Potential antidiabetic phytochemicals in plant roots: a review of in vivo studies

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Received: 28 February 2021 / Accepted: 3 July 2021 / Published online: 12 July 2021
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Abstract

Background  Medicinal plants are used to treat various disorders, including diabetes, globally in a range of formulations. While attention has mainly been on the aerial plant parts, there are only a few review studies to date that are focused on the natural constituents present in the plant roots with health benefits. Thus, the present study was performed to review in vivo studies investigating the antidiabetic potential of the natural compounds in plant roots.

Methods  We sorted relevant data in 2001–2019 from scientific databases and search engines, including Web of Knowledge, PubMed, ScienceDirect, Medline, Reaxys, and Google Scholar. The class of phytochemicals, plant families, major compounds, active constituents, effective dosages, type of extracts, time of experiments, and type of diabetic induction were described.

Results  In our literature review, we found 104 plants with determined antidiabetic activity in their root extracts. The biosynthesis pathways and mechanism of actions of the most frequent class of compounds were also proposed. The results of this review indicated that flavonoids, phenolic compounds, alkaloids, and phytosteroids are the most abundant natural compounds in plant roots with antidiabetic activity. Phytochemicals in plant roots possess different mechanisms of action to control diabetes, including inhibition of α-amylase and α-glucosidase enzymes, oxidative stress reduction, secretion of insulin, improvement of diabetic retinopathy/nephropathy, slow the starch digestion, and contribution against hyperglycemia.

Conclusion  This review concludes that plant roots are a promising source of bioactive compounds which can be explored to develop against diabetes and diabetes-related complications.

Keywords  Diabetes · Medicinal plant · Natural product · α-glucosidase · Phytochemical · In vivo

Introduction

A recent analysis of the prevalence of diabetes mellitus, with type 2 diabetes (T2D) being the dominant form, estimated 4.2 million deaths worldwide due to diabetes in 2019. The direct medical cost for treatment of this metabolic disorder was estimated at 760 billion U.S. dollars, corresponding to 10% of the total health care expenses [1]. The common risk factors for developing T2D are obesity and lacking exercise. With a worldwide general obesity epidemic, the projected numbers of individuals with T2D are expected to increase dramatically from 463 million in 2019 to 700 million in 2045, highlighting the need for efficient drugs for managing T2D [1]. Weight-reduction and lifestyle improvements, such as the increase in physical activity and intake of functional foods (i.e., foods with health-promoting effects beyond their nutritional values), are effective methods for controlling blood glucose levels, alleviating some of the T2D complications [2, 3]. Pharmaceutical methods for the treatment of T2D include metformin, which can reduce 30% of the T2D progression even without lifestyle changes, at the cost of possible side effects such as vitamin B12 deficiency [2, 4]. Generally, T2D is manifested by decreased insulin-stimulated glucose uptake by the skeletal muscles.
The resulting low peripheral glucose disposition and high hepatic glucose production are primary contributors to diabetic hyperglycemia, leading to micro- and macro-vascular complications, including retinopathy, neuropathy, nephropathy, cardiovascular disease, stroke, and amputations [5–8]. The existing clinical agents targeting these complications, such as acarbose, voglibose, and miglitol, are associated with gastrointestinal side effects such as nausea, constipation, and diarrhea due to the nature of their mechanism of action [9]. Thus, alternative agents with fewer side effects, such as natural products derived from plants and microorganisms, are in demand for future T2D management. In addition, the increased incidence of diabetes calls for the development of useful and novel therapy procedures. Plant-based remedies, in the forms of teas, capsules, extracts, or isolated phytochemicals, are commonly used as complementary therapies to control T2D complications [10]. Different plant parts often exhibit distinctive chemical profiles contributing to antidiabetic bioactivities. Alkaloids, flavonoids, phytosteroids, and phenols are the most abundant compound classes with demonstrated antidiabetic effects in plant roots [11, 12].

Plants have always been an outstanding source of food, drug, and recent numbers show that more than 45% of all approved drugs from 1981 to 2019 are of natural origin or mimics thereof [13]. With accelerated improvements in novel analytical techniques [14, 15] and an increase in the number of studies on natural products with antidiabetic bioactivity, a range of new compounds from various unique plants has been found to possess antidiabetic activities [16]. While existing reviews predominantly focus on the antidiabetic bioactivity of the aerial plant parts, there is limited knowledge of in vivo antidiabetic effects of natural constituents present in the plant roots and rhizomes.

Thus, the main aim of this review was to summarize the potential antidiabetic natural products in plant roots and rhizomes with emphasis on in vivo effects.

**Methods**

To build and collect data for this review, several databases and search engines, including Web of Knowledge, PubMed, Science Direct, Medline, Reaxys, and Google Scholar were used. The used keywords were included: “medicinal plant roots”, “antidiabetic natural products”, “diabetic rats”, “in vivo studies”, and “herbal medicine”. In vitro studies and investigations that did not concern root and rhizomes were excluded. The search was limited to studies in English, and the dates of the studies ranged from 2001 to 2019.

**Results and discussion**

In the past decades, people have used different parts of medicinal plants as antidiabetic remedies. Recently, several traditional plant-based treatments have been reported to manage diabetes, according to in vitro, in vivo, and clinical investigations. Plant roots contain a diverse range of phytochemicals such as flavonoids, phenols, alkaloids, tannins, phytosterol, and saponins [17], with studies showing that some compounds are being uniquely biosynthesized in the root system [18–20].

