Review Article

Medicinal Plant Extracts Evaluated In Vitro and In Vivo for Antidiabetic Activities in Ethiopia: Bases for Future Clinical Trials and Related Investigations

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Background. Diabetes mellitus (DM) is a metabolic disorder characterized by a persistent rise in the blood glucose level resulting from defects in cellular insulin function, secretion, or both, which affects millions of people every year. Several drawbacks have been stated with the use of marketed antidiabetic medicines such as drug resistance, adverse effects, toxicities, and even costs. Due to these several limitations, searching for novel antidiabetic medicines from medicinal plants (MPs) is becoming an active area of research. Therefore, MPs are exemplary sources of medicines with many accessible agents being obtained from them because numerous active constituents are isolated from them for direct use as pharmacological medicines or act as lead compounds. This paper was aimed to synthesize a concluding remark using in vitro and in vivo evaluations of extracts and fractions for antidiabetic potentials in Ethiopia, which can be used to direct future clinical trials and related investigations.

Method. So as to get data on the different investigations, publications related to experimental evaluations on animal diabetic models in Ethiopia were searched from databases, such as Google Scholar, Web of Science, Medline, PubMed, and Scopus using English key terms.

Results. In this paper, about 37 research findings based on data from various areas of Ethiopia published until the end of November 2020 were included. A total of 37 MP species extracts and fractions belonging to 19 families have been revealed in vitro or in vivo for potential antidiabetic activities. Crude extracts were carried out mostly by hydromethanolic whereas fractions were done mostly by chloroform. Leaves were the most commonly experimentally investigated plant part. Among the MP species experimentally studied, the most frequently used to treat DM in Ethiopia were Thymus schimperi Ronniger (Lamiaceae), Moringa stenopetala (Baker f.; Moringaceae), Ajuga remota Benth (Lamiaceae), and Datura stramonium Linn. (Solanaceae).

Conclusion. This paper gives aggregate evidences on the potential antidiabetic activities of MPs in Ethiopia. Antidiabetic MPs used in Ethiopia represent crucial input for the future development of novel antidiabetic drugs. To this end, more pharmacological and toxicological investigations need to be considered to prove the safety of constituents obtained from these MPs. Finally, we recommend upcoming research to ensure future success in the clinical study and development of novel medicines for DM treatment from these frequently evaluated MPs.

1. Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by a persistent rise in blood glucose level (BGL) caused by ineffective insulin function, secretion, or both on target tissues [1–3]. Chronic hyperglycemia is associated with lifelong microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (coronary and peripheral arterial diseases and stroke) complexities, which are the typical features in all forms of DM. These complications result in damage and death of various organs that are diagnosed very late or have inappropriate medical follow-up [4–6].

Currently, it becomes one of the leading public health problems and the cause of morbidity and death universally
In 2019, the International Diabetes Federation (IDF) estimates that 463 million (9.3%) adults aged 20–79 worldwide are currently living with diabetes. The total number is predicted to rise to 578.4 million (10.2%) by 2030 and 700.2 million (10.9%) by 2045 [10] with the highest increment in regions where economies are moving from low- to middle-income status without sufficient action to address the pandemic [1, 7, 10–12]. The number of deaths resulting from diabetes and its complications in 2019 is estimated to be 4.2 million [10].

Nearly 79.4% of diabetic patients live in low- and middle-income countries [10]. Around 19.4 million aged 20–79 had DM in Africa region with a prevalence of 3.9% in 2019. The Africa region is estimated to have the highest future increase in the number of people with diabetes compared to other parts of the world. By 2030 and 2045, there will be 28.6 million (47.5% increase), and 47.1 million (142.9% increase) adults aged 20–79 with diabetes, respectively, more than double the number in 2019 and the highest increase compared to other IDF regions [10].

Among the highly populated African nations that have the highest number of people with diabetes, including South Africa (4.6 million), Nigeria (2.7 million), the Democratic Republic of Congo (1.8 million), and Ethiopia (1.7 million). More than half (55.8%) of all 20–79-year-old adults with diabetes in the region live in one of these four countries [10]. Studies in various parts of Ethiopia showed that the prevalence of diabetes varies from 0.3 to 7.0% [13]. The IDF estimated that the total health expenditure due to diabetes in 2019 was USD 760 billion worldwide. It is projected that expenditure will reach USD 825 billion by 2030 and USD 845 billion by 2045 [10].

1.1. Challenges in the Treatment of DM. The existing approaches to the management of DM relied on keeping BGLs with normal limits via administration of appropriate medications together with lifestyle modifications [2, 14]. So far, the accessible medicines for DM are various preparations of insulin and oral antihyperglycemic agents [15–19]. The older hyperglycemics are sulphonylureas, alpha-glucosidase inhibitors, thiazolidinediones, and biguanides [19, 20] while the newer medicines include incretin-based therapies, sodium-glucose cotransporter 2 (SGLT-2) inhibitors, glucokinase activators, and injectable glucagon-like peptide (GLP-1) agonists [21]. These medicines are used either as monotherapy or in combination to achieve better treatment outcomes [19].

The conventional and newer agents are still with their shortcomings, and successful treatment of diabetes is being a global challenge requiring further investigations. In fact, these medications are associated with unnecessary drug reactions or side effects [3, 19] including hepatocellular injury, exacerbate renal diseases, blood dyscrasias, gastrointestinal irregularities, hypoglycemias, hypersensitivity reactions, weight gains, and lactic acidosis [22], which decrease their effectiveness and compliance rates [4, 22]. For instance, 3.9 and 32.7% severe and nonsevere hypoglycemic events were reported in 826 (2.8%) patients during their most recent year of sulfonylurea treatment, respectively [23]. Clearly, the weight gain associated with the use of thiazolidinediones (pioglitazone and rosiglitazone), sulphonylureas (glibenclamide), and insulin is also the major drawback for treating diabetes [24].

Several drawbacks have been reported associated with the use of antihyperglycemic medications, such as decreasing effectiveness and increasing adverse effects and toxicities. For instance, sulphonylureas lose their efficacy after six years of therapy in nearly 44% of patients, while BG lowering medicines are stated to be unable to control hyperlipoproteinemia [25]. Due to numerous limitations related to the use of existing synthetic BG-lowering medicines, the search for newer antihyperglycemic medicines from natural sources continues [25].

In spite of the extensive improvement made in the management of DM using various antihyperglycemic medicines in the past, the results of treatment are still far from successful. Because of the limitations of these agents, there remains a clear need for the identification of new antidiabetic drugs. Therefore, seeking extra safe and effective antidiabetic medicines from plant sources is becoming an active area of research in the scientific community. There are limited studies in Ethiopia, which compile in vivo and in vitro evaluations of extracts from medicinal plants (MPs) for antidiabetic potentials as a guide for future clinical trials and other related investigations. Therefore, this review provides a summary of MP extracts used for the treatment of DM.

1.2. Medicinal Plants (MPs) as Potential Sources of Antidiabetic Drugs. Internationally, MPs have been used as sources of medicines, and more than 80% of people depend on them using their extracts for their primary health care desires [26, 27]. Plant-based formulations become the key players of all available treatments due to accessibility, affordability, and minimum adverse effects, particularly in rural parts [19, 25].

Globally, WHO has estimated that more than 1,200 MP species are used in treating DM, mainly in developing nations [28], which represent above 725 genera in 183 families. Although, nearly 350 of them have been identified to possess antihyperglycemic effects, and few of them still require extensive investigations to prove their safety and effectiveness in humans [28].

In developing nations, especially MPs are used in treating DM to overcome the economic burden of medicines to the people [25, 29–31]. These days, treating DM using MPs is recommended [32] since these MPs contain various phytocomponents such as flavonoids, terpenoids, saponins, carotenoids, alkaloids, and glycosides, which might have effects [25]. The combined effects of biologically active constituents (such as polyphenols, carotenoids, and glucosinolates) also result in the potential valuable properties of each MP, and this can act as the first stage to understand their biological effects and beneficial activities [25, 33, 34].

Numerous MPs are well documented for their medicinal values to treat DM in the traditional methods of medica-

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for their hypoglycemic effectiveness [29, 35], many active constituents were isolated from MPs for direct uses as medicines or represent as lead compounds or pharmacological drugs. For instance, metformin, a BG-lowering medicine, was isolated from MP *Galega officinalis* L., which was used historically in primitive Europe in treating DM [19, 36].

Many studies revealed the uses of MPs with antihyperglycemic activities in the treatment of DM [14]. The activities of these MPs could delay the progress of DM complications and ameliorate the metabolic defects. During the past few years, some of the new bioactive medicines isolated from antihyperglycemic MPs indicated BG-lowering effects with better efficiency than oral antihyperglycemic medicines used in clinical treatment [14].

1.3. Possible Mechanism of Actions of Medicinal Plants in Treating DM. Bioactive compounds that are obtained from various MPs have been reported to have potent BG-lowering potentials [37–45]. The mechanism of lowering BGL might be a result of activation of releasing insulin from β-cells, reduction of glucose absorption, stimulation of glycogenesis, and/or enhancement of glucose use [28, 46, 47]. In addition to lowering BGL, secondary metabolites obtained from MPs have the capacity to restore the impaired β-cells and terminate oxidative stress on β-cells [35, 37–40].

