the most commonly investigated medicinal plant part. Plant-based products which are rich in phytoconstituents like flavonoids, coumarins, terpenoids, phenolic compounds, and other bioactive compounds have revealed the blood-glucose-lowering effect [38].

Some traditional medicines used for the treatment of diabetes mellitus include Vernonia amygdalina (Asteraceae) [39,40], Justicia schimperiana (Acanthaceae) [39], Croton macrostachys (Euphorbiaceae) [39–41], Aloe vera (Aloceae) [40,41], Momordica Charantia Linn (Cucurbitaceae) [42,43], Moringa Oleifera (Moringacea) [44], Trigonellafoenum-GraecumL (Fabaceae) [40,41,45], Euphorbia sp. Gmel, (Euphorbiace) [40,46], and AlliumSativum (Amaryllidaceae) [45].

4. Methods

Previously published articles were searched using Medline, Google Scholar, SCOPUS, Web of Science, and PubMed databases to extract the antidiabetic activities of medicinal plants done in Ethiopia. The search terms used were “medicinal plants,” “hypoglycemic activity,” “antihyperglycemic activity,” “antidiabetic effect,” “antidiabetic potential,” “hypoglycemic effect,” “diabetes in Ethiopia” “antihyperglycemic effect,” “blood glucose-lowering effect,” and “antidiabetic activity”. Only experimental investigations done in Ethiopia were contained within using English keywords. Published articles available online before May 30, 2020, were included in the current study. A total of 38, 347 published articles were collected through database searching. All published papers not conducted in Ethiopia were removed, and we obtained 711 articles. Forty-two research articles were identified after removing the 669 duplicate articles. Finally, these full-text published articles were evaluated for eligibility, and data were extracted from the remaining 28 experimentally investigated medicinal plants.

5. Extraction of medicinal plants

The antidiabetic activities of the crude extracts and solvent fractions of different medicinal plant parts using different chemicals were investigated as displayed in Fig. 1. Most of the investigations were completed with hydro-methanolic extracts to obtain a higher percentage of yield. Prominently, 80% methanol is more efficient in the cell wall and seed degradation as well as having low or no enzyme activity when compared with water. Furthermore, the methanolic extract of the medicinal plant

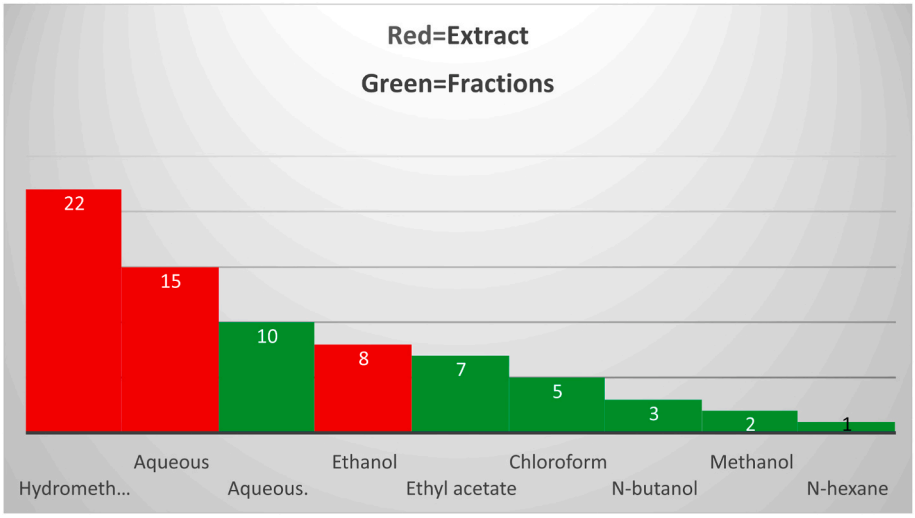

Fig. 1. Extracted and fractionated antidiabetic plants in Ethiopia.

comprises a wide variety of polar (and moderately nonpolar) constituents [47–49]. Among solvents, hydro-methanol was the most commonly used solvent for the extraction of medicinal plants, followed by aqueous and ethanol solvents. Regarding the solvent fractionation, chloroform was the most commonly used solvent for fractionation. Different medicinal plant parts were used experimentally for antidiabetic effects in Ethiopia. Among these, leaves (69%) were the most commonly investigated medicinal plant parts followed by roots (14%) and seeds (7%) as shown in Fig. 2.