From the literature review, a total of 104 plant species from 56 families were found to contain antidiabetic compounds in their roots and rhizomes (Table 1). The most frequent plant families which were reported in the reviewed studies were Fabaceae, Araliaceae, Asparagaceae, Asteraceae, and Zingiberaceae, respectively. While not all reviewed studies report the chemical constituents or bioactive compounds, the results showed that flavonoids and phenols, alkaloids, phytosteroids, saponins, tannins, terpenoids, anthraquinones, and cardiac glycosides were the most abundant bioactive components in plant roots and rhizomes (Fig. 1) as described in detail below. In the reviewed studies, a range of solvents was used for the extraction of natural constituents. The most common were ethanol (28%), water (27%), and methanol (22%). The time of experiments varied among the studies from 2 h to 120 days. Therefore, we categorized the time of experiments into two categories: short time (less than one day) and long-time experiments (more than one day). The results showed that 17% of the experiments were performed within a day (short time), while 83% of the experiments were performed in more than one day (long time). The average time of the two categories were 5 h and 25 days, respectively (Fig. 2).

**Phenols and flavonoids**

Phenols constitute the largest group of natural products, with a chemical structure consisting of an aromatic ring and a hydroxyl group ($C_6H_4OH$). Within this group, flavonoids, which can be sub-categorized into flavonols, flavones, flavan-3-ols, anthocyanidins, flavanones, and isoflavones, are the largest subgroup [12]. Generally, flowers, fruits, leaves, and seeds are rich in phenols and flavonoids. However, studies have also reported phenols and flavonoids as the major chemical constituents in plant roots [125, 126]. Phenols and flavonoids are synthesized through the phenylpropanoid pathway, transforming L-phenylalanine by phenylalanine ammonia lyase or L-tyrosine by tyrosine ammonia lyase into p-coumaroyl-CoA, which eventually enter the phenol and flavonoid biosynthesis pathway (Fig. 3). Studies have shown plant-derived
| Scientific name                  | Common name              | Family          | Major chemical constituents                                      | Bioactive compound                  | Extract type     | Dose (mg/kg) | Effective dose (mg/kg) | Time (days) | Induction of diabetes | Experimental animals | References |
|----------------------------------|--------------------------|-----------------|-----------------------------------------------------------------|-------------------------------------|-----------------|--------------|----------------------|-------------|------------------------|----------------------|------------|
| Acanthus ilicifolius             | Sea holly                | Acanthaceae     | Flavonoids, alkaloids, terpenoids, tannins, phytosteroids       | -                                   | Ethanolic       | 200, 400     | ≥200                 | 14          | Alloxan                | Male albino Wistar rats | [21]       |
| Acorus calamus L.                | Sweet flag or calamus    | Acoraceae       | -                                                               | -                                   | Ethyl acetate   | 100          | 100                  | 28 for STZ induced and 35 for db/db | -          | Streptozotocin         | Male mice           | [22]       |
| Actinidia kolomikta (Maxim. et Rur.) Maxim | Variegated kiwi vine     | Actinidaceae    | Polyphenols                                                     | -                                   | Ethanolic       | 300          | 300                  | 0.1         | -                      | Male Sprague–Dawley rats | [23]       |
| Aerva lanata (L.) Juss. ex Schult. | Knotgrass                | Amaranthaceae   | Alkaloids                                                       | Canthin-6-one derivatives           | Methanolic      | 10, 20       | -                    | 15          | Streptozotocin-nicotinamide | Male–female Wistar albino rats | [24]       |
| Alpinia calcarata                | Snap ginger or cardamom ginger | Zingiberaceae | -                                                               | -                                   | Ethanolic       | 200          | 200                  | 30          | Streptozotocin         | Albino rats         | [25]       |
| Alpinia galanga L.               | Greater galangal         | Zingiberaceae   | Alkaloids, saponins, glycosides, flavonoids, phytosteroids, terpenoids | -                                   | Ethanolic       | 200, 400     | ≥200                 | 21          | -                      | Wistar rats          | [26]       |
| Aneacyclus pyrithrum DC          | Pelliory or Akarkara     | Asclepiadaceae  | Flavonoids                                                     | -                                   | Aqueous         | 150, 300     | ≥150                 | 0.1         | Alloxan                | Albino wistar rats    | [27]       |
| Andrographis paniculata (Burm. f.) Nees | Creat or Green chirera | Acanthaceae     | -                                                               | -                                   | Choloroform     | 50, 100, 150 | 250                 | 1           | Allloxan               | Sprague–Dawley rats  | [28]       |
| Anemarrhena asphodeoxide Bunge   | Zhi Mu                   | Aspargaceae     | -                                                               | Mangiferin, mangiferin-7-Oβ-D-glucoside | Aqueous         | 90           | 90                   | 0.3         | -                      | Swiss albino mice and rats | [29]       |
| Anthocleista dyssemens A. Chevalier | Tagare, foreta lafira   | Loganiaceae     | Flavonoids, saponins, tannins, cardiac glycosides, anthraquinones | -                                   | Ethanolic       | 37, 74, 111  | ≥37                  | 14          | Allloxan               | Swiss albino mice and rats | [30]       |
| Anthocleista vogeli (Planch.)    | Cabbage tree             | Gentianaceae    | Flavonoids, terpenes, phenols, lipids, alkaloids, fatty acids  | Quebrachitol, loganin, sweroside, oleside 11-methyl ester and fatty acid | Methanolic, chloroform | 100,2000    | -                    | (acute study)0.1 day study)21 days | Allloxan   | Streptozotocin         | Male Sprague–Dawley rats | [31]       |
| Aporosa lindleyana (wt.) Bail     | Kotili                   | Euphorbiaceae   | -                                                               | -                                   | Alcoholic       | 100          | -                    | 0.1         | Allloxan               | Male Albino wistar Rats | [32]       |
| Aralia elata                     | Angelica-tree,Taranoki   | Araliaceae      | -                                                               | -                                   | Aqueous         | 125           | -                    | 0.1         | -                      | Male ddw mice        | [33]       |
| Aralia tai-baensis               | Spikenard                | Araliaceae      | Triterpenoids, saponins                                        | 28-O-β-D-glucopyranosyl ester       | Alcoholic       | 75,150,300   | ≥75                  | 28          | Streptozotocin         | Male Albino wistar rats | [34]       |