Furthermore, inhibiting cellular apoptosis, reducing renal glucose reabsorption [37, 38, 45], enhancing the metabolic rate of oxygen consumption [45], and promoting glucose transporter (GLUT-2) expression and translocation of GLUT-4 [38, 43] are also important mechanisms illustrated with certain secondary metabolites that are responsible for antidiabetic effects [38, 43]. Blocking pancreatic β-cell K⁺ channel [48], stimulating cyclic adenosine monophosphate (cAMP), and providing some essential elements (calcium, zinc, magnesium, manganese, and copper) for the β-cell [37] are also some mechanisms that are possibly participated in β-cell dysfunction found in DM [37, 48].

Blocking the actions of α-amylase and α-glycosidase enzymes, which are essential for carbohydrate digestion, is used as an optional treatment approach for type 2 diabetes. Folkloric MPs with antihyperglycemic effects via inhibition of these enzymes and their free radical scavenging potentials are becoming promising modalities in treating type 2 DM and associated complications [41]. Medicinal plants have central roles to discover newer medicines and have begun to get greater attention as sources of bioactive constituents as well as antioxidants. Antioxidant activity has a protective effect in restoring β-cell function in diabetes. Because free radicals are known to damage and mutation of cells, and hence, oxidative stress has a vital role in the pathogenesis of DM and its complications, MPs with antioxidant effect will have paramount importance in treating diabetes and its complications via scavenging free radicals [37].

1.4. Important Phytochemicals for Treatment of DM. Phytochemicals that are obtained from various MP sources containing flavonoids, phenolic compounds, alkaloids, terpenoids, saponins, tannins, glycosides, glycolipids, dietary fibers, carotenoids, and anthocyanins have demonstrated potential BG-lowering activities [38] through different mechanisms [43].

Flavonoids and other polyphenols show BG-lowering activities by enhancing GLUT-2 expression in pancreatic β-cells [38, 43, 49], enhancing insulin release [25, 46, 49–51], and increasing expression and promoting translocation of GLUT-4 [25, 38, 43, 49, 51], which can increase glucose uptake by the muscle, liver, and adipose tissue [49, 50]. Flavonoids also regenerate pancreatic beta cells [37, 43, 47, 52–54], reduce aldose reductase [46], increase calcium ion uptake [46], retard the gastric emptying rate [46], and inhibit α-glycosidase [46, 49, 54] and α-amylase [43, 49]. In addition, they have antiapoptotic activities [25, 49].

Tannins [35, 53] and phenols might contribute to BG-lowering activities due to their potential to stimulate insulin secretion or possess insulin-like effects [43], reduce carbohydrate absorption by impeding α-glucohydrolases [35, 43], enhance β-cells propagation and restoration [43], and prevent β-cells impairment through free radical scavenging effects [43, 55, 56].

Saponins exhibit their antihyperglycemic effects through the probable mechanisms of protecting pancreas β-cells, stimulating insulin release/secretion [35, 46, 57, 58], and ameliorating insulin resistance [58].

Triterpenoids seem to have promising antidiabetic properties that can be achieved through the inhibition of α-glucosidase, α-amylase [59, 60], aldose reductase, hepatic glycogen phosphorylase, and sweetness [60]. They have also agonistic properties of emerging G-protein-coupled receptor (TGR5). Additionally, they prevent pancreatic β-cell dysfunction, increase insulin-stimulated GLUT-4 translocation, and decrease oxidative stress and body weight. Some triterpene compounds possess the ability to suppress the formation of advanced glycation end products (AGEs) and are promising agents in the prevention and treatment of DM complications [60].

Alkaloids, in recent years, have received extra attention due to their potential role in the treatment of diabetes through inhibition of α-glucosidase, α-amylase [59, 61], dipeptidyl peptidase-4 (DPP-4), and AGES by possessing potent protein tyrosine phosphatase 1B (PTP1B) inhibitory effects [61]. They activate 50 adenosine monophosphate-activated protein kinases (AMPK) and GLUT = 4 translocation. Alkaloids are effective for pancreatic regeneration and insulin release. They also show protective effects on oxidative tissue damage [61, 62].

Potential BG-lowering substances from plant extracts, which are used for many diseases with identified drug targets and proven safety, are required in treating diabetes [38, 62–64]. Therefore, developing new antihyperglycemic agents from plant-derived substances, which are easily available, seems highly attractive research areas as currently accessible medicines have drawbacks regarding safety, efficiency, and affordability [65, 66]. Effective novel compounds with multiple targets, BG-lowering effect, and proven continuous safety have to be targeted in clinical settings for
users with concomitant pertinent lipid and glucose metabolic abnormalities. Consequently, this paper opens the way to develop medicines in treating chronic multigenic metabolic and cardiovascular disorders, for which therapy is currently inadequate or nonexistent [63, 67, 68]. Therefore, the attempt of our work is to look at different in vitro and in vivo antidiabetic evaluations of MPs in Ethiopia. Furthermore, this work could pave a way for other complementary studies plus the development of numerous accessible and inexpensive antidiabetic phytomedicines and provide direction for future clinical and other related investigations.

2. Methods

We have searched relevant articles to the scope of our work using Google Scholar, Medline, Web of Science, SCOPUS, and PubMed databases to extract in vitro and in vivo BG-lowering agents’ investigations of MPs conducted in Ethiopia. The search terms used were “antidiabetic activity,” “antidiabetic effect,” “antidiabetic potential,” “anti-hyperglycemic activity,” “antihyperglycemic effect,” “medicinal plants,” “hypoglycemic effect,” “hypoglycemic activity,” “blood glucose-lowering effect,” and “diabetes in Ethiopia.” Only studies conducted in Ethiopia were included using English keywords. If studies were done in Ethiopia plus other countries, the data obtained from Ethiopia were used. Original articles and studies written in English were included, whereas studies whose full articles were not accessible online were excluded from the study. We thereby provide scientific evidences based on evaluations on MPs as potential sources of antidiabetic drugs in Ethiopia.

The identification of records, screening of titles and abstracts, and evaluation of eligibility of full texts for final inclusion was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram [69]. Research papers available online before November 30, 2020, were considered for our study. A total of 47,928 articles were identified through database searching. All articles not done in Ethiopia were removed, and we obtained 884 articles. Eighty-six (86) research articles were obtained after removing the 798 duplicate articles, following the initial screening by titles and abstracts. Finally, as shown in Figure 1, these full-text articles were assessed for eligibility, and data were extracted from the remaining 37 experimental investigations of MPs. All research articles were summarized in the table and figures clearly with the key information and findings.

3. Results

3.1. Pharmacological Investigations. Overall, 37 MP species belonging to 19 families were investigated that showed potential antidiabetic activities in vitro or in vivo in Ethiopia as presented in Table 1.

From these families, Lamiaceae accounted the greatest number of species followed by Aloaceae and Fabaceae. Medicinal plants belonging to the Lamiaceae family have many active phytochemical substances [11, 46, 47, 54, 77–80].

The antidiabetic effects of crude extracts and fractions of different MPs parts using different chemicals were conducted as presented in Figure 2. Most experiments were performed with hydromethanolic extracts to get a greater percentage of extract yield based on previous studies conducted. Importantly, 80% methanol is more efficient in the cell wall and seed degradation as well as having low or no enzyme activity as compared to water. Additionally, the methanol extract of plant materials contains a wide variety of polar (and moderately nonpolar) compounds [70, 91, 92].

Among chemicals used for crude extraction of aqueous, methanol was mostly used, followed by the use of aqueous. Mostly, solvent fractionations were carried out using chloroform. Different MPs parts were used experimentally for antidiabetic activities in Ethiopia. Among these, leaves were the most commonly experimentally evaluated plant parts followed by roots and seeds as shown in Figure 3. Pharmacological studies on antidiabetic activities of MPs, which have been investigated directly or indirectly in Ethiopia, are presented in Table 1. Among MP species studied experimentally, Thymus schimperi Ronniger (Lamiaceae), Moringa stenopetala Baker f. (Moringaceae), Ajuga remota Benth (Lamiaceae), and D. stramonium Linn. (Solanaeaceae) were the most commonly used MPs in treating DM as discussed below.