6. *In vitro* studies

Medicinal plants such as *Hagenia abyssinica* [50], *Aloe megalacantha* and *Aloe moticola* Reyonolds [51,52], *Aloe pulecherrima* Gilbert & sebseb [53], *Thymus schemperi* and *Thymus vulgaris* [54,55], *Bersama abyssinica* fresen [56], and *Rubus Erlangeri* Engl 22], have shown *in vitro* α-amylase inhibitory activity. However, only *Hagenia abyssinica* [50], *Thymus schemperi* R, and *Thymus vulgaris* L [54,55], have exhibited α-glucosidase inhibitory activity. Likewise, only the extract of *Aloe pulecherrima* Gilbert & sebseb posses' maltase and sucrose inhibitory activity [53]. All the crude extract and solvent fractions exhibited less activity when compared with the reference drug (acarbose). The *in vitro* antidiabetic activities of medicinal plants, which have been investigated in Ethiopia, are summarized in Table 1.

7. *IN VIVO* studies

There was significant variance in the duration of treatment among *in vivo* studies, ranging from 4 h to 30 days. Most of the *in vivo* studies used mice, and a few studies used rats as experimental animals. Noteworthy glycemic control was observed with Terminalia brownie Fresen for 14 days, better blood glucose level control when compared with diabetic control. Three similar studies [57–59], also revealed significant blood glucose level reduction when compared with diabetic control. These studies were done respectively for 14, 15, and 30 days in Calpurnia aurea, Thymus schimperi, and Persea Americana. Comparable antidiabetic activities to the reference drug (Glibenclimide) were reported in Moringa stenopetala and Persea Americana [58,60–62]. Significant acute blood glucose level control was reported in Urtica simensis Hochst.ex. A. Rich, Thymus schimperi, and Indigofera spicata Forssk [63–65]. The *in vivo* antidiabetic activities of medicinal plants, which have been investigated in Ethiopia, are summarized in Table 1.

8. Possible mechanism of actions of medicinal plants for DM management

Phytoconstituents that are obtained from various medicinal plants have shown significant blood glucose-lowering activities [66–70]. The mechanism of reducing the blood glucose level could be due to

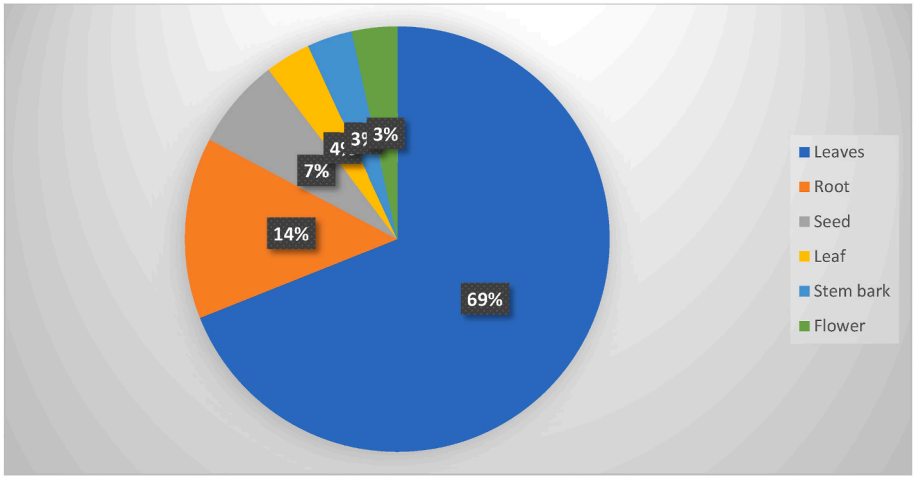

Fig. 2. Medicinal plants parts used for antidiabetic activities in Ethiopia.

