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REVIEW ARTICLE

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

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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.

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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_5OH). 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

Table 1 The list of plants with antidiabetic activity in their roots and rhizomes extracts

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 rat	[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 Flavonoids	-	Ethanolic	300 100,200,400	300 400	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, terpinoids	-	Ethanolic	200, 400	≥200	21	-	Wistar rats	[26]
Anacyclus pyrethrum DC	Pellitory or Akarkara	Asteraceae	Flavonoids	-	Aqueous	150, 300	≥150	0.1	Alloxan	Albino wistar rats	[27]
Andrographis paniculata (Burm.f.) Nees	Creat or Green chirera	Acanthaceae	-	-	Chloroform	50, 100, 150 150	≥50 150	1 28	Alloxan	Sprague–Dawley rat	[28]
Anemarrhena asphodeloides Bunge	Zhi Mu	Asparagaceae	-	Mangiferin, mangiferin-7-*O*-β-glucoside	Aqueous	90	90	0.3	-	KK-Ay Mice	[29]
Anthocleista djalonensis A. Chevalier	Tagare, foreta lafira	Loganiaceae	Flavonoids, saponins, tannins, cardiac glycosides, anthraquinones	-	Ethanolic Chloroform Ethyl acetate Methanolic	37, 74, 111 74 74 74	≥37 74 74 74	14	Alloxan	Swiss albino mice and rats	[30]
Anthocleista vogelii (Planch)	Cabbage tree	Gentianaceae	Flavonoids, terpenes, phenols, lipids, alkaloids,fatty acids	Quebrachitol, loganin, sweroside, oleoside 11-methyl ester and ferulic acid	Methanolic, chloroform	100,200	-	(acute study)0.1 day study)21 days	Alloxan	Male Sprague–Dawley rats	[31]
Aporosa lindleyana (wt.) Bail	Kotili	Euphorbiaceae	-	-	Alcoholic	100	-	0.1	Alloxan	Male Albino wistar Rats	[32]
Aralia elata	Angelica-tree,Taranoki	Araliaceae	-	-	Aqueous	125	-	0.1	-	Male ddy mice	[33]
Aralia taibaiensis	Spikenard	Araliaceae	Triterpenoids, saponins	28-*O*-β-D-glucopyranosyl ester	Alcoholic	75,150,300	≥75	28	Streptozotocin	Male Albino wistar rats	[34]
Artocarpus communis Forst	Breadfruit,Gbere	Moraceae	-	-	Aqueous	100	100	7	Streptozotocin	Wistar rats	[35]
Asparagus racemosus (Wild)	Shatavari	Asparagaceae	-	-	Ethanolic	200, 400	≥200	21	Streptozotocin	Wistar rats	[36]

Table 1 (continued)

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	Albino wistar rats	[38]
Berberis aristata DC	Daruharidra	Berberidaceae	-	Berberine, berbamine, palmatine	Aqueous, Ethanolic	250	-	21	Alloxan	Male albino wistar rats	[39]
Berberis lyceum Royle	Indian barberry	Berberidaceae	-	-	Aqueous	50, 100	≥50	5	Alloxan	Wistar rats	[40]
					Ethanolic						
Berberis vulgaris L	Barberry	Berberidaceae	Tannins, alkaloids, saponins, phytosteroids, anthraquinones	-	Aqueous	25	25	21	Streptozotocin	Male Wistar rats	[41]
					Alcoholic	62.5	62.5				
Boerhavia diffusa L	Punarnava,spreading hogweed,tarvine	Nyctaginaceae	Phenols, flavonoids	Gallic acid, quercitin	Methanolic	200		7	Streptozotocin	Male Wistar rats	[42]
Brassica rapa L	Turnip	Brassicaceae	Flavonoids, polyphenols	-	Ethanolic	2600	2600	35	-	Db/db mice	[43]
Bruguiera gymnorrhiza L	Black mangrove or afrikaans	Rhizophoraceae	Alkaloids, phytosteroids, saponins	-	Ethanolic	400	400	21	Streptozotocin	Rats	[44]
Caesalpinia digyna Rottler	Teri pods or udakiryaka	Fabaceae	-	Bergenin	Ethanolic	2.5, 5, 10	10	14	Streptozotocin-Nicotinamide	Male albino rats	[45]
Cajanus cajan L	Arhar(Pigeon pea)	Fabaceae	Phenols	-	Methanolic	200, 400	≥200	5	Alloxan	Swiss albino mice	[46]
Casearia esculenta (Roxb.)	Kadala zhinjill,wild cowrie fruit,saptarangi	Flacourtiaceae	-	-	Aqueous	200,300		45	Streptozotocin	Male albino rats	[47]
Ceiba pentandra L	Silk cotton tree	Sterculiaceae	-	-	Ethanolic	300	300	30	alloxan	Male Wistar rat	[48]
Cichorium intybus	Chicory	Asteraceae	Inulin, lipids, alkaloids, glycosides, tannins	-	Methanolic	400	400	21	Streptozotocin	Male, Wistar albino rats	[49]
Citrullus colocynthis	Bitter cucumber,Bitter apple,egusi	Cucurbitaceae	Glycosides, saponins, triterpenoids, alkaloids, flavonoids, resins	-	Aqueous	200	200	7	Alloxan	Male Wistar rats	[50]
					Chloroform	200	-				
					Ethanolic	200	-				
Clausena anisata (Willd) Hook	Isifudu	Rutacaea	-	-	Methanolic	100–800	≥800	-	Streptozotocin	Male Wistar rats	[51]
Coptis chinensis Franch	Goldthread	Ranunculaceae	Alkaloids	Berberine, palmatine, jatrorrhizine	Aqueous	125,250,500	≥125	21	Alloxan	Wistar rats	[52]