4. Discussion

Numerous MPs are being used traditionally for the management of DM in Ethiopia for a long period though the number of plants studied is limited. This review summarized studies conducted and emphasizing the need for further investigations. Potential plant-derived antidiabetic
| Family/species | Plant crude extracts and fractions used | Models used | Dose(s) (mg/kg) | Standard drug used | Phytochemical constituents | Effects | LD_{50} (mg/kg) | Ref |
|----------------|----------------------------------------|-------------|----------------|-------------------|---------------------------|---------|----------------|-----|
| **Acanthaceae** | (1) *Acanthus polystachyus* Delile | 80% methanol root extract | STZ-induced diabetic rats | 100, 200, and 400 | GL | Tannins, flavonoids, saponins, polyphenols, terpenoids, glycosides, and anthraquinone | ↓ BGL (P < 0.05) at the extract (100, 200, and 400 mg/kg) for 28 days. | >2,000 | [70] |
|                | (2) Justicia *Schimperiana* T. Anderson | Aqueous leaf extract | Normal and STZ-induced diabetic mice | 200 and 400 | GL | Alkaloids, phenols, and terpenoids | Showed significant tolerance (P < 0.05) at 1 and 2h. ↓ BGL (P < 0.05) at 4h in normoglycemic mice. ↓ BGL (P < 0.05) at 400 mg/kg extract at 2, 3, and 4h of treatment in diabetic mice. | >2,000 | [71] |
| **Aloaceae**    | (3) *Aloe debrana* Christian | Ethanolic extract of leaves | STZ-induced diabetic rat | 300 | GL | ND | Showed antidiabetic activity (P < 0.05). | ND | [72] |
|                | (4) *Aloe megalacantha* Baker | Leaf latex extract | STZ-induced diabetic mice | 100, 200, and 400 | GL | Alkaloids, flavonoids, phenols, tannins, saponins, glycosides, anthraquinone, and terpenoids | ↓ BGL (P < 0.05 and P < 0.001) with 100, 200, and 400 mg/kg doses at the 7th and 14th days, respectively. | >2,000 | [18] |
|                | (5) *Aloe megalacantha* Baker | 80% methanol and TLC fraction of leaves latex | Chromogenic DNSA | 20, 40, 60, 80, and 100 μg/mL | Acarbose | ND | Possessed α-amylase suppression activity at both the leaf latex and the fraction (R_{f} value of 0.49) with IC_{50} value of 74.76 ± 1.98 and 96.75 ± 1.98 μg/mL, respectively (P < 0.001). | ND | [41] |
|                | (6) *Aloe monticola* Reynolds | 80% methanol and TLC fraction of the leaves | Chromogenic DNSA | 20, 40, 60, 80, and 100 μg/mL | Acarbose | ND | Possessed α-amylase suppression activity at both the leaf latex and the fraction (R_{f} value of 0.27 and 0.61) with IC_{50} value 78.10 ± 1.88, 56.95 ± 1.88, and 64.03 ± 3.60 μg/mL, respectively (P < 0.001) | ND | [41] |
| Family/species | Plant crude extracts and fractions used | Models used | Dose(s) (mg/kg) | Standard drug used | Phytochemical constituents | Effects | LD<sub>50</sub> (mg/kg) | Ref |
|----------------|---------------------------------------|-------------|----------------|-------------------|--------------------------|---------|-----------------------|-----|
| **Asteraceae** | | | | | | | |
| (7) Aloe pulcherrima Gilbert and Sebsebe | Leaf latex | Normoglycemic, glucose-loaded, and STZ-induced diabetic mice | 200, 400, and 600 GL | GL | Flavonoids, anthraquinone, saponins, glycosides, tannins, phenols, and alkaloids | Inhibited sucrase (IC<sub>50</sub> = 2.92 μg/ml), maltase (IC<sub>50</sub> = 11.81 μg/ml), and α-amylase (IC<sub>50</sub> = 14.92 μg/ml). ↓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 (200mg/kg), P < 0.01 (400mg/kg), and P < 0.001 (600mg/kg)). | ND [42] |
| (8) Artemisia afra Jacq. ex Willd | Aqueous and methanolic extract of aerial parts | Alloxan-induced diabetic Swiss albino mice | 500, 750, and 1,000 GL | GL | Tannins, saponins, chromophores, phosphosteroid, withaonoids, flavonoids, and anthraquione | ↓BGL by 24% (p < 0.005) and 56.9% (P < 0.0004) at doses of 500 and 750 mg/Kg aqueous extract, respectively. ↓BGL by 49.8% (P < 0.0001) at dose of 1,000 mg/kg methanolic extract at 5 hr. | >5,000 [9] |
| (9) Stevia rebaudiana Bertoni | Ethanol and aqueous extract of leaf | Alloxan-induced diabetic mice | 300 and 500 | GL | Alkaloids, steroids, phenols, and flavonoids | ↑Fasting BGL from 223.7 ± 27.6 to 106 ± 18.2 mg/dl, at the end of study (PP < 0.05). The crude extract and solvent fractions showed a dose-dependent α-amylase inhibitory activity. The highest α-amylase inhibitory potential with the lowest IC<sub>50</sub> value of 63.41 μg/mL by chloroform fraction. | >5,000 [11] |
| Celastraceae | | | | | | | |
| (10) Catha edulis Forsk | Fresh juice stem tips and leaves with water | STZ-induced diabetic rats | 4.5 ml/kg | GL | ND | ND [45] |
| Combretaceae | Methanol extract, chloroform, ethyl acetate, and n-butanol fraction of stem bark | Chromogenic DNSA | 10, 50, and 100 μg/mL | Acarbose | Tannins, saponins, polyphenols, flavonoids, terpenoids, and steroids | | >2,000 [1] |
| Family/species | Plant crude extracts and fractions used | Models used | Dose(s) (mg/kg) BW | Standard drug used | Phytochemical constituents | Effects | LD50 (mg/kg) | Ref |
|----------------|----------------------------------------|-------------|-------------------|--------------------|--------------------------|---------|--------------|-----|
| (11) *Terminalia brownii* Fresen. | Normoglycemic, OGTT, and STZ-induced diabetic mice | 250, 500, and 750 GL | ↓BGL by 20.8, 28.2, and 32.6% after 4 h of treatment of crude extract at dose of 250, 500, and 750 mg/kg, respectively, in normoglycemic mice. ↓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 mins. ↓BGL ($P < 0.01$) with ethyl acetate and aqueous fractions at 500 mg/kg in diabetic model. ↓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 mins of glucose loading. ↓BGL ($P < 0.05$) by 20.39% at 5.5 mg/kg at 6 h. ↓BGL by 32.72% and 46.11% with 11 mg/kg extract at 4 h ($P < 0.001$) and 6 h ($P < 0.001$) h, respectively, in normoglycemic mice. ↓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. ↓Hyperglycemia ($P < 0.05$) at all doses of extract (100, 200, and 400 mg/kg) at the 7th and 14th day of repeated daily dose administration. |
| (12) *Croton macrostachys* Hocsht. ex Del. | Hydroalcoholic root extract | OGTT and STZ-induced diabetic mice | 100, 200, and 300 GL | Alkaloids, phenols, tannins, terpenoids, saponins, phlobatannins, and flavonoids | ↓BGL ($P < 0.05$) by 20.39% at 5.5 mg/kg at 6 h. ↓BGL by 32.72% and 46.11% with 11 mg/kg extract at 4 h ($P < 0.001$) and 6 h ($P < 0.001$) h, respectively, in normoglycemic mice. ↓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. ↓Hyperglycemia ($P < 0.05$) at all doses of extract (100, 200, and 400 mg/kg) at the 7th and 14th day of repeated daily dose administration. |
| Fabaceae | 80% methanolic seed extract | Normoglycemic, OGTT, and STZ-induced diabetic mice | 2.75, 5.5, and 11 GL | Alkaloids, phenols, flavonoids, and terpenoids |
| (13) *Calpurnia aurea* (Ait.) Benth. | Hydromethanolic leaf extract | STZ-induced diabetic mice | 100, 200, and 400 GL | Phenols, alkaloids, terpenoids, and flavonoids |
| (14) *Calpurnia aurea* (Ait.) Benth. | | | | |
| Family/species | Plant crude extracts and fractions used | Models used | Dose(s) (mg/kg) BW | Standard drug used | Phytochemical constituents | Effects | LD<sub>50</sub> (mg/kg) | Ref |
|----------------|--------------------------------------|-------------|-------------------|--------------------|----------------------------|---------|----------------|------|
| (15) *Lens culinaris* | 80% methanol extract of seed | STZ-induced diabetic mice | 100, 200, and 400 | GL | Polyphenols, flavonoids, saponins, triterpenoids, phytates, lectins, phytochemicals, and defensins | ↓BGL at all doses of the extract (<i>P</i> < 0.05) at days 7, 14, and 21. Antidiabetic activity (<i>P</i> < 0.05) exhibited by 400 mg/kg compared to 100 mg/kg. | >2,000 | [74] |
| Medik | Hydroalcoholic crude extract of leaves | Normoglycemic, OGTT, and alloxan-induced diabetic mice | 100, 200, and 400 | GL | Alkaloids, glycoside, tannins, saponins, Phytochemicals, flavonoids, and diterpenes | ↓BGL at 200 and 400 mg/kg in normoglycemic mice (<i>P</i> < 0.05). ↓BGL (<i>P</i> < 0.05) in only 400 mg/kg exposed groups at the 120 mins of postexposure in OGTT model. ↓BGL (<i>P</i> < 0.05) at all doses of the extract at 4, 6, and 10 h on diabetic mice. | >2,000 | [75] |
| (17) *Vigna radiata* | Aqueous extract of grain | STZ-induced diabetic mice | 200 and 300 | GL | Anthocyanin and free and bound phenolic acids | ↓BGL at 200 and 300 mg/kg extracts (<i>P</i> < 0.05). | ND | [76] |