Table 1
Summary of medicinal plants with confirmed antidiabetic activity.

Scientific name	Family	Local name	*In vivo* Test	*In vitro* Test	Plant part	Effect	References
Ajuga remota	Lamiaceae	Akoraracha	Normoglycemic, OGTT and STZ induced DM	–	Leaf	↓BGL ($P < 0.0001$) at aqueous extracts 300 and 500 mg/kg by 27.83 ± 2.96% and 38.98 ± 0.67%, respectively. ↓BGL ($P < 0.05$) at 70% ethanol extracts 300 and 500 mg/kg by 27.94 ± 1.92% and 28.26 ± 1.82%, respectively.	[107]
Satvia rebaudiani	Asteraceae	Sugar leaf	OGTT and Alloxan induced DM	–	Leaf	↓BGL ($P < 0.05$) at the extract (100, 200, and 400 mg/kg) 14 days.	[85]
Thymus schemperi and Thymus vulgaris	Lamiaceae	Tosign	Alloxan induced DM	α-amylase α-glucosidase	Leaf	↓BGL at all doses of the extract ($P < 0.05$) at days 7, 14, and 21. Antidiabetic activity ($P < 0.05$) exhibited by 400 mg/kg compared to 100 mg/kg. It also showed significant α-amylase α-glucosidase inhibitory activities.	[54,55]
Hagenia abyssinica	Rosaceae	Kosso	Normoglycemic, OGTT and STZ induced DM	α-amylase	Flower	Inhibited α-amylase activity by 54.23% with IC50 20.78 μg/mL at 800 μg/mL ethyl acetate fraction. Inhibited α–amylase activity with IC50 52.11 ± 0.63, 49.08 ± 0.97 μg/mL, and 28.09 ± 0.75 μg/mL of water and chloroform fraction, and crude extract, respectively.	[108]
Hagenia abyssinica	Rosaceae	Kosso	STZ induced DM	–	Leaf	↓BGL ($P < 0.05$) at the extract (100, 200, and 400 mg/kg) 14 days.	[50]
Calpurnia aurea	Fabaceae	Digta	Normoglycemic, OGTT and STZ induced DM	–	Leaf	↓Hyperglycemia ($P < 0.05$) with 5.5 and 11 mg/kg at 2 h in OGTT mice. ↓BGL with 2.75 ($P < 0.05$), 5.5 ($P < 0.01$) and 11 mg/kg ($P < 0.001$) extract on the 7th and 14th day of repeated doses in diabetic mice. ≥175 [52] (14) Calpurnia aurea (Ait.) Benth. Hydromethanolic leaf extract STZ-induced diabetic mice 100, 200, and 400 GL Phenols, alkaloids, terpenoids, and flavonoids ↓Hyperglycemia ($P < 0.05$) at al	[109]
Datura stramonium	Solanaceae	Astenagir	Normoglycemic, OGTT and STZ induced DM	–	Seed	BGL ($P < 0.05$) at 100 mg/kg ($P < 0.01$) and 200 and 400 mg/kg. ↓BGL ($P < 0.0l$) at all doses of extract on day 7 and 14. ↓BGL ($P < 0.05$) at doses of 200 and 400 mg/kg extract. Improved BW of diabetic mice on day 7 and 14.	[110]