| Artocarpus communis              | Breadfruit,Gbere         | Moraceae        | -                                                               | -                                   | Aqueous         | 100           | 100                  | 7           | Streptozotocin         | Wistar rats           | [35]       |
| Asparagus racemosus (Wild)       | Shatavari                | Aspargaceae     | -                                                               | -                                   | Ethanolic       | 200, 400     | ≥200                 | 21          | Streptozotocin         | Wistar rats           | [36]       |
| Scientific name                      | Common name | Family       | Major chemical constituents                                                                 | Bioactive compound                              | Extract type | Dose (mg/kg) | Effective dose (mg/kg) | Time (days) | Induction of diabetes | Experimental animals | References |
|--------------------------------------|-------------|--------------|---------------------------------------------------------------------------------------------|-------------------------------------------------|--------------|--------------|------------------------|--------------|-----------------------|----------------------|------------|
| Atractylodes japonica Koidz          | Japanese atractylodes | Asteraceae | -                                                                                           | -                                               | -            | 100          | 100                    | 28           | High fat diet and Streptozotocin | Sprague-Dawley rats | [37]       |
| Azadirachta indica A.Juss             | Neem        | Meliaceae    | -                                                                                           | -                                               | Alcoholic    | 200, 400, 800 | 800                    | 15           | Alloxan               | Albinor wistar rats | [38]       |
| Berberis aristata DC                 | Daruhiudra   | Berberidaceae | - Berberine, berhamine, palmatine                                                           | Aqueous, Ethanol                                | -            | 250          | -                      | 21           | Alloxan               | Male albino wistar rats | [39]       |
| Berberis hyrcan Royce                | Indian barberry | Berberidaceae | -                                                                                           | Aqueous, Ethanol                                | -            | 50, 100      | ≥50                    | 5            | Alloxan               | Wistar rats          | [40]       |
| Berberis vulgaris L                  | Barberry     | Berberidaceae | Tannins, alkaloids, saponins, phytosteroids, anthraquinones                                 | -                                               | Aqueous      | 25           | 25                     | 21           | Streptozotocin         | Male Wistar rats     | [41]       |
| Boerhavia diffusa                    | Punarnava, spreading hogweed, tarvine | Nyctaginaceae | Phenols, flavonoids                                                                          | Gallic acid, quercitin                          | Methanolic   | 200          | 2600                   | 35           | Streptozotocin         | Male Wistar rats     | [42]       |
| Brassica rapa                        | Turnip       | Brassicaceae | Flavonoids, polyphenols                                                                      | -                                               | Ethanol      | 2600         | 2600                   | -            | -                     | DBB mice             | [43]       |
| Bruguiera gymnorrhiza L              | Black mangrove or afrikaans | Rhizophoraceae | Alkaloids, phytosteroids, saponins                                                           | -                                               | Ethanol      | 400          | 400                    | 21           | Streptozotocin         | Male Wistar rats     | [44]       |
| Caesalpinia digyna Rottler           | Teri pods or udakiriyaka | Fabaceae | - Bergenin                                                                                 | Ethanol                                         | 2.5, 5, 10  | 10           | 14                     |              | Streptozotocin-Nicotinamide | Male albino rats | [45]       |
| Cajanus cajan L                      | Ashrat(Pigeon pea) | Fabaceae | Phenols                                                                                    | Methanolic                                      | 200          | ≥200         | 5                      |              | Alloxan               | Swiss albino mice    | [46]       |
| Cassia angustifolia (Roxb.)          | Kadala hujji,l, wild cowrie fruit, sapitangi | Flacourtiaceae | -                                                                                           | Aqueous                                         | 200,300      | 45           | -                      |              | Streptozotocin         | Male albino rats     | [47]       |
| Celastrus pentandra L                | Silk cotton tree | Sterculiaceae | -                                                                                           | Ethanol                                         | 300          | 300          | 30                     |              | alloxan               | Male Wistar rats     | [48]       |
| Cichorium intybus                    | Chicory      | Asteraceae   | Imulin, lipids, alkaloids, glycosides, tannins                                             | Methanolic                                      | 400          | 400          | 21                     |              | Streptozotocin         | Male, Wistar rats     | [49]       |
| Citrullus colocynthis                | Bitter cucumber, Bitter apple, ogusi | Cucurbitaceae | Glycosides, saponins, triterpenoids, alkaloids, flavonoids, resins                         | Aqueous                                         | 200          | 200          | 7                      |              | Alloxan               | Male Wistar rats     | [50]       |
| Clausena anisata (Willd) Hook        | Isifudu      | Rutaceae     | -                                                                                           | Methanolic                                      | 100-800      | ≥800         | -                      | Streptozotocin     | Male Wistar rats     |                     | [51]       |
| Coptis chinensis Franch              | Goldthread   | Ranunculaceae | Alkaloids                                                                                  | Berberine, palmatine, jatrohine                 | Aqueous      | 125,250,500 | ≥125                   | 21           | Streptozotocin         | Male Wistar rats     | [52]       |
| Scientific name          | Common name          | Family         | Major chemical constituents | Bioactive compound | Extract type | Dose (mg/kg) | Effective dose (mg/kg) | Time (days) | Induction of diabetes | Experimental animals | References |
|--------------------------|----------------------|----------------|-----------------------------|--------------------|--------------|--------------|------------------------|--------------|-----------------------|----------------------|-----------|