| Lamiaceae | Ethanol and aqueous extract of leaf | Alloxan-induced diabetic mice | 300 and 500 | GL | Steroids, phenols, flavonoids, and tannins | ↓Fasting mean BGL in diabetic mice with crude aqueous extract 300 and 500 mg/kg and crude ethanol extract 300 and 500 mg/kg by 27.96, 38.98, 28.09, and 28.25%, respectively (<i>P</i> < 0.05). ↓BGL (<i>P</i> < 0.0001) at aqueous extracts 300 and 500 mg/kg by 27.83 ± 2.96% and 38.98 ± 0.67%, respectively. ↓BGL (<i>P</i> < 0.05) at 70% ethanol extracts 300 and 500 mg/kg by 27.94 ± 1.92% and 28.26 ± 1.82%, respectively. | >5,000 | [11] |
| (18) *Ajuga remota* Benth | Aqueous and 70% ethanol extracts of leaves | Alloxan-induced diabetic mice | 300 and 500 | GL | Phenols, flavonoids, saponins, tannins, and steroids | ↓Fasting BGL (<i>P</i> < 0.05) treated with 200 and 400 mg/kg ethanol extract on 21st and 14th day of treatment, respectively. | ND | [77] |
| | Ethanol extract of leaves | STZ-induced diabetic rats | 200 and 400 | GL | Diterpenoids, phytoceratodterpenoids, phenolics, flavonoids, and glycosides | ↓Fasting BGL (<i>P</i> < 0.05) at 600 mg/kg extract at the 5th day. ↓BGL at all doses of the extract at the end of the 15th day of treatment by 17.61, 22.52, and 24.62%, respectively. | ND | [78] |
| (19) *Becium grandiflorum* Lam. | Ethanolic leaves extract | STZ-induced diabetic mice | 200, 400, and 600 | GL | Flavonoids, terpenoids, tannins, saponins, phenols, and steroids | | >5,000 | [54] |
| Family/species          | Plant crude extracts and fractions used                                      | Models used                      | Dose(s) (mg/kg) | Standard drug used | Phytochemical constituents                                                                 | Effects                                                                                                                                  | LD₅₀ (mg/kg) | Ref |
|------------------------|------------------------------------------------------------------------------|----------------------------------|----------------|--------------------|---------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|----------------|-----|
| **(20) Otostegia integrifolia Benth.** | 80% methanolic leaf extract                                                  | Hypoglycemic, OGTT, and STZ-induced diabetic mice | 100, 200, and 400 | GL                 | Phenols, saponins, reducing sugars, and flavonoids                                           | ↓ 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. ↓ BGL at methanolic crude extract of 250 mg/kg (14.76 ± 6.1%), 500 mg/kg (25.12 ± 11.5%), and 750 mg/kg (27.15 ± 10.0%) in a dose dependent manner. ↓ Postprandial hyperglycemia by methanol extract. ↓ BGL at a dose of 500 and 250 mg/kg n-butanol fraction by 36 ± 7.3% and 22.2 ± 4.3%, respectively. ↓ BGL at a dose of aqueous fraction 250 and 500 mg/kg by 17.6 ± 6.0% and 18.4 ± 5.0%, respectively. ↓ BGL (P < 0.05) at 500 mg/kg aqueous and 500 mg/kg 80% methanol extract at 14 and 21 days. ↓ BGL (P < 0.05) at 500 mg/kg 80% methanol and (P < 0.001) at 250 mg/kg aqueous and 80% methanol. Inhibited α-amylase activity (P < 0.05) by 68.6 ± 5.9% and 48.7 ± 7.1% at 2.5 mg/mL. 80% methanol and boiling water extracts with IC₅₀ 0.33 ± 0.05 mg/mL and IC₅₀ 2.24 ± 0.53 mg/mL, respectively. Inhibited α-glucosidase activity (p < 0.05) by 96.8 ± 10.5% and 84.4 ± 8.5% at 2.5 mg/mL. hot water and 80% methanol extract with IC₅₀ 0.05 ± 0.01 mg/mL and IC₅₀ 0.69 ± 0.04 mg/mL, respectively. | >5,000          | [47] |
| **(21) Thymus schimperi Ronniger** | Methanolic crude leaves extract, n-butanol, ethyl acetate, and aqueous fraction of leaves | STZ-induced diabetic mice         | 250, 500, and 750 | GL                 | Alkaloids, polyphenols, flavonoids, tannins, saponins, and terpenoids.                       | ↓ BGL at methanolic extract of 250 mg/kg (14.76 ± 6.1%), 500 mg/kg (25.12 ± 11.5%), and 750 mg/kg (27.15 ± 10.0%) in a dose dependent manner. ↓ Postprandial hyperglycemia by methanol extract. ↓ BGL at a dose of 500 and 250 mg/kg n-butanol fraction by 36 ± 7.3% and 22.2 ± 4.3%, respectively. ↓ BGL at a dose of aqueous fraction 250 and 500 mg/kg by 17.6 ± 6.0% and 18.4 ± 5.0%, respectively. ↓ BGL (P < 0.05) at 500 mg/kg aqueous and 500 mg/kg 80% methanol extract at 14 and 21 days. ↓ BGL (P < 0.05) at 500 mg/kg 80% methanol and (P < 0.001) at 250 mg/kg aqueous and 80% methanol. Inhibited α-amylase activity (P < 0.05) by 68.6 ± 5.9% and 48.7 ± 7.1% at 2.5 mg/mL. 80% methanol and boiling water extracts with IC₅₀ 0.33 ± 0.05 mg/mL and IC₅₀ 2.24 ± 0.53 mg/mL, respectively. Inhibited α-glucosidase activity (p < 0.05) by 96.8 ± 10.5% and 84.4 ± 8.5% at 2.5 mg/mL. hot water and 80% methanol extract with IC₅₀ 0.05 ± 0.01 mg/mL and IC₅₀ 0.69 ± 0.04 mg/mL, respectively. | >2,000          | [46] |
| Aqueous and methanolic extracts of leaves | Alloxan-induced diabetic mice | 250 and 500 | GL | Terpenoids | ↓ BGL at methanolic extract of 250 mg/kg (14.76 ± 6.1%), 500 mg/kg (25.12 ± 11.5%), and 750 mg/kg (27.15 ± 10.0%) in a dose dependent manner. ↓ Postprandial hyperglycemia by methanol extract. ↓ BGL at a dose of 500 and 250 mg/kg n-butanol fraction by 36 ± 7.3% and 22.2 ± 4.3%, respectively. ↓ BGL at a dose of aqueous fraction 250 and 500 mg/kg by 17.6 ± 6.0% and 18.4 ± 5.0%, respectively. ↓ BGL (P < 0.05) at 500 mg/kg aqueous and 500 mg/kg 80% methanol extract at 14 and 21 days. ↓ BGL (P < 0.05) at 500 mg/kg 80% methanol and (P < 0.001) at 250 mg/kg aqueous and 80% methanol. Inhibited α-amylase activity (P < 0.05) by 68.6 ± 5.9% and 48.7 ± 7.1% at 2.5 mg/mL. 80% methanol and boiling water extracts with IC₅₀ 0.33 ± 0.05 mg/mL and IC₅₀ 2.24 ± 0.53 mg/mL, respectively. Inhibited α-glucosidase activity (p < 0.05) by 96.8 ± 10.5% and 84.4 ± 8.5% at 2.5 mg/mL. hot water and 80% methanol extract with IC₅₀ 0.05 ± 0.01 mg/mL and IC₅₀ 0.69 ± 0.04 mg/mL, respectively. | >2,000          | [2]  |
| **(22) 80% methanol and boiling water extract of leaves** | Chromogenic DNSA and yeast α-glucosidase enzyme | 0.5, 1, 1.5, 2, and 2.5 mg/ml | Acarbose | Phenols and flavonoids | | | | ND | [79] |
| Family/species | Plant crude extracts and fractions used | Models used | Dose(s) (mg/kg) BW | Standard drug used | Phytochemical constituents | Effects | LD<sub>50</sub> (mg/kg) | Ref |
|----------------|---------------------------------------|-------------|--------------------|--------------------|--------------------------|---------|------------------------|-----|
| 22) Thymus vulgaris L. | 80% methanol and boiling water extract of leaves | Chromogenic DNSA and yeast α-glucosidase enzyme | 0.5, 1, 1.5, 2, and 2.5 mg/ml | Acarbose | Phenols and flavonoids | Inhibited α-amylase activity (P < 0.05) by 60.7 ± 9.2% and 27.1 ± 3.9% at 80% methanol and hot water extract with IC<sub>50</sub> 1.56 ± 0.09 mg/ml and IC<sub>50</sub> > 2.5 mg/ml. Inhibited α-glucosidase activity (P < 0.05) by 86.7 ± 8.3% and 60.7 ± 9.2% at 2.5 mg/mL hot water and 80% methanol extract with IC<sub>50</sub> 0.24 ± 0.09 and IC<sub>50</sub> 0.51 ± 0.02, respectively. | ND [79] |
| 23) Salvia tiliifolia | 80% methanolic aerial extracts | Alloxan-induced diabetic mice | 400 | GL | Alkaloid, saponins flavonoids, and phytosterols | ↓fasting BGL (P < 0.001) at the extract 400 mg/kg at 2, 4, and 6 h. ↓BGL with the continuous treatment of the extract for a period of 15 days. ↓BGL at 200, 300, and 400 mg/kg at all the time points (P < 0.05–0.001). ↓Parallel fasting BGL (all P < 0.001) at 200 and 400 mg/kg in the long-term effects over the 3-week period. ↓insulin levels progressively (P < 0.01–0.001) over the 3-week treatment period with 200 or 400 mg/kg. | >2,000 [80] |
| Malvaceae | Methanolic extract of leaf | STZ-induced diabetic rats | 400 | GL | Phytosterols, flavonoids, and glycosides | ↓fasting BGL (P < 0.001) at the extract 400 mg/kg at 2, 4, and 6 h. ↓BGL with the continuous treatment of the extract for a period of 15 days. ↓BGL at 200, 300, and 400 mg/kg at all the time points (P < 0.05–0.001). ↓Parallel fasting BGL (all P < 0.001) at 200 and 400 mg/kg in the long-term effects over the 3-week period. ↓insulin levels progressively (P < 0.01–0.001) over the 3-week treatment period with 200 or 400 mg/kg. | >5,000 [81] |
| 24) Hibiscus deflersii Schweinf. ex Cufod. | Aqueous leaf extract | Glucose in ob/ob mice | 200, 300, and 400 | GL | ND | | |
| 25) Melia azedarach Linn. | | | | | | | |