Aloe megalacantha and Aloe moticola	Aloeceae and Asparagaceae, respectivily	Eret	Normoglycemic, OGTT and STZ induced DM	α-amylase inhibitory	Leaf latex	↓BGL ($P < 0.05$ and $P < 0.001$) with 100, 200, and 400 mg/kg doses at the 7th and 14th days, respectively. Possessed α-amylase suppression activity at both the leaf latex and the fraction (Rf value of 0.49) with IC50 value of 74.76 ± 1.98 and 96.75 ± 1.98 μg/mL, respectively ($P < 0.001$).	[51,52]
Ajuga integrifolia	Lamiaceae	Anamaro	OGTT and STZ induced DM		Root	The extract and aqueous fraction of *A. integrifolia* exhibited a significant BGL reduction effect at all tested doses. Both the repeated daily doses of the crude extract and aqueous fraction of *A. integrifolia* showed similar activity in reducing the fasting BGL in streptozotocin-induced diabetic mice models	[91]
Aloe pulecherrima	Aloeceae	Eret	Normoglycemic, OGTT and STZ induced DM	α-amylase, Sucrose and Maltase inhibitory	Leaf latex	Inhibited sucrase, maltase, and α-amylase. ↓BGL ($P < 0.05$) in OGTT mice. ↓BGL of diabetic mice ($P < 0.05$) on week 1 and 2. ↓BGL with increasing the doses on week 1 ($P < 0.05$ (200 mg/kg), $P < 0.01$(400 mg/kg), and $P < 0.001$ (600 mg/kg)).	[53]
Bacium grandiflorum Lam	Lamiaceae	Mentesie	Normoglycemic, OGTT and STZ induced DM	–	Leaf	↓BGL ($P < 0.05$) at the extract (100, 200, and 400 mg/kg) 14 days.	[100]
Bersama abyssinica	Melianthaceae	Azamira	Normoglycemic, OGTT and STZ induced DM	α-amylase	Leaf	↓BGL by 25.71, 33.27, 40.71, and 48.39% at 400 mg/kg chloroform, ethyl acetate and aqueous fraction, and crude extract, respectively, in diabetic mice. Inhibited α-amylase with different IC50 values of crude extract, water fraction, ethyl acetate fraction, and the chloroform fraction.	[56]
Pentas schimperiana	Rubiaceae	Not stated	Normoglycemic, OGTT and Alloxan-induced DM	–	Leaf	↓BGL at a dose of 1,000 mg/kg for fresh leaf hydroalcoholic and dried leaf aqueous extracts by 26.7% ($P < 0.01$) and 26.97% ($P < 0.001$), respectively. ↓BGL with hydroalcoholic dried leaf extract by 19.27% ($P < 0.001$) at 1,000 mg/kg dose on 3 h ↓BGL with methanol and aqueous at a dose of 500 mg/kg ($P < 0.001$).	[111]
Moringa stenopetala	Moringaceae	Shifraw	OGTT and STZ induced DM	–	Leaf	↓BGL for ethanol extract at 60 ($P < 0.05$) and 120, 180, and 240 min ($P < 0.001$). ↓BGL for aqueous extract at 120 min ($P < 0.01$) and 180 and 240 min ($P < 0.001$) of single dose in diabetic mice. ↓BGL for the ethanol extract ($P < 0.001$) at 3rd day. ↓BGL for aqueous extract on the 3rd ($P < 0.01$) and 5th and 8th days ($P < 0.001$). ↓BGL for chloroform and butanol fractions on 5th day ($P < 0.01$) and 8th day ($P < 0.001$) in diabetic mice.	