| *Costus speciosus* (Koen.) Sm | Crepe ginger       | Costaceae      | -                           | -                  | Hexane       | 250          | 250                    | 60           | Streptozotocin         | Wistar rats [53]     |
| *Curculegio orchisodes* Gaertn | Talamuli, musali, nilapanai | Hypoxidaceae | -                           | -                  | Ethanolic    | 500, 1000    | ≥500                   | 21           | Alloxan                | Swiss albino mice [54] |
| *Curcuma aromatica* | Turmeric             | Zingiberaceae  | Phenols, flavonoids, flavonols | -                  | Methanol     | 200, 400     | ≥200                   | 21           | Streptozotocin         | Wister albino rats [55] |
| *Curcuma longa*          | Turmeric             | Zingiberaceae  | -                           | -                  | Aqueous      | 400          | 400                    | 28           | Alloxan                | Albino rats [56]     |
| *Cyperus rotundus* L     | Mustaka              | Cyperaceae     | -                           | -                  | Ethanolic    | 250, 500     | ≥250                   | 21           | Streptozotocin         | Swiss albino mice [57] |
| *Datura stramonium* L    | Jimsonweed           | Solanaceae     | Flavonoids, phenols, tannins, alkaloids, phytosteroids, glycosides, and anthraquinones | -                  | Methanolic   | 100, 200, 400 | ≥100                   | 14           | Streptozotocin         | Swiss albino mice [58] |
| * Dioscorea dumetorum* Pax | Bitter yam or cluster yam | Dioscoreaceae | Flavonoids, alkaloids, sapo- nins, cardiac glycosides | -                  | Aqueous      | 400          | 400                    | 7            | Alloxan                | Albino Wistar rats [59] |
| *Elephantopus scaber*    | Elephant’s foot      | Asteraceae     | -                           | -                  | Methanolic   | 250          | -                      | 60           | Streptozotocin         | Male Albino Wistar rats [60] |
| *Euclea undulata* Thumb var. myrtina | Guari | Ebenaceae     | -                           | -                  | Acetone      | 50, 100      | 100                    | 21           | Streptozotocin-nicotinamide | Male Wistar rats [61] |
| *Glycyrrhiza globra*     | Licorice             | Fabaceae       | -                           | -                  | Methanolic   | 100, 200, 300 | ≥200                   | 0.1          | Streptozotocin         | Albino rats [62]     |
| *Glycyrrhiza urundensis* Fisch | Licorice             | Fabaceae       | Glycyrrhizin, glycyrrhetinic acid | Ethanol            | 1           | 1           | 56                     | -            | -                     | Male C57BL6 mice [63] |
| *Gmelina asiatica* L    | Nilakkumil or gopabhandra | Verbenaceae   | -                           | -                  | Alcoholic    | 100, 250, 500 | ≥100                   | 16 h         | Alloxan                | Spangie Dawley rats [64] |
| *Gynandropsis gynandra* | Shona cabbage or African cabbage | Capparidaceae | Flavonoids, phenolic com- pounds, glycosides, phytosteroids, phenolic | -                  | Aqueous      | 100, 200, 400 | ≥100                   | 0.7          | Streptozotocin         | Albino rats [65]     |
| *Harpagophytum procumbens* DC | Devil’s claw or grapple plant | Pedaliaceae | -                           | -                  | Aqueous      | 50, 100, 200, 400 | -                      | 0.3          | Streptozotocin         | Wistar rat [66]     |
| *Helicteres inora* L    | Screw tree           | Sterculiaceae  | Triterpenoidal glycosides | -                  | Butanolic    | 250          | 250                    | 10           | Alloxan                | Male Wistar rats [67] |
| Scientific name                | Common name          | Family         | Major chemical constituents                                      | Bioactive compound | Extract type | Dose (mg/kg) | Effective dose (mg/kg) | Time (days) | Induction of diabetes | Experimental animals | References |
|-------------------------------|----------------------|----------------|-----------------------------------------------------------------|---------------------|--------------|--------------|------------------------|--------------|------------------------|----------------------|------------|
| Hemidesmus indicus R.Br       | Indian sarsaparilla  | Asclepiadaceae | Flavonoids, alkaloids, saponins, triterpenoids, tannins, phytosteroids | -                   | Ethanolic    | 250          | 250                    |             | Streptozotocin          | Albino Wistar rat    | [68]       |
| Ibibilia sonora               | Variegated           | Cucurbitaceae  | Phenols, phytosteroids                                          | -                   | Dichlormethane, methanolic | 300, 600     | ≥300                   | 41           |                        |                      | [69]       |
| Ichnoscarpus frutescens        | (L.) R.Br            | Apocynaceae    | -                                                               | -                   | Aqueous      | 250, 500     | ≥2.50                  | 15           | Streptozotocin          | Male albino Wistar rats | [70]       |
| Ipomoea batatas L             | Sweet potato         | Convolvulaceae | -                                                               | -                   | Ethanol      | 100          | 100                    | 6            |                        | Male Wistar rats     | [71]       |
| Justicia adhatoda L           | Malabar nut          | Acanthaceae    | -                                                               | -                   | Aqueous      | 100, 200     | ≥100                   | 28 (FBS)     | Streptozotocin          | Male BABL/c mice      | [72]       |
| Liriope spicata var. prolifera | Creeping lilyturf & monkey grass | Liliaceae | -                                                               | -                   | Aqueous      | 80, 160      | - (in serum)           | 14 (OGTT)    |                        |                      | [73]       |
| Lucii radices or Lycium chinense Miller | Goji berry or wolfberry | Solanaceae | -                                                               | -                   | Aqueous      | 50, 100, 150 | ≥50                    | 21           | Streptozotocin          | Male albino Wistar rats | [74]       |
| Merremia tridentata (L.) Hall F | Madiakumthul or savoolik, Thrippamulpo | Convolvulaceae | -                                                               | -                   | Aqueous      | 500          | 800                    |             | Streptozotocin          | Male albino Wistar rats | [75]       |
| Mimosa pudica                 | Sensitive plant, humble plant, Lajwanti | Fabaceae | -                                                               | -                   | Aqueous      | 2, 4, 6      | 6                      | 20           |                        | Albino rabbits       | [76]       |
| Morus alba L                  | Mulberry tree        | Moraceae       | Flavonoids, terpenoids                                         | Morusin, cyclomorusin, neocylostomusin, kwason E, 2-aryl-benzofuran, moracin M betulonic acid, methyl ursolate | Ethanol       | 200,400,600 | 600                    | 10           | Streptozotocin          | Male Wistar rats     | [77]       |
| Musa paradisiaca L            | Banana                | Musaceae       | -                                                               | -                   | Methanolic   | 800          | 800                    | 14           | Streptozotocin          | Male albino rats      | [78]       |