Table 1: Continued.
| Family/species | Plant crude extracts and fractions used | Models used | Dose(s) (mg/kg) | Standard drug used | Phytochemical constituents | Effects | LD$_{50}$ (mg/kg) | Ref |
|----------------|-----------------------------------------|-------------|----------------|--------------------|---------------------------|---------|------------------|-----|
| Melianthaceae (26) Bersama abyssinica Fresen. | Leaves 80% methanol crude extract and water, ethyl acetate, and chloroform fractions | Chromogenic DNSA | Normoglycemic, OGTT, and STZ-induced diabetic mice | 100, 200, 400, 50, 100, 200, 400, 600, 800, and 1000 μg/mL | Alkaloids, glycosides, flavonoids, steroids, phenols, tannins, triterpene, anthraquinone, polysterols, and coumarins | ↓BGL by 25.59%, 42.60%, and 49.42% for 100, 200, and 400 mg/kg, respectively, in normoglycemic mice. ↓BGL (P < 0.05) at all doses of the crude extract in OGTT mice. ↓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 IC$_{50}$ values of crude extract, water fraction, ethyl acetate fraction, and the chloroform fraction 6.57 ± 0.74 μg/mL, 13.33 ± 0.57 μg/mL, 20.34 ± 0.67 μg/mL, and 30.97 ± 0.84 μg/mL, respectively. ↓BGL (P < 0.05) for crude aqueous extract at all periods except at 6 h. ↓BGL (P < 0.05) for chloroform, n-butanol, and aqueous residue fractions at all periods. ↓BGL (P < 0.005) for n-butanol and aqueous residue fractions at 1.5h of their administration. | >2,000 [37] |
| Moringaceae | Crude aqueous extract, chloroform, and n-butanol leaves fraction | Alloxan-induced diabetic mice | 500 | GL | Alkaloids, saponins, glycoproteins, amino acids, and proteins | | >50.6 g/kg [82] |
| Family/species                  | Plant crude extracts and fractions used | Models used | Dose(s) (mg/kg) | Standard drug used | Phytochemical constituents | Effects | LD₅₀ (mg/kg) | Ref |
|--------------------------------|----------------------------------------|-------------|----------------|--------------------|---------------------------|---------|-------------|-----|
| *(27) Moringa stenopetala* Baker f. | Ethanol and aqueous extract, petroleum ether, butanol, and chloroform fraction of leaves | *In vitro*  | 300            | GL                 | ND                        | ↓ BGL for ethanol extract at 60, 180, and 240 mins \(P < 0.01\) and 120 mins \(P < 0.001\) in normoglycemic mice. ↓ BGL for aqueous and chloroform extracts at 120 \(P < 0.01\), 180 \(P < 0.05\), and 240 mins \(P < 0.05\). ↓ BGL \(P < 0.05\) for aqueous crude extract, butanol, and chloroform fraction starting from 180 mins. ↓ BGL for ethanol extract at 60 \(P < 0.05\) and 120, 180, and 240 mins \(P < 0.001\), ↓ BGL for aqueous extract at 120 mins \(P < 0.01\) and 180 and 240 mins \(P < 0.001\) 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. ↓ BGL for aqueous ethanol and n-butanol extracts 500 mg/kg \(P < 0.05\) in diabetic rats after 14 days. ↓ postprandial BGL for the extracts \(P < 0.001\) at the dose of 750 mg/kg. | >50 g/kg | [83] |
| Aqueous, ethanol extract, and n-butanol fraction of leaf | STZ-induced diabetic rats | 250, 500, and 750 | Metformin | Polyphenols, flavonoids, phenols, and flavonoids | ↓ BGL for the extracts \(P < 0.05\) with dose dependent manner. | ND | [67] |
| Maltodextrin (9%) and pectin (1%) leaves extract | STZ-induced diabetic mice models | 500, 750, and 1,000 | GL | ND | | >5,000 | [84] |
| Family/species | Plant crude extracts and fractions used | Models used | Dose(s) (mg/kg) BW | Standard drug used | Phytochemical constituents | Effects | LD$_{50}$ (mg/kg) | Ref |
|----------------|----------------------------------------|-------------|-------------------|-------------------|---------------------------|---------|------------------|-----|
| **Myrtaceae** | 70% ethanol crude extract and $n$-hexane, dichloromethane, $n$-butanol, and chromatographic fractions (1,2,3,4) of leaves | Alloxan-induced male diabetic mice | 500 GL | Flavonoids, phenolic compounds, phenolic, and glycosides | ↓ BGL ($P < 0.01$) with hexane fraction at 2 and 4h. ↓ BGL ($P < 0.01$) with dichloromethane fractionate after 2, 4, and 6 h. ↓ BGL with butanol fraction after 2 and 4 h ($P < 0.001$), with aqueous residue ($P < 0.01$) at 2 and 4 h ($P < 0.05$). ↓ BGL ($P < 0.01$) with fraction 2 and 3 after 3h/ ↓ BGL ($P < 0.05$) with fraction 1 at 6h. ↓ BGL ($P < 0.01$) with fraction 4 at 3h and ($P < 0.01$) at 4, 5, and 6h. Inhibited AGEs formation ($P < 0.05$) by 54.75 ± 0.94% at 2 mg/ml of the extract. ↓ concentration of fructosamine. ↓ Formation of N$\varepsilon$-(carboxymethyl) lysine (CML). ↓ Amount of amyloid cross $\beta$-structure. | No toxic reaction for 300 and 600 mg/kg in 13-week subchronic toxicity study | ND [85] |
| **(28) Myrtus communis L.** | Aqueous and methanolic extracts of leaves | Alloxan-induced diabetic mice | 500, 750, and 1000 GL | Polyphenols | ↓ BGL ($P < 0.05$) by 28.76% at 750 mg/kg dose level. ↓ BGL ($P < 0.05$) by 28.76% at 750 mg/kg dose level. ↓ BGL ($P < 0.05$) by 48% ($P < 0.00003$) at 1,000 mg/kg dose level. ↓ BGL ($P < 0.05$) by 28.76% at 750 mg/kg dose level. ↓ BGL ($P < 0.05$) by 48% ($P < 0.00003$) at 1,000 mg/kg dose level. ↓ BGL ($P < 0.05$) by 48% ($P < 0.00003$) at 1,000 mg/kg dose level. | >5,000 [87] |
| **(29) Psidium guajava L.** | Aqueous and ethanol extracts of leaves | Normoglycemic and STZ-induced diabetic mice | 250, 500, and 750 GL | Alkaloids, phenols, flavonoids, tannins, and saponins | ↓ 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 2nd h in diabetic mice. ↓ BGL by 100 mg/kg extract ($P < 0.01$) at 120 mins and 200 mg/kg ($P < 0.001$) at 60 mins in OGTT. | >5,000 [88] |
| **Resedaceae** | 80% methanolic leaf extract | Induction of diabetes by STZ and OGTT | 100, 200, and 300 GL | Saponins, flavonoids, and alkaloids | | >2,000 [89] |
| Family/species | Plant crude extracts and fractions used | Models used | Dose(s) (mg/kg) BW | Standard drug used | Phytochemical constituents | Effects | LD<sub>50</sub> (mg/kg) | Ref |
|----------------|----------------------------------------|-------------|-------------------|-------------------|---------------------------|---------|----------------|-----|
| (31) *Caylusea abyssinica* (Fresen.) Fisch. and Mey. | Methanol, chloroform, and aqueous fractions of leaves | Normoglycemic, OGTT, and STZ-induced diabetic rodents | 200 and 300 | Glibenclamide | Alkaloids, tannins, terpenoids, saponins, steroids, flavonoids, and glycosides | ↓ BGL by 55.37% (P < 0.05) and 59.54% (P < 0.001) within 2 h of OGTT by 200 and 300 mg/kg of methanol fraction, respectively. ↓ BGL by 80.24% (P < 0.001) and 81.05% (P < 0.001) with the same fraction and doses, respectively. ↓ BGL by 55.33% with 300 mg/kg aqueous fraction. | >2,000 [53] |
| Rosaceae (32) *Hagenia Abyssinica* (Bruce) J.F.Gmel. | 80% methanol flower crude extract and chloroform, water, and ethyl acetate fractions | Chromogenic DNSA | 25, 50, 100, 200, 400, and 800 μg/mL | Acarbose | Saponins, tannins, terpenoids, phenols, flavonoids, glycosides, steroids, and anthraquinones | Inhibited α-amylase activity by 54.23% with IC<sub>50</sub> 20.78 μg/mL at 800 μg/mL ethyl acetate fraction. Inhibited α-amylase activity with IC<sub>50</sub> 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. ↓ BGL (P < 0.05) at 400 mg/kg crude extract of single dose and ethyl acetate fraction at 8 h. ↓ BGL at 200 mg/kg crude extract and ethyl acetate fraction (P < 0.05, on the 7th and 14th days) and crude extract 400 mg/kg (P < 0.05 and P < 0.01, on the 7th and 14th days, respectively). ↓ BGL at 400 mg/kg ethyl acetate fraction (P < 0.01 and P < 0.001, on the 7th and 14th days, respectively). | >2,000 [35] |
| Family/species            | Plant crude extracts and fractions used                                                                 | Models used                               | Dose(s) (mg/kg) | Standard drug used | Phytochemical constituents                                                                 | Effects                                                                 | LD_{50} (mg/kg) | Ref       |
|--------------------------|----------------------------------------------------------------------------------------------------------|-------------------------------------------|-----------------|--------------------|-------------------------------------------------------------------------------------------|------------------------------------------------------------------------|-----------------|-----------|
| Rubiaceae (33) Pentas schimperiana (A. Rich.) | Hydroalcoholic and aqueous dried leaf extract and hydroalcoholic fresh leaf extract, chloroform, acetone, and methanol fractionation of leaves | Alloxan-induced diabetic mice             | 500 and 1,000   | GL                 | Flavonoids, saponins, steroids, and tannins                                               | ↓ BGL (P < .01) from 296.2 to 258.6 mg/dL on 3 h at 500 mg/kg of the fresh leaf hydroalcoholic extract. ↓ BGL (P < 0.01) from 283.2 to 227.6 mg/dL and from 264.6 to 213 mg/dL on 3 h at 500 mg/kg of each of the hydroalcoholic and the aqueous dried leaf extract, respectively. ↓ 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). ↓ BGL by 26.97%, 21.90%, and 26.70% at 1,000 mg/kg of each of the aqueous dried leaf, hydroalcoholic fresh, and dried leaf extracts, respectively. ↓ BGL by 23 and 27.2% at a dose of 500 mg/kg the aqueous and methanol fractions prepared from the dried plant material, respectively. Inhibited α-amylase activity by 80.10 ± 4.37% at 2.5 mg/mL acetone extracts followed by methanol 80% (63.70 ± 2.53%), water (62.78 ± 4.00%), methanol (58.66 ± 3.50%), and petroleum ether (51.34 ± 8.58%) extracts, respectively (P < 0.05). | >4,000          | [14]       |
| (34) Pentas schimperiana (A. Rich) | Aqueous dried leaf and hydroalcoholic fresh and dried leaf extracts, aqueous, and methanol fractions | Alloxan-induced diabetic mice             | 500 and 1,000   | GL                 | Saponins, flavonoids, steroids, and tannins                                               | ↓ BGL by 26.7%, 21.90%, and 26.70% at 1,000 mg/kg of each of the aqueous dried leaf, hydroalcoholic fresh, and dried leaf extracts, respectively. ↓ BGL by 23 and 27.2% at a dose of 500 mg/kg the aqueous and methanol fractions prepared from the dried plant material, respectively. Inhibited α-amylase activity by 80.10 ± 4.37% at 2.5 mg/mL acetone extracts followed by methanol 80% (63.70 ± 2.53%), water (62.78 ± 4.00%), methanol (58.66 ± 3.50%), and petroleum ether (51.34 ± 8.58%) extracts, respectively (P < 0.05). | >4,000          | [14]       |
| Solanaceae (35) Capsicum frutescens L. | Acetone, 80% methanol, water, methanol, and petroleum ether extract of green pepper chili paste | Chromogenic DNSA                          | 2.5 mg/mL       | Acarbose           | Phenols and flavonoids                                                                       | ND                                                                 | ND              | [90]      |
| Family/species | Plant crude extracts and fractions used | Models used | Dose(s) (mg/kg) | Standard drug used | Phytochemical constituents | Effects | LD$_{50}$ (mg/kg) | Ref |
|---------------|----------------------------------------|-------------|----------------|-------------------|----------------------------|---------|-----------------|-----|
| (36) *Datura stramonium* Linn. | Hydromethanolic seed extract | STZ-induced diabetic mice | 100, 200, and 400 | GL | Saponins, alkaloids, flavonoids, phenols, tannins, terpenoids, glycosides, and steroids | ↓BGL ($P < 0.05$) at $100\, \text{mg/kg}$ ($P < 0.01$) and $200\, \text{mg/kg}$ ($P < 0.01$). ↓BGL at all doses of extract on day 7 and 14. ↓BGL ($P < 0.05$) at doses of $200\, \text{mg/kg}$ extract. Improved BW of diabetic mice on day 7 and 14. ↓BGL at doses of $100\, \text{mg/kg}$ ($P < 0.05$) and $200\, \text{mg/kg}$ ($P < 0.05$) at 1 and 2h post OGTT mice. ↓BGL at doses of $100\, \text{mg/kg}$ ($P < 0.05$) and $200\, \text{mg/kg}$ ($P < 0.05$) at 1 and 2h post OGTT mice. ↓BGL at doses of $100\, \text{mg/kg}$ ($P < 0.05$) and $200\, \text{mg/kg}$ ($P < 0.05$) at 1 and 2h post OGTT mice. ↓BGL for aqueous and methanol extracts by 32.3 and 25.1% ($300\, \text{mg/kg}$), respectively, at 3h ($P < 0.01$). ↓BGL for aqueous and methanol fractions at a dose of $300\, \text{mg/kg}$ ($P < 0.01$). ↓BGL for aqueous fraction ($P < 0.01$) at the 3h ($100, 200$, and $300\, \text{mg/kg}$). | >2,000 | [43] |
| Urticaceae | Hydromethanolic root extract | Normoglycemic, OGTT, and STZ-induced diabetic mice | 100, 200, and 400 | GL | Flavonoids, phenols, tannins, alkaloids, steroids, glycosides, and anthraquinone | ↓BGL for aqueous and methanol extracts by 32.3 and 25.1% ($300\, \text{mg/kg}$), respectively, at 3h ($P < 0.01$). ↓BGL for aqueous and methanol fractions at a dose of $300\, \text{mg/kg}$ ($P < 0.01$). ↓BGL for aqueous fraction ($P < 0.01$) at the 3h ($100, 200$, and $300\, \text{mg/kg}$). | >2,000 | [38] |