(*continued on next page*)

Table 1 (*continued*)

Scientific name	Family	Local name	*In vivo* Test	*In vitro* Test	Plant part	Effect	References
Calpunia aure	Fabaceae	Ligita	Normoglycemic, OGTT and STZ induced DM	–	Leaf	↓BGL at all doses of the extract ($P < 0.05$) at days 7, 14, and 21. Antidiabetic activity ($P < 0.05$) exhibited by 400 mg/kg compared to 100 mg/kg.	[109]
Thymus schimperi	Lamiaceae	Tosign	Normoglycemic, OGTT and STZ induced DM	–	Leaf	↓BGL ($P < 0.05$) at the extract (100, 200, and 400 mg/kg) 14 days.	
Justicia schimperiana	Acanthaceae	Smiza	Normoglycemic, OGTT and STZ induced DM	–	Leaf	Showed significant tolerance ($P < 0.05$) at 1 and 2 h ↓BGL ($P < 0.05$) at 4 h in normoglycemic mice. ↓BGL ($P < 0.05$) at 400 mg/kg extract at 2, 3, and 4 h of treatment in diabetic mice.	[112]
Terminalia brownie	Combrefaceae	Abalo	Normoglycemic, OGTT and STZ induced DM		Stem bark	↓Hyperglycemia with OGTT by the crude extract at a dose of 500 mg/kg ($P < 0.01$), 750 ($P < 0.05$) after 60 min, and 750 mg/kg ($P < 0.01$) after 120 min ↓BGL ($P < 0.01$) with ethyl acetate and aqueous fractions at 500 mg/kg in diabetic model.	[113]
Croton macrostachys	Euphorbiaceae	Bisana	Normoglycemic, OGTT and STZ induced DM	–	Root	↓Hyperglycemia by 300 mg/kg compared to 100 ($P < 0.001$) and 200 mg/kg ($P < 0.01$) in diabetic mice. ↓BGL in OGTT at doses of 100 ($P < 0.01$), 200 ($P < 0.001$), and 300 mg/kg ($P < 0.001$) after 60, 90, and 120 min of glucose loading.	[114]
Indigofera spicata	Fabaceae	Not stated	Normoglycemic, OGTT and Alloxan-induced DM	–	Leaf	↓BGL at 200 and 400 mg/kg in normoglycemic mice ($P < 0.05$). ↓BGL ($P < 0.05$) in only 400 mg/kg exposed groups at the 120 min of postexposure in OGTT model. ↓BGL ($P < 0.05$) at all doses of the extract at 4, 6, and 10 h on diabetic mice.	[115]
Otostegia integrifolia	Lamiaceae	Tinjut	Normoglycemic, OGTT and STZ induced DM	–	Leaf	↓BGLs at 200 mg/kg extract in the hypoglycemic and OGTT models. ↓Fasting BGL ($P < 0.001$) at 100 and 200 mg/kg doses at 4 h in diabetic mice.	[116]
Caylusea abyssinica	Resedaceae	Akorarach	Normoglycemic, OGTT and STZ induced DM	–	Leaf	↓BGL by 100 ($P < 0.05$) and 300 mg/kg extract ($P < 0.01$) starting from the 3rd h, and by 200 mg/kg ($P < 0.001$) as early as the 2 nd h in diabetic mice. ↓BGL by 100 mg/kg extract ($P < 0.01$) at 120 min and 200 mg/kg ($P < 0.001$) at 60 min in OGTT.	[117]
Rubus Erlangeri	Rosaceae	Not stated	Normoglycemic, OGTT and STZ induced DM	α-amylase	Leaf	↓BGL ($P < 0.05$) at the extract (100, 200, and 400 mg/kg) 14 days.	[118]
Lens culinaris	Leguminosae	Not stated	Normoglycemic, OGTT and STZ induced DM	–	Seed	↓BGL at all doses of the extract ($P < 0.05$) at days 7, 14, and 21. Antidiabetic activity ($P < 0.05$) exhibited by 400 mg/kg compared to 100 mg/kg.	[119]
Aloe camperi	Asphadelaceae	Ere	OGTT and Alloxan-induced DM	–	Leaf	Showed a significant ($P<0.001$) reduction of BGL as compared to the diabetic control group.	[120]
Acanthus polystachyus	Acanthaceae	Not stated	Normoglycemic, OGTT and STZ induced DM	–	Root	↓BGL ($P < 0.05$) at the extract (100, 200, and 400 mg/kg) 14 days.	
Capparis tomentosa	Capparaceae	Gumero	Alloxan-induced DM	–	Root	↓BGL at all doses of the extract ($P < 0.05$) at days 7, 14, and 21. Antidiabetic activity ($P < 0.05$) exhibited by 400 mg/kg compared to 100 mg/kg.	[121]
Catha Edulis	Celastracea	Khat	Normoglycemic, OGTT and STZ induced DM	–	Leaf	↓Fasting BGL from 223.7 ± 27.6 to 106 ± 18.2 mg/dl, at the end of study ($P < 0.05$).	[122]

Note: SZT: Streptozotocin; +: *in vivo* antidiabetic activity; IC50: inhibitory concentration; BGL: blood glucose level; OGTT: oral glucose tolerance test; DM: Diabetes mellitus.