| Nauclea latifolia Sm           | Pin cushion tree     | Rubiaceae      | Tannins, saponins, alkaloids, terpenes, cardiac glycosides, flavonoids, anthraquinones | -                   | Ethanol      | 150, 300, 450 | ≥4.50                  | 14           |                        | Swiss albino mice and rats | [79]       |
| Nicotiana arbor-tristis L     | Harsinghar or night jasmine | Oleaceae | -                                                               | -                   | Methanolic   | 250, 500     | ≥500                   | 0.1          |                        | Male albino Wistar rats | [80]       |
| Nymphaea alba                  | White water rose or white nenuphar | Nymphaeaceae | Glycosides, alkaloids, phenols, tannins, flavonoids, saponins, terpenoids, phytosteroids | -                   | Ethanol      | 200, 400     | ≥500                   | 13           |                        | Albino rats          | [81, 82]   |
| Nymphaea palustris            | Red water lily        | Nymphaeaceae   | Alkaloids, flavonoids, glycosides, terpenoids, tannins, phenols, saponins, phytosteroids | -                   | Ethanol      | 200, 500     | ≥200                   | 14           |                        | Albino Wistar rats   | [83]       |
| Scientific name                  | Common name                        | Family               | Major chemical constituents                                      | Bioactive compound                              | Extract type | Dose (mg/kg) | Effective dose (mg/kg) | Time (days) | Induction of diabetes | Experimental animals | References |
|----------------------------------|------------------------------------|----------------------|-----------------------------------------------------------------|-------------------------------------------------|--------------|--------------|------------------------|--------------|------------------------|-----------------------|------------|
| Ophiopogon japonicus             | Mondo grass                        | Asparagaceae         | Polysaccharides                                                 | -                                               | Aqueous      | 300          | 300                    | 56           | -                      | KK/Ay mouse           | [84]       |
| Panax ginseng                    | Ginseng                            | Araliaceae           | Ginsenosides                                                    | -                                               | Ethanol      | 150          | 150                    | 12           | -                      | Ob/ob Mice            | [85]       |
| Panax notoginseng                | Chinese ginseng or notoginseng     | Araliaceae           | Saponins, Ginsenosides                                          | -                                               | Ethanol      | 50, 200      | ≥50                    | 30           | -                      | Male kk/Ay mice       | [86]       |
| Panax quinquefolius              | American ginseng                    | Araliaceae           | Ginsenosides                                                    | -                                               | Alcoholic    | 200          | 200                    | 30–60        | Streptozotocin         | Male Wistar rats      | [75]       |
| Pandanus fasciculatus            | Screw-pine                         | Pandanaceae          | Saponins, tannins, phenols, alkaldoids, flavonoids              | -                                               | Ethanol      | 250          | 250                    | 0.1          | Streptozotocin         | Male albino rats      | [87]       |
| Pandanus odoratissimus           | Screwpinea                         | Pandanaceae          | Phytoestrogens, phenols, isoflavonoids                          | -                                               | Ethanol      | 75, 150, 300 | -                      | 10           | Alloxan                | Rats                  | [88]       |
| Picrorhiza kurroa ex. Benth.     | Kutki                              | Scrophulariaceae     | Cucurbitacins, polyols, phenols, iridoids, flavonoids           | Picrorhizines I and II                          | Alcoholic    | 100, 200     | -                      | 30           | Streptozotocin         | Male Wistar rats      | [89]       |
| Piper longum                     | Indian long pepper or pipph.pippul mula | Piperaceae          | Glycosides, alkaloids                                           | -                                               | Aqueous      | 200          | 200                    | 0.2          | Streptozotocin         | Male albino Wister rats | [90]       |
| Plumbago zeylanica               | Ceylon leadwort, or wild           | Plumbaginaceae       | -                                                               | Plumbagin                                       | Aqueous      | 200, 300, 400 | ≥200                    | 30           | Streptozotocin         | Albino Wistar rats     | [91]       |
| Plumeria alba                    | White frangipani or nosegay        | Apocynaceae          | -                                                               | -                                               | Alcoholic    | 250          | 250                    | 14           | Streptozotocin         | Male Sprague Dawley rats | [92]       |
| Potentilla fulgens L             | Bajradantii                        | Rosaceae             | -                                                               | -                                               | Ethanol      | 100          | -                      | 30           | Streptozotocin         | Male Sprague Dawley rats | [93]       |
| Premnus corymbosa (Burm. F) Rottl | Buss-bus                          | Verbenaceae          | -                                                               | -                                               | Ethanol      | 200, 400     | ≥200                    | 0.3          | Alloxan                | Albino Wister rats     | [94]       |
| Quercus infectoria Olivier       | Aleppo oak                         | Fagaceae             | -                                                               | -                                               | Methanol     | 250, 500     | ≥250                    | 0.3          | Alloxan                | Albino rats            | [95]       |
| Rauwolfia serpentina             | Indian snakeroot or devil pepper   | Apocynaceae          | Alkaloids, glycosides, cardiac glycosides, tannins, resins, saponins, phytoestrogens, triterpenoids | -                                               | Methanol     | 10, 30, 60   | ≥10                     | 14           | Alloxan                | Male Wister mice       | [96]       |
| Rheum glutinosum (Di Huang)      | Chinese foxglove                    | Scrophulariaceae     | -                                                               | -                                               | Ethanol      | 5, 10, 20, 50 | ≥10                     | 14           | Streptozotocin         | Male Wister mice       | [97]       |
| Rheum honoratum                  | Rhusbub                            | Polygonaceae         | Anthraquinones, Emodin                                         | -                                               | Methanol     | 2 mg.kg of pure Emodin | 0.1         | Streptozotocin         | Male albino Wister rats | [98]       |