Table 1 (continued)

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	Costaseae	-	-	Hexane	250	250	60	Streptozotocin	Wistar rats	[53]
					Ethyl acetate	400	400				
					Methanolic	400	400				
Curculigo orchioides Gaertn	Talamuli,musali, nilapanai	Hypodoxiaceae	-	-	Ethanolic	500, 1000	≥500	21	Alloxan	Swiss albino mice	[54]
					Aqueous	500,1000					
Curcuma aromatica	Turmeric	Zingiberaceae	Phenols, flavonoids, flavonols	-	Toluene	200, 400	≥200	21	Streptozotocin	Wister albino rats	[55]
Curcuma longa	Turmeric	Zingiberaceae	-	-	Aqeous	400	400	28	Alloxan	Albino rats	[56]
					Methanolic	400	400				
					Hexane	400	400				
Cyperus rotundus L	Mustaka	*Cyperaceae*	-	-	Ethanolic	250, 500	≥250	21	Streptozotocin	Swiss albino mice	[57]
Datura stramonium L	Jimsonweed	Solanacaea	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, saponins, 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]
					Ethyl acetate	250	250				
					Hexane	250	-				
Euclea undulata Thunb. var. myrtina	Guarri	Ebenaceae	-	-	Acetone	50, 100	100	21	Streptozotocin-nicotinamide	Male Wistar rats	[61]
Glycyrrhiza glabra	Licorice	Fabaceae	-	-	Methanolic	100,200,300	≥200	0.1	Streptozotocin	Albino rats	[62]
Glycyrrhiza uralensis Fisch	Licorice	Fabaceae	-	Glycyrrhizin, glycyrrhetinic acid	Ethanolic	1	1	56	-	Male C57BL6J mice	[63]
Gmelina asiatica L	Nilakkumil or gopabhandra	Verbenaceae	-	-	Alcoholic	100, 250, 500	≥100	16 h	Alloxan	Sprague Dawley rats	[64]
Gynandropsis gynandra	Shona cabbage or African cabbage	Capparidaceae	Flavonoids, phenolic compounds, 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	50,100,200,400,800	-	0.3	Streptozotocin	Wistar rat	[66]
Helicteres isora L	Screw tree	Sterculiaceae	Triterpenoidal glycosides	-	Butanolic	250	250	10	Alloxan	Male Wistar rats	[67]

Table 1 (continued)