stimulation of glycogenesis, reduction of glucose absorption, activation of releasing insulin from ß-cells, and/or increment of glucose use [59,63,71]. In addition to reducing the elevated blood glucose level, bioactive compounds obtained from medicinal plants can terminate oxidative stress on ß-cells and restore the impaired ß-cells [66–69,72]. Moreover, enhancing the metabolic rate of oxygen consumption [73], inhibiting cellular apoptosis, reducing renal glucose reabsorption [66,67,73], and promoting translocation of GLUT-4 and glucose transporter (GLUT-2) expression [67], are also important mechanisms demonstrated with certain phytoconstituents that are accountable for antihyperglycemic activities [67]. Stimulating cyclic adenosine monophosphate (cAMP), providing some essential elements such as magnesium, calcium, manganese, zinc, and copper for the β-cell [66], and Blocking pancreatic β-cell K+ channel [74], are also some mechanisms that are possibly participated in β-cell dysfunction found in diabetes mellitus [66,74]. The enzymatic inhibition of α-glycosidase and α-amylase enzymes, which are crucial for carbohydrate digestion, is used as an alternative treatment modality for diabetes mellitus. Folkloric medicinal plants with antidiabetic activities through inhibition of these enzymes and their free radical scavenging potentials are becoming hopeful approaches in the management of diabetes mellitus and its associated complications [70]. Medicinal plants have a significant role in the discovery of potential antidiabetic activities and have begun to get greater attention as sources of bioactive constituents as well as antioxidants. The antioxidant effect of medicinal plants has protective activity in restoring β-cell function in DM. As free radicals are known to damage and mutation of cells, and hence, oxidative stress has a significant role in the pathogenesis of diabetes mellitus and diabetic complications. Thus, medicinal plants with antioxidant activity will have significant importance in managing diabetes mellitus and its complications through scavenging free radicals [66].

Generally, the mechanisms of action could be grouped as preventing oxidative stress that is possibly involved in pancreatic β-cell dysfunction; pancreatic β-cell potassium channel blocking; cyclic adenosine monophosphate stimulation; providing certain necessary elements like zinc, calcium, manganese, copper, and magnesium for the β-cells; Inhibition of α-glucosidase and β-galactosidase [75]; inhibition of glycogenolysis and gluconeogenesis; stimulation of glycolysis, citric acid cycle, glycogenesis, and hexose monophosphate shunt [76]; enhancement indigestion along with a reduction in urea and blood sugar; promotion of regeneration and protection of destruction of the β-cells, initiate insulin release; reduction in insulin resistance and/or inhibition in renal glucose reabsorption [77]. Table 1 summarizes the *in vitro* and *in vivo* antidiabetic activities of several medicinal plants in Ethiopia.

9. Toxicological profile of medicinal plants

Acute toxicity testes via *in vivo* model confirmed the relative safety of the medicinal plant's extract. Seven plants, *Ajuga remota, Hagenia abyssinica, Datura stramonium, Aloe megalacantha, Ajuga integrifolia, Bacium grandiflorum Lam, Bersama abyssinica, Justicia schimperiana, Terminalia brownie, Indigofera spicata, Capparis tomentosa, Capparis tomentosa, Aloe camperi, and Acanthus polystachyus* showed LD50 greater than 2000 mg/kg [71,78–84]. Other plants such as *Satvia rebaudiani*, *Croton macrostachys*, and *Otostegia integrifolia* revealed LD50 greater than 5000 mg/kg [64,85–88]. The LD50 of Moringa stenopetalla were 50.6 g/kg [85] and 50 g/kg [88]. The LD50 of *Pentas schimperiana* was greater than 4000 mg/kg [89]. The sub-chronic toxicity of Moringa Stenopetala exhibited normal hematological, significantly higher platelet counts compared to controls, significant changes were observed in the clinical chemistry parameters such as (CA125, urea, TSH, FT3, ALT, creatinine, cholesterol, TGs, and AST) were significantly higher, and FT4 significantly reduced in the mice received the treatment [90] Table 2.