| Scientific name | Common name | Family | Major chemical constituents | Bioactive compound | Extract type | Dose (mg/kg) | Effective dose (mg/kg) | Time (days) | Induction of diabetes | Experimental animals | References |
|----------------|-------------|--------|----------------------------|-------------------|--------------|--------------|----------------------|-------------|-----------------------|----------------------|-----------|
| Rheum rubra L. | Rhubarb | Polygonaceae | - | Rutin, quercetin-3-D-galactoside, quercetin, fisetin, emodin, chrysophanol | Aqueous | 50 | 50 | 8 | Alloxan | Male Swiss-Webster mice | [100] |
| Rheum turkestanicum | Rhubarb, Rivas | Polygonaceae | - | - | Aqueous | 200, 400, 600 | ≥200 | 21 | Streptozotocin | Male Wistar rats | [101] |
| Rhizoma myrrha var. Heyne | Myrtae | Anacardiaceae | Terpenoids, flavonoids, tannins, flavonoids, Cardiac glycosides, saponins | - | Aqueous | 200, 400, 800 | ≥400 | 21 | Streptozotocin | Male Wistar rats | [102] |
| Ricinus communis | Castor oil | Euphorbiaceae | Alkaloids, tannins, flavonoids, anthrones, saponins | - | Ethanolic | 500 | 500 | 20 | Alloxan | Male Sprague-Dawley rats | [103] |
| Rubia cordifolia L. | Madder | Rubiaceae | - | - | Aqueous | 1000 | 100 | 56 | Streptozotocin | Male albino Wistar rats | [104] |
| Salacia chinensis | Saptarangi | Hippocrateaceae | Xanthonoid, phenols | Mangiferin | Isolated mangiferin | 40 | 40 | 30 | Streptozotocin | Male Wistar rats | [105] |
| Salacia oblonga Wall | Oblong leaf salacia | Hippocrateaceae | - | - | Hydroalcoholic | 50, 100 | ≥50 | 94 | Streptozotocin | Albino Wistar rats | [106] |
| Salacia reticulata var. β-diandra | Kotalahimbatu or marking nut tree | Hippocrateaceae | - | - | Ether | 233 | - | 0.2 | Alloxan | Male Sprague-Dawley rats | [107] |
| Salvadora persica | Miswak, toothbrush tree or mustard tree | Salvadoraceae | - | Ferulic acid, caffeic acid, heptadecanoic acid, sinapyl alcohol, gallic acid, 4-hydroxyceamic acid, 4-hydroxy-3-methoxybenzoic acid, protocatechic acid, oleic acid, vanillin, hydroquinone, 4-hydroxybenzaldehyde, ergosterol, stigmasterol | Aqueous | 50, 100 | ≥50 | 28 | Streptozotocin | Wistar albino rats | [82] |
| Sansevieria roxburghiana | Indian bowstring hemp | Asparagaceae | Phenols, phytosteroids, fatty acids | - | Ethanolic | 200, 400 | 400 | 21 | Streptozotocin | Wistar albino rats | [108] |
| Sansevieria trifasciata | Mother-in-law’s tongue, Snake plant | Asparagaceae | Phenols, flavonoids, alkaloids, terpenoids, saponins, phytosteroids, glycosides | - | Methanolic | 50, 100 | 100 | 15 | Streptozotocin | Male Swiss albino rats | [109] |
| Smilax china L. | China root | Smilacaceae | Phytosteroids, alkaloids, resin, tannin, saponins, phenols | - | Ethanolic | 1000 | 1000 | 10 | Alloxan | Albino rats | [110] |
| Smilax morrenesis M | Cocalmeatl | Smilacaceae | - | 3-O-cafeoyl-quinic acid, 5-O-cafeoyl-quinic acid & trans-resveratrol | Ethanolic | 80 | 80 | 42 | Streptozotocin | Wistar rats | [111] |
| Scientific name                  | Common name                              | Family       | Major chemical constituents                  | Bioactive compound               | Extract type | Dose (mg/kg) | Effective dose (mg/kg) | Time (days) | Induction of diabetes | Experimental animals | References |
|---------------------------------|-------------------------------------------|--------------|-----------------------------------------------|---------------------------------|--------------|--------------|------------------------|-------------|------------------------|----------------------|------------|
| *Sphaeranthus indicus*          | East Indian globe thistle                 | Asteraceae   | -                                              | Gallic acid, quercetin           | Ethanolic    | 100, 200     | ≥100                   | 28          | Streptozotocin          | Wistar albino rats     | [112]      |
| *Tectona grandis* L.            | Teak tree                                 | Verbenaceae  | -                                              | -                               | Methanolic   | 250, 500     | ≥250                   | 7           | Alloxan                | Male albino Wistar rats | [113]      |
| *Terminalia superba*            | Limba or afara                            | Combretaceae | -                                              | Methyl gallate                   | Methanolic   | 200          | 200                    | 14          | Alloxan                | Wistar rats           | [114]      |
| *Tetrapleura tetrapetra*        | Prekese                                   | Fabaceae     | -                                              | -                               | Aqueous      | 150, 300     | ≥150                   | 35          | Streptozotocin          | Wistar rats           | [115]      |
| *Trapa natans*                  | Water caltrop                             | Lythraceae   | Flavonoids, phenols, tannins, phytosteroids   | Ferulic acid, caffeic acid      | Ethanolic    | 50, 100, 200 | ≥100                   | -           | Streptozotocin          | Wistar rats           | [116]      |
| *Trichosanthes dioica*          | Chinese cucumber or snakegourd            | Cucurbitaceae | -                                              | -                               | Aqueous      | 500, 1200    | -                      | 0.1         | Streptozotocinnicotinamide | Mice              | [117]      |
| *Trichosanthes triqueterata*    | Indrayan                                  | Cucurbitaceae | Glycosides, terpenoids                         | -                               | Ethanolic    | 200, 400     | ≥100                   | 21          | Alloxan                | Male albino Wistar rats | [118]      |
| *Triticum repens* L. or Agropyron repens | Couch grass, N’jm L'houri or  | Poaceae      | -                                              | -                               | Aqueous      | 20           | 20                     | 14          | Streptozotocin          | Male Wistar rats       | [119]      |
| *Withania somnifera* L.         | Ashwagandha, Indian ginseng or poison gooseberry | Solanaceae  | Flavonoids                                     | -                               | Ethanolic    | 100, 200     | ≥100                   | 56          | Alloxan                | Male albino Wistar rats | [120]      |
| *Zaleya decandra* L. N. Burm. F | Bherani or pindalu                       | Rubiaceae    | -                                              | -                               | Methanolic   | 500          | -                      | 7           | Alloxan                | Evan's Rats           | [121]      |
| *Ziziphus mucronata* Willd      | Horse purslane                            | Aizoaceae    | Flavonoids, alkaloids, phytosterol, cardiac glycosides, tannins, phenols | -                               | Ethanolic    | 200          | 200                    | 15          | Alloxan                | Albino Wistar rat      | [122]      |
| *Zingiber officinale*           | Ginger                                    | Zingiberaceae | -                                              | -                               | Ethanolic    | 50, 100, 200, 400, 800 | ≥50        | 0.3                    | Streptozotocin          | Wistar rats           | [123]      |