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
					Ethanolic	250	250				
Hemidesmus indicus R.Br	Indian sarsaparilla	Asclepiadaceae	Flavonoids, alkaloids, saponins, triterpenoids, tannins, phytosteroids, phenols	-	Methanolic	200, 400	400	90	Streptozotocin	Albino Wistar rat	[68]
Ibervillea sonorae	Wareque	Cucurbitaceae	Phenols, phytosteroids	-	Dichloromethane, methanolic	300, 600	≥300	41	Alloxan	Wistar rats	[69]
Ichnocarpus frutescens (L.) R.Br	Black creeper or dudhilata	Apocynaceae	-	-	Aqueous	250, 500	≥250	15	Streptozotocin-nicotinamide	Male albino Wistar rats	[70]
Ipomoea batatas L	Sweet potato	Convolvulaceae	-	-	Methanolic	4000	-	14	Alloxan	Male Wistar rats	[71]
Justicia adhatoda L	Malabar nut	Acanthaceae	-	-	Ethanolic	100	100	6	Alloxan	Wistar rats	[72]
Liriope spicata var. prolifera	Creeping lilyturf & monkey grass	Liliaceae	-	-	Aqueous	100, 200	≥100	28 (FBS) 14(OGTT)	Streptozotocin	Male BABL/c mice	[73]
Lycii radices or *Lycium chinense* Miller	Goji berry or wolfberry	Solanaceae	-	-	Aqueous	80, 160	- (in serum) ≥80(in kidney)	14	Streptozotocin	Male Sprague–Dawley rats	[74]
Merremia tridentata (L.) Hall. F	Mudiarkunthal or savulikodi,Thrippanpullo	Convolvulaceae	-	-	Aqueous	50, 100, 150	≥50	21	Streptozotocin	Male albino Wister rats	[75]
Mimosa pudica	Sensitive plant, humble plant, Lajwanti	Fabaceae	-	-	-	2, 4, 6	6	20	Alloxan	Albino rabbits	[76]
Morus alba L	Mulberry tree	Moraceae	Flavonoids, terpenoids	Morusin, cyclomorusin, neocyclomorusin, kuwanon E, 2-arylbenzofuran, moracin M betulinic acid, methyl ursolate	Ethanolic	200,400,600	600	10	Streptozotocin	Male Wister 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	-	Ethanolic	150, 300, 450	≥450	14	Alloxan	Swiss albino mice and rats	[79]
Nyctanthes arbor-tristis L	Harsinghar or night jasmine	Oleaceae	-	-	Methanolic	250, 500	≥500	0.1	Alloxan	Male albino Wister rats	[80]
Nymphaea alba	White water rose or white nenuphar	Nymphaeacea	Glycosides, alkaloids,phenols,tanins,flavonoids,saponin,trepenoids, phytosteroids	-	Ethanolic	200, 400	≥500	13	Alloxan	Albino rats	[81, 82]
Nymphaea pubescens Willd	Red water lily	Nymphaeacea	Alkaloids, flavonoids, glycosides,terpenoids, tannins, phenols, saponins, phytosteroids	-	Ethanolic	200, 500	≥200	14	Alloxan	Albino Wistar rats	[83]

Table 1 (continued)

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	-	Aqoues	300	300	56	-	KKAy mouse	[84]
Panax ginseng	Ginseng	Araliaceae	Ginsenosides	-	Ethanolic	150	150	12	-	Ob/ob Mice	[85]
Panax notoginseng	Chinese ginseng or notoginseng	Araliaceae	Saponins	Ginsenosides, notoginsenosides	Ethanolic	50,200	≥50	30	-	Male kk/Ay mice	[86]
Panax quinquefolius	American ginseng	Araliaceae	Ginsenosides	-	Alcoholic	200	200	30–60	Streptozotoin	C57BL/6 mice	[87]
									-	db/db mice	
Pandanus fascicularis Lamk	Screw-pine	Pandanaceae	Saponins, tannins, phenols, alkaloids, flavonoids	-	Ethanolic	250	250	0.1	Streptozotoin	Male albino rats	[88]
Pandanus odoratissimus	Screwpine	Pandanaceae	Phytosteroids, phenols, isoflavones	-	Ethanolic	75, 150, 300	-	10	Alloxan	Rats	[89]
Picrorhiza kurroa Royle ex. Benth	Kutki	Scrophulariaceae	Cucurbitacins, polyols, phenols,iridoids,flavonoids	Picroside I and II	Alcoholic	100, 200	-	30	Streptozotocin	Male Wistar rats	[90]
Piper longum	Indian long pepper or pipli,pippali mula	Piperaceae	Glycosides, alkaloids	-	Aqueous	200	200	0.2	Streptozotocin	Male albino Wister rats	[91]
					Hexane	200	-				
					Ethyl acetate	200	-				
					Methanolic	200	200				
					Aqueous	200,300,400	≥200	30			
Plumbago zeylanica	Ceylon leadwort, or wild leadwort	