Note. BGL: blood glucose level; BW: body weight; DNSA: 3,5-dinitrosalicylic acid; GL: glibenclamide; IC$_{50}$: inhibitory concentration; LD$_{50}$: lethal dose 50; ND: result not determined; OGTT: oral glucose tolerance test; $R_f$: retention factor; and STZ: streptozocin.
compounds that can act on multiple disease-related drug targets with proven long-term safety are needed for the treatment of DM. Natural products are promising lead candidates for discovering and also easily available, affordable, and tolerable [19, 25, 38]. Bioactive compounds that are obtained from various medicinal plant sources have been reported to have potent antidiabetic activity [38, 43, 46, 55–62, 67, 79, 82, 85, 86] through different mechanisms as we have discussed below in the text. The effect could act either individually and/or synergistically.

4.1. *Thymus schimperi* (*T. schimperi*) Ronniger (*Lamiaceae*). T. schimperi, locally known as Tosign in Amharic, is endemic to Ethiopia [46]. The antidiabetic activity of methanol extract plus butanol and the aqueous fraction of *T. schimperi* leaves were tested in both normal and STZ-induced diabetic mice. Significant reduction of BGL at all given doses was seen with methanolic crude extract in diabetic mice and was in a dose-dependent way (250 mg/kg (14.76 ± 6.1%), 500 mg/kg (25.12 ± 11.5%), and 750 mg/kg (27.15 ± 10%)). Percentage reduction of BGL was shown in n-butanol fraction at 500 mg/kg (36.7 ± 3.3%) and 250 mg/kg (22.2 ± 4.3%) doses. The aqueous fraction with the dose of 250 and 500 mg/kg also decreased the BGL by 17.6% ± 6.0% and 18.4 ± 5.0%, respectively [46].