**Table 1 (continued)**
phenols, and flavonoids protect against oxidative stress, which results in improved protection against diabetes [127]. Phenols and flavonoids are furthermore well-recognized for their health benefits, including antioxidant, anti-inflammatory, antidiabetic, anti-ulcer, and anti-cancer effects [128–132].

Phenols, such as resveratrol, curcumin, chlorogenic acid, gallic acid, and ellagic acid, as well as flavonoids, such as quercetin, hesperidin, naringin, rutin, and myricetin, are well-known natural compounds for their potential antidiabetic properties. Quercetin, as one of the most abundant flavonoids in the plant kingdom, has been shown to possess several biological activities related to diabetes, such as glucose homeostasis, increased insulin sensitivity and secretion, glucose utilization in peripheral tissues, and the inhibition of intestinal glucose absorption [133, 134]. Despite promising activities in in vitro models, the low oral bioavailability of the flavonoid aglycones often results in vivo concentrations being too low to reach the relevant therapeutic concentrations [135]. Such challenges can, however, be alleviated by suitable formulations as reviewed by Zhao et al. [136].

Alkaloids

Alkaloids cover a wide range of natural products, which are mainly found in plants [137]. Alkaloids are defined by containing a non-amide nitrogen atom in their structure [138]. Amino acids such as histidine, lysine, ornithine, tryptophan, and tyrosine are the key precursors of most alkaloids in plants. Generally, due to the pharmacological properties of the alkaloids, the primary physiological function in plant roots of this compound class is protection against herbivores. Alkaloids are widely distributed within the plant kingdom and routinely isolated from plant families such as Solanaceae, Fabaceae, Papaveraceae, Berberidaceae, and Cannabaceae. The classification of alkaloids is mainly based on either their heterocyclic ring system or the name of the plant origin. Nicotine, atropine, berberine, morphine, and caffeine are some examples of currently marketed alkaloids for the treatment of cardiovascular, inflammatory, and mental diseases [139, 140]. Alkaloids mainly possess activities related to the central nervous system as well as anti-inflammatory effects, but antidiabetic activities have also been demonstrated [11]. Particularly the benzylisoquinoline alkaloids berberine and palmatine, found in root and rhizomes of the Berberidaceae plant family, have shown promising activities for the treatment of diabetes. Lee has recently reported that berberine could potentially activate AMPK (5-adenosine monophosphate-activated protein kinase) to improve insulin sensitivity and subsequently decrease the serum glucose level [142].

Phytosteroids

Phytosteroids are an important group of secondary metabolites produced by plants. Phytosteroids, found in plant roots in the two main forms of glycolipids and fatty acid esters [143], are involved in plant growth regulation, reproduction and respond to various biotic and abiotic stresses. The sterol primarily constitutes lipid-like molecules with intriguing antidiabetic potential. In a clinical study, Baker et al. have shown that the sterols present in vegetables, fruits, and seeds have the ability to decrease the concentration of cholesterol in diabetic patients [144]. Today, sterol-rich plant-based foods have become a focus of attention because of their enormous health benefits [145]. Nissinen et al. reported a lowering of the low-density lipoprotein (LDL) cholesterol concentrations by inhibiting cholesterol absorption in the small intestine [146], while Semova and co-workers showed that sterol-rich plant-based food enhanced the effects of antidiabetic drugs and reduced the blood glucose level [147].

Saponins

Saponins consist of triterpenoid or steroidal aglycones linked to oligosaccharide moieties (Fig. 4) and are widely distributed in the plant kingdom. These secondary metabolites
Fig. 2 The time of experiments in the reviewed in vivo studies. A: long-time (more than one day, n: 90), B: short-time (less than one day, n: 18)

Fig. 3 Biosynthesis pathway of phenols and flavonoids in the plant root system.
are biosynthesized in leaves, flowers, and roots. Saponins have an important role in plant ecology as a defense system against pests and herbivores. Saponins are furthermore also broadly used in the food (additives), cosmetic (soaps), agricultural (pesticides), and pharmaceutical industries (production of steroid hormones) [148].

These molecules are well-known for inhibiting α-amylase, α-glucosidase enzymes, and aldose reductase, which are key enzymes for managing T2D by lowering the carbohydrate absorption in the small intestine and colon [149]. Several in vivo studies supported in vitro findings of the potential of saponins for the management of T2D. These include an investigation by Ezzat et al., which demonstrated how furostanol saponins from Balanites aegyptiaca reduced the blood glucose level in rats [150]. Chen et al. showed that a daily injection of saponins isolated from P. notoginseng resulted in a significant decrease in the blood glucose level and body mass index of male mice after 12 days [86]. Diosgenin, as the main sapogenin in Trigonella. foenum-graecum seeds were shown by Uemura and co-workers to decrease plasma and hepatic triglycerides in obese diabetic mice and resulted in lowered blood glucose levels [151]. Twelve triterpenoid saponins isolated from A. taibaiensis effectively decreased the blood glucose level, triglyceride, and Low-Density Lipoprotein-Cholesterol (LDL-C) levels in diabetic rats. Li et al. suggested that the triterpenoid saponins might activate the AMPK and can be used as an adjunctive treatment for metabolic disorders [34].