10. Phytochemistry of medicinal plants

Medicinal plants were screened phytochemically and reported that phenolic compounds, terpenoids, saponins, glycosides, tannins, flavonoids, glycolipids, dietary fibers, alkaloids, carotenoids, and anthocyanins were most commonly isolated biologically active principles responsible for its medicinal properties [90–92].

Phenols and Tannins [72,93] might contribute to antidiabetic effects due to their potential to possess insulin-like effects or stimulate insulin

Table 2
Phytochemical screening and toxicity study of medicinal plants used for diabetes mellitus management.

Scientific name	LD_{50} (mg/kg)	Phytochemical constituents	References
Ajuga remota	>2,000	Saponins, phenolic compounds, steroids, flavonoids, and tannins	[92]
Satvia rebaudiani	>5,000	Triterpenes, rebaudioside A-F, steviolbioside, sterols, ducloside A, stevioside, and flavonoids	[123]
Hagenia abyssinica	>2,000	Tannins, anthraquinones, terpenoids, steroids, flavonoids, glycosides, phenols, and saponins	[108]
Datura stramonium	>2,000	Alkaloids, saponins, steroids, phenols, flavonoids, tannins, glycosides, and terpenoids	[110]
Aloe megalacantha	>2,000	Terpenoids, alkaloids, tannins, flavonoids, saponins, anthraquinones, and phenolic compounds	[52]
Ajuga integrifolia	>2,000	Alkaloids, terpenoids, flavonoids, glycosides, phenols, steroids, tannins, and saponins	[124]
Aloe pulecherrima	ND	Nataloin, chrysophanol, 7-hydroxyaloin, and aloesaponarin	[125].
Bacium grandiflorum Lam	>2,000	Anthraquinones, saponins, phytosterols tannins, alkaloids, terpenoids, flavonoids, glycosides, and coumarins	[126]
Bersama abyssinica	>2,000	Steroids, glycosides, terpenes, carotenoids, alkaloids, phenols, anthraquinones, tannins, triterpene, flavonoids, fatty acids, coumarins, and vitamins	[127,128]
Pentas schimperiana	>4,000	phenolic compounds, flavonoids, saponins, steroidal, and tannins	[89]
Moringa stenopetala	>50 g/kg	Alkaloid, flavonoids, glycoside, flavanol, glycosinolate, and sterol	[129]
Justicia schimperiana	>2,000	Triterpenes, polyphenols, flavonoids, alkaloids, saponins, glycosides, quinines, and phytosterols	[130]
Terminalia brownie	>2,000	Flavonoids, phytosterols, polyphenols, saponins, and tannins	[131]
Croton macrostachys	>5,000	Flavonoids, phenolic compounds, alkaloids, terpenoids, tannins, and saponins	[114]
Indigofera spicata	>2,000	Glycoside, alkaloid, saponin, tannins, diterpenes, phytosterol, and flavonoids	[115]
Otostegia integrifolia	>5,000	Saponins, flavonoids, reducing sugars, and phenolic compounds. gas chromatography, GC-mass spectrometry and NMR techniques confirms the identification of many constituents such as stigmasterol, pentatriacontane, (15, 16-epoxy3a, 9a-dihydroxy-labda-13(16) & 14-diene and 9(13), (+)-1-methyl-4-(5, 9-dimethyl1-methylene-deca-4, 8-dienyl)-cyclohexene41, 15(16) - diepoxy-3a-hydroxy-16- dihydrolabda-14-ene]	[89,116]
Caylusea abyssinica	>2,000	Reducing sugars, saponins, tannins, alkaloids, steroidal compounds, flavonoids, phenolic compounds, and cardiac glycosides	[117]
Aloe camperi	>2,000	Saponins, phenols, steroids, alkaloids, glycosides, phenols, tannins, terpenoids, flavonoids, coumarins, proteins, and carbohydrates	[132]
Acanthus polystachyus	>2,000	Flavonoids, alkaloids, tannins, steroidal compounds, polyphenols, glycosides, saponins, anthraquinones, and terpenoids	[133]

Note: LD50: lethal dose 50; ND: result not determined.

secretion [63], prevent β-cells impairment through free radical scavenging effects [94,95], enhance β-cells propagation and restoration [95], and reduce carbohydrate absorption by impeding α-amylase and α-glucosidase [72].