Aqueous and 80% methanolic extracts of *T. schimperi* Ronniger leaves with the same dose 500 mg/kg indicated substantial reduction of BGL (*P < 0.05*) at 14 days in alloxan-induced diabetic mice. Significant reduction of BGL in 80% methanol 500 mg/kg (*P < 0.001*), aqueous 250 mg/kg, and 80% methanol extracts (*P < 0.05*) was also detected at 21 days [2]. Other investigations, α-amylase and glucosidase inhibitory assays, were conducted in 80% methanol and boiling water leaves extracts of *T. schimperi*. The α-amylase inhibitory activity at 2.5 mg/mL of the 80% methanol and boiling water extracts were 68.6 ± 5.9% (IC50 0.33 ± 0.05 mg/mL) and 48.7 ± 7.1% (IC50 2.24 ± 0.53 mg/mL) at *P < 0.05*, respectively. At the dose of 2.5 mg/mL, both hot water and 80% methanol extracts also revealed α-glucosidase inhibition activities 96.8 ± 10.5% (IC50 0.69 ± 0.04 mg/mL) and 84.4 ± 8.5% (IC50 0.05 ± 0.01 mg/mL) at *P < 0.05*, respectively [79]. Bioactive constituents that are obtained from *T. schimperi*, such as alkaloids, polyphenols [46], flavonoids [46, 79], tannins, saponins [46], terpenoids [2, 46], and phenols [79], have been reported to have potent BG-lowering potentials.

The results of the studies indicated the potential antihyperglycemic effect of the extract due to many explanations with these findings. The inhibition of α-amylase activity describes one of the treatment methods commonly used for the prevention and control of hyperglycemia in type 2 DM patients after food intake by dropping the absorption of glucose [2], which involved the delaying of postprandial hyperglycemia [2, 79]. This result agreed with other *in vitro* evaluations of the plants [35, 37, 41, 90]. The antidiabetic result of thymus plants is also due to α-glucosidase enzyme inhibitory effect and antioxidant activity *in vitro* of the plant [2, 79] in line with *in vitro* study of *T. vulgaris* 79. These α-amylase and α-glucosidase activities may be due to the presence of alkaloids [59, 61], triterpenoids [59, 60], tannins [35, 43], and flavonoids [49]. Furthermore, *T. schimperi* may prevent the destruction or regenerate the destroyed beta cells of the pancreas by the presence of different secondary constituents, triterpenoids [60], saponins [35, 46, 57, 58], tannins [43, 55, 56], flavonoids [38, 43, 49], and polyphenolic [2] and contribute to a significant BGL effect. Thus, the antidiabetic result of the *T. schimperi* extract may be associated with the existence of different secondary metabolites in plants. Therefore, these properties might be contributed to the clinical study of *T. schimperi* leaves extract.
4.2. *Moringa stenopetala* (M. stenopetala) Baker f. (Moringaceae). *M. stenopetala*, Shiferaw in Amharic, which is endemic to East African countries mainly located in southern parts of Ethiopia [67, 82] and northern Kenya [82]. The effects of aqueous extract and an isolated fraction of *M. stenopetala* leaves in normal and alloxan-induced mice models were examined by Mussa et al. [82]. Crude aqueous extract (except at 6h), chloroform, n-butanol, and aqueous residue fractions significantly (*P* < 0.05) reduced BGLs at all periods. N-butanol and aqueous residue fractions significantly (*P* < 0.005) decreased BGLs at 1.5 h of their administrations.

Ethanol and aqueous crude extracts, petroleum ether, chloroform, and butanol fractions of the leaf extracts of *M. stenopetala* were also tested in normoglycemic and alloxan-induced mice models. The ethanol extract significantly lowered BGL at 60, 180, and 240 mins (*P* < 0.01) and 120 mins (*P* < 0.001) of single dose in normoglycemic mice. Aqueous and chloroform extracts showed the same reduction of BGLs at 120 mins (*P* < 0.01), 180 mins (*P* < 0.05), and 240 mins (*P* < 0.05). Likewise, butanol fraction significantly (*P* < 0.05) decreased starting from 180 mins. The ethanol extracts significantly reduced BGL at 60 mins (*P* < 0.05) as well as 120, 180, and 240 mins (*P* < 0.001). Aqueous extract also reduced BGL significantly (*P* < 0.01) at 120, 180, and 240 mins (*P* < 0.001) of single dose in alloxan-induced diabetic mice. After administration of ethanol and aqueous extracts, significant reduction was resulted in BGL starting from the 3rd (*P* < 0.001) and on the 5th day (*P* < 0.01). Chloroform and butanol fractions showed meaningful changes on the 5th day (*P* < 0.01) and 8th day (*P* < 0.001) of repeated doses in alloxan-induced mice model [83].

According to another study, aqueous ethanol and n-butanol extracts of *M. stenopetala* leaves 500 mg/kg significantly decreased BGL (*P* < 0.05) in STZ-induced rat model after 14 days. The extracts also decreased postprandial BGL (*P* < 0.001) at 750 mg/kg dose [67]. The maltodextrin (9%) and pectin (1%) of leaves extract of *M. stenopetala* had also shown significant (*P* < 0.05) decrease in BGL with dose-dependent manner in the same model [84].

The antihyperglycemic activity of *M. stenopetala* was supported by leaves extraction and fractionation in alloxan-induced male diabetic mice. Significant BGL reduction (*P* < 0.01) was seen with hexane fraction at 2 and 4 h whereas dichloromethane fractionate was seen at 2, 4, and 6 h of administrations, respectively. Decreasing BGL with butanol fraction was exceedingly significant *P* < 0.001 at 2 and 4 h, while aqueous residue was very significant *P* < 0.01 at 2 h and *P* < 0.05 at 4 h of administrations. Chromatographic fraction 2 and 3 showed very significant BGL reduction (*P* < 0.01) at 3 h after administrations. Chromatographic fraction 1 reduced BGL significantly (*P* < 0.05) at 6 h after administration [85].

Another investigation was also done to describe the antiglycation effect of hydroalcoholic leaves extract in bovine serum albumin (BSA)/fructose method. The *M. stenopetala* leaves extract significantly (*P* < 0.05) inhibited advanced glycation end products (AGEs) formation by 54.75 ± 0.94% at 2 mg/ml. Besides, the extract decreased the concentration of fructosamine, formation of Ne-(carboxymethyl) lysine (CML), and the extent of amyloid cross-β-structure in fructose-induced BSA glycation test [86].

Alkaloids, saponins, glycoproteins, amino acids and proteins [82], polyphenols [67, 85, 86], flavonoids [67, 85], phenolic compounds, and glycosides [85] were the major findings that could also have antidiabetic potentials through different mechanisms as cited above. The previous study on the chemical composition of the leaves of *M. stenopetala* revealed the presence of rutin, 4-(4′-o-acetyl-a-L-rhamnopyranosyloxy)-benzyl isothiocyanate, 4-(4′-0-acetyl-a-L-rhamnosylxy)benzaldehyde, and O-(rhamnopyranosyloxy)-benzyl glucosinate [82, 85, 93].

The results of the findings indicate that the extracts of *M. stenopetala* produced potential antihyperglycemic effects due to various descriptions. It produced regeneration/proliferation of the pancreatic β-cells possibly due to the prevention of free radical formation [67, 84]. Antiglycation activities may be associated with the presence of a high amount of phytochemicals such as polyphenolic compounds in the plant materials. Aggregation of advanced glycation end products may result in pancreatic islet amyloidosis that causes the damage of β-cell and compromised insulin secretion. Hence, the extract suppressed the formation of amyloid cross-β structure of fructose-induced BSA. The antioxidant activity of the extract also contributes to anti-glycation activity [86]. These beneficial effects of the extract of *M. stenopetala* may ameliorate risks of degenerative diseases in diabetic patients. Therefore, due to these investigations, the extracts of *M. stenopetala* could be an attractive source of alternative treatment and for further clinical studies.

4.3. *Ajuga remota* Benth (A. remota) (Lamiaceae). *A. remota* grows widely in East Africa (different regions of Ethiopia) [78], Saudi Arabia, Yemen, and Afghanistan to East Asia [11, 77]. Different investigations validated the antidiabetic activity of *A. remota* Benth in alloxan diabetic mice [11, 77] and STZ-induced diabetic rats [78]. The fasting mean BGL of alloxan-induced mice model treated with aqueous leaves extract 300 and 500 mg/kg and ethanol extract 300 and 500 mg/kg was reduced by 27.96%, 38.98%, 28.09%, and 28.25%, respectively (*P* < 0.05) [11].