**Tannins**

In plants, the physiological role of the polyphenolic tannins is to provide protection against herbivores while also negatively affect neighboring plant growth. These secondary metabolites can be classified into hydrolyzable and non-hydrolyzable tannins. Structurally, the hydrolyzable tannins consist of a central polyhydric alcohol (often glucose) which is esterified by phenolic groups such as gallic acid (gallotannins) or hexahydroxydiphenic acid (ellagitannins) as shown in Fig. 5.

Non-hydrolyzable tannins are distinctively different from hydrolyzable tannins as they are polymerized products of flavan-3-ols and flavan-3,4-diols [152] as depicted in Fig. 5. It is well-established that tannins cause a decrease in feed intake, growth rate, feed efficiency, and protein digestibility, resulting in increased excretion of proteins and essential amino acids followed by a decrease of the body mass index [152–154]. In a study by Venkataiah et al., tannins in the root of A. ilicifolius were shown to significantly decrease the blood glucose level in diabetic rats when orally administering 200 mg/kg of the extract for two weeks [21]. Shokeen et al. treated normal and diabetic mice with 50% ethanolic extract of R. communis, which is a tannin-rich plant, daily for 20 days and showed a significant decrease in their fasting blood glucose level, total lipid profile, and liver and kidney functions [103]. Former in vitro studies have also shown that hydrolyzable tannins may inhibit the α-glucosidase activity while also slowing the starch digestion. This indicates a polypharmacological antidiabetic potential of this compound class [155, 156].

**Terpenoids**

The terpenoids originate from one to several isoprene molecules (C₅H₈) and are widely distributed in plants and are classified based on the number of their isoprene units. The most simple class of terpenoids is the hemiterpenoids (C₅H₈) with additional isoprene units leading to the monoterpenoids (C₁₀H₁₆), sesquiterpenoids (C₁₅H₂₄), diterpenoids (C₂₀H₃₂), sesterterpenoids (C₂₅H₄₀), triterpenoids (C₃₀H₄₈), tetraterpenoids (C₄₀H₆₄), and polyterpenoids ([C₅H₈]ₙ). Terpenoids are known for their antibacterial, antifungal, and anti-inflammatory bioactivity. Furthermore, in vivo and in vitro antidiabetic activities, targeting α-glucosidase, α-amylase, and protein tyrosine phosphatase have also been reported, indicating their pharmacological potential [101, 157]. Several in vivo studies show that terpenoids enhance glucose metabolism, prevent the development of insulin resistance, and normalize plasma glucose and insulin levels [158].

**Anthraxinones**

Anthraxinones structurally consist of two aromatic rings joined together by two carbonyl groups, creating a planar, aromatic structure. In plants, anthraxinones are synthesized through two main biosynthetic pathways: the polyketide pathway and the chorismate/O-succinylbenzoic acid pathway [159]. These metabolites are present in aerial parts and roots as both O- and C-glycosides as well as aglycons (Fig. 6).

Several in vivo studies have shown that anthraxinones possess activities for treatment of diabetes, suggesting this compound class as potential antidiabetic candidates [30, 41, 160]. Emodin, aloe-emodin, catenarin, chrysophanol, and rhein are the most frequently isolated aglycon anthraxinones in the root system possessing α-amylase and α-glucosidase inhibitory activities [160] (Fig. 6).

**Cardiac glycosides**

The cardiac glycosides consist of a steroid molecule bound to one or more carbohydrates. The functional groups, which include methyl, hydroxyl, or aldehyde groups, are attached to the cardiac glycosides skeleton and play a pivotal role in
Cardiac glycosides enhance the heart output force and increase its rate by acting on the sodium–potassium ATPase pump [161] and are marketed for the treatment of various heart diseases. With the sodium–potassium ATPase being involved in metabolic diseases such as diabetes and obesity, regulation and enhancement of the ATPase have the potential to benefit the treatment of diabetes [161]. Several in vivo studies indicate the antidiabetic activity of cardiac glycosides present in plants [30, 59, 97].

Fig. 4 Chemical structure of selected triterpenoid and steroidal aglycones of saponins present in the plant root system

Fig. 5 Chemical structure of hydrolyzable (punicalagin) and non-hydrolyzable (Gallotannin) tannins
Conclusion

This review focuses on the literature survey of in vivo anti-diabetic effects of root and rhizome extracts on streptozotocin-induced or alloxan-induced diabetic mice or rats. The literature study revealed that most of the phytochemicals with antidiabetic bioactivity in the plant root system are involved in the management of diabetes through reducing hyperglycemia and hyperlipidemia, α-glucosidase inhibition, and insulin secretion regulation. However, as in vivo studies of purified secondary metabolites from root extracts are limited, plant roots constitute a largely uninvestigated source of candidates for the treatment of diabetes. This literature review found that flavonoids, phenolic compounds, alkaloids, and phytosteroids are the most abundant chemical constituents in the root system possessing antidiabetic activities. Based on our findings, the plant families Fabaceae, Araliaceae, Asparagaceae, Asteraceae, and Zingiberaceae are considered the plant families with root extracts most likely to include natural antidiabetic compounds. As the majority of studies on antidiabetic bioactivities of plants are performed on the aerial parts, whereas root extracts are less investigated with unique natural products, the root system is a promising source of new natural compounds with antidiabetic activities. This review provides comprehensive information about the promising plants and plant families with potential antidiabetic constituents in their root system.

Acknowledgements We would like to thank V. Calabrese and G. Dionisio for their feedback.

Declarations

Conflict of interest None.

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