Flavonoids and other polyphenols showed antidiabetic activities through enhancing insulin release [59,96–99], enhancing the expression and promoting translocation of GLUT-4 [67,96,97], and enhancing GLUT-2 expression in pancreatic β-cells [67,97], which can increase glucose uptake by the liver, adipose tissue, and muscle [97,98]. Flavonoids also reduce aldose reductase [59], inhibit α-glycosidase [59,97], and α-amylase [97], retard the gastric emptying rate [59], increase calcium ion uptake [59], and regenerate pancreatic beta cells [100,101].

Saponins display their antidiabetic activities through the possible mechanisms of ameliorating insulin resistance [58], stimulating insulin release/secretion, and protecting pancreas β-cells [59,102].

Alkaloids have received extra attention due to their potential role in the management of diabetes mellitus through inhibition of dipeptidyl peptidase-4 (DPP-4), protein tyrosine phosphatase 1B (PTP1B), AGEs [103], and α-amylase and α-glucosidase [104]. In addition, they also activate GLUT-4 translocation and 50 adenosine monophosphate-activated protein kinases (AMPK). Alkaloids have shown a significant effect on insulin release, pancreatic regeneration, and protective effects on oxidative tissue damage [103,105].

Triterpenoids seem to have promising antihyperglycemic effects through inhibition of aldose reductase, hepatic glycogen phosphorylase [106], and α-amylase and α-glucosidase [104,106]. In addition, they increase insulin-stimulated GLUT-4 translocation, prevent pancreatic β-cell dysfunction, decrease body weight, decrease oxidative stress and agonistic properties of emerging G-protein-coupled receptor (TGR5). Triterpene compounds have also shown a significant effect on the formation of advanced glycation end products (AGEs) and are promising agents in the prevention and management of diabetes mellitus complications [106]. Several medicinal plants summarized in this review contain various phytoconstituents Table 2.

11. Strengths and limitations of the studies

The evidence synthesized from this review will have paramount for further investigations in human studies. It will show directions of further the studies and promote the traditional use. Although we reviewed all previous antidiabetic studies that were conducted in Ethiopia, some limitations could limit the findings of this review. The methods used for the induction of DM were STZ or alloxan which mostly induces T1DM. The challenge in an *in vivo* study is as the induction method mostly induces T2DM. Most of the medicinal plants included in this study lack identification and isolation of the active constituents that could join the adventure of modern drug discovery. No clinical trials were conducted and also no clearly defined preparation for clinical trials in Ethiopia. Moreover, most of the studies didn't report the standardization protocols, the composition of the formulation, and preparation procedures.

12. Conclusion

Herbal medicines are gaining importance as they are cost-effective and also display improved therapeutic effects with lesser side effects. In Ethiopia, most medicinal plants with antidiabetic claims were studied in different animal models such as normoglycemic mice, oral glucose-loaded mice, streptozotocin-induced diabetic mice, and alloxan-induced diabetic mice. However, *in vitro* antidiabetic activity was conducted for a few of them. Medicinal plants which are rich in phytoconstituents like flavonoids, coumarins, terpenoids, phenolic compounds, and other bioactive compounds have revealed a significant blood-glucose-lowering activity. Further *in vitro* studies and bioassay-guided isolation and characterization of the active principle responsible for the antidiabetic activity of the medicinal plants are recommended to substantiate the use of the plant as a potential target for the development of antidiabetic agents. Antidiabetic medicinal plants used in Ethiopia denote a key role in the future development of novel antidiabetic agents. To this end, more toxicological and pharmacological investigations need to be considered to prove the safety of bioactive compounds obtained from these medicinal plants. Finally, we recommend ensuring future success in the clinical study and development of novel medicines for diabetes management from these medicinal plants.

Availability of data and materials

Most of the data is included in the manuscript. Additional can be found from the corresponding author based on reasonable request.

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Ethics approval and consent to participate

Not applicable.

Declaration of competing interest

The authors declare that they have no competing interests.

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