Another investigation showed the hypoglycemic effect of this plant in alloxan-induced mice model. Aqueous extract of leaves 300 and 500 mg/kg decreased BGL by 27.83 ± 2.96% and 38.98 ± 0.67% (*P* < 0.0001), respectively. Seventy percent ethanol extract 300 and 500 mg/kg also caused a reduction of 27.94 ± 0.94% at 2mg/ml and 38.98 ± 0.97% (*P* < 0.001) at 4mg/ml. The extract decreased fructosamine by 29.37 ± 0.96% and 38.98 ± 0.97% (*P* < 0.001) and 38.98 ± 0.97% (*P* < 0.001), respectively. The extract significantly reduced advanced glycation end products (AGEs) by 54.75 ± 0.94% at 2mg/ml [86].

Assefa et al. [78] showed the ethanolic leaves extract of *A. remota* can have a hypoglycemic effect in the STZ-induced rat model. The dose of 200 and 400 mg/kg ethanol leaves extract significantly decreased (*P* < 0.05) fasting BGL on the 21st and 14th day of treatment, respectively. Steroids, phenols, flavonoids [11, 77, 78], tannins [11, 77], saponins,
The mechanism of antidiabetic effects of the extracts of
A. remota leaves might be due to the presence of well-known antioxidant phytochemicals such as flavonoids, polyphenols, tannins [11, 43, 55, 56], and triterpenoids [60–62], which acts as free radical scavengers. The presumed mechanism of action of these antioxidants was because of an insulin-mimetic effect on the peripheral tissues by either stimulation of regeneration process or release of pancreatic secretion of insulin from existing β-cells [11, 78]. The activities also might be due to inhibition activity against α-glucosidase enzymes in the small intestine [78]. Thus, the significant antidiabetic effect of the extracts of A. remota could be due to the presence of these properties in the extracts, which could act synergistically and/or independently to enhance the activity of glycolytic enzymes.

4.4. Datura stramonium (D. stramonium) Linn. (Solanaeae). D. stramonium is widely distributed throughout the world, including Ethiopia [43]. Belayneh et al. [38] and Melaku and Getnet [43] stated the hypoglycemic activity of hydromethanolic root and seed extracts of D. stramonium, respectively, in animal models. The hydromethanolic root extracts of D. stramonium at doses 100 and 200 400 mg/kg (P < 0.05) and 400 mg/kg (P < 0.01) meaningfully decreased BGL at 1 and 2 h postprandial glucose test. The 100 and 200 400 mg/kg (P < 0.05 on day 7 and 14, respectively) and 400 mg/kg (P < 0.05 on day 7 and P < 0.01 on day 14) significantly decreased BGL in STZ-induced mice model [38].

The administration of hydromethanolic seed extract from D. stramonium significantly reduced BGL (P < 0.05 at dose of 100 mg/kg and P < 0.01 at doses of 200 and 400 mg/kg) in STZ-induced diabetic mice. At all strengths of seed extract significantly (P < 0.01) decreased BGL on 7th and 14th day. Seed extract at doses of 200 and 400 mg/kg also meaningfully (P < 0.05) ameliorated body weight of diabetic mice on these days [43].

Flavonoids, phenols, tannins, steroids, glycosides, alkaloids [38, 43], anthraquinones [38], saponins, and terpenoids [43] are also reported which could have antidiabetic activities.

Hydromethanolic root extract showed significant anti-hyperglycemic activities possibly due to pancreatic β-cell regeneration or protective effects due to their antioxidant activities [38]. This was revealed by different studies of plant extracts [11, 35, 78, 98]. Leaf extract of in vitro study of this plant supported this activity [99] Crude aqueous leaf extract and methanolic seed extract of D. stramonium possess in vitro α-amylase enzyme inhibitory activity suggesting the plant to be a potential candidate for DM [43, 100, 101]. Significant improvement in body weight by the plant extract might have protective effects against protein catabolism and muscle wasting possibly due to the enhancement of insulin secretion and/or action [38]. Additionally, the plant extract may have a direct effect on lipid absorption and metabolism that can lead to the improvement of diabetic dyslipidemia [38, 102]; hence, augmenting insulin secretion and/or action is a potential approach to treat this disorder [38]. Therefore, extracts from plant material of D. stramonium have the potential antidiabetic activities, which can be the indication for further clinical investigation.

4.5. Clinical Studies of Trigonella foenum-graecum L. (Fenugreek). Trigonella foenum-graecum is a useful MP belonging to the family Fabaceae distributed throughout the world including Ethiopia [103]. T. foenum-graecum seed powder solution (by the administration of 25 mg for 30 consecutive days) significantly improved dyslipidemia in newly diagnosed type II diabetic patients as dyslipidemia is common in type 2 diabetes, as both insulin deficiency and resistance affect enzymes and pathways of lipid metabolism [103]. Disturbances of lipid metabolism appear to be an early event in the development of type 2 diabetes [104]. It showed significantly (P < 0.001) lower total cholesterol level by 13.6% as compared with the baseline level and the control group. Triglyceride level also reduced by 23.53% compared with the baseline level (P < 0.001) and compared with the control group (P < 0.05). Low-density lipoprotein cholesterol level also reduced by 23.4% as compared to the baseline level (P < 0.001) and the control group (P < 0.001), but the treatment group showed significantly increased high-density lipoprotein cholesterol level by 21.7% as compared to the baseline level, within group (P < 0.001), and the control group, between groups (P < 0.001). Therefore, the seed powder solution showed a significant reduction in total cholesterol, low-density lipoprotein cholesterol, and triglycerides levels and an increase in high-density lipoprotein cholesterol level. Hence, it had pronounced effects in improving lipid metabolism in type II diabetic patients with no adverse effects [103]. Different clinical trials have shown that plants cause significant antidiabetic and antisyndrome activities in humans [105–108]. Therefore, T. foenum-graecum seed may provide new alternatives for the clinical management of type II diabetes.

5. Limitations of the Study

Even if we used all previous findings that were done in Ethiopia, there are some limitations that might limit the results of this work. The methodological quality (alloxan or STZ induction method induces mostly type 1 DM), which
Methodological quality could be a challenge since there might exist an overlap between type 1 and type 2 DM during diabetic induction with alloxan or STZ. Use of terminology when searching evidence might be the other limitation.

6. Conclusion and Perspectives

Medicinal plants have provided clinically beneficial sources of antidiabetic medicines. Due to the rising of multidrug-resistant DM, adverse drug reactions, and toxicities of currently available conventional drugs, TMs might be indispensable, inexpensive, and alternative potential sources of therapy. Therefore, an urgent need for the development of novel medicines in treating DM is required. Using confirmed investigation systems, the potential of MPs to produce new antidiabetic medicines has been supported with in vitro and in vivo studies in Ethiopia, as shown in this paper. Biological investigation of MPs used traditionally in primary health care is among evidences in which searching for new leading compounds should focus on. Preliminary phytochemical constituents and toxicity profiles of MPs have also been evaluated to some extent to assure their safety profiles even though they need further investigations. Hence, it is crucial to identify their active constituents and validate the efficacy and safety of MPs. Studying the effects of unexplored MP species on DM, isolating the active substances, evaluating the possible mechanisms of actions of extracts to obtain further data on the pharmacological and clinical effects, and exploring additional new lead compounds and drugs for the treatment of DM are also needed in more detail.

Consequently, this paper provides baseline data to other researchers of MPs that have the potential BGL-lowering effects and scientific knowledge in Ethiopia. Further investigations for antidiabetic medicines discovery and development should also focus on pharmacokinetic profiles of the promising candidates studied so far in the area.

Towards the assessments of other beneficial properties of these MPs in DM treatment should be directed. The development of more effective, reasonably priced, and standardized phytopharmaceuticals in close cooperation with clinicians and industries would also be advisable. Therefore, extracts from the leaves of T. schimperi Ronniger (Lamiaceae), M. stenopetala Baker f. (Moringaceae), and A. remota Benth (Lamiaceae) and root and seed of D. stramonium Linn. (Solanaceae), which were mostly investigated in treating DM in Ethiopia might comprise interesting samples for development of new drugs. Besides, more pharmacological (pharmacodynamic and pharmacokinetic parameters) and toxicological investigations should be pursued to validate the safety of these MPs’ source constituents. Finally, we recommend upcoming researches to ensure future success in the clinical studies and development of novel medicines for DM treatment from these commonly evaluated MPs.

Abbreviations

| Abbreviation | Full Form |
|--------------|-----------|
| BGL: | blood glucose level |
| cAMP: | cyclic adenosine monophosphate |
| CML: | Nε-(carboxymethyl) lysine |
| DM: | diabetes mellitus |
| GLP-1: | glucagon-like peptide 1 |
| GLUT-2: | glucose transporter 2 |
| GLUT-4: | glucose transporter 4 |
| IC50: | inhibitory concentration |
| LD50: | lethal dose 50 |
| MP: | medicinal plants |
| SGLT-2: | sodium-glucose cotransporter 2 |
| STZ: | streptozocin |
| WHO: | World Health Organization |

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors’ Contributions

Both the authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave the final approval of the version to be published; and agreed to be accountable for all aspects of the work.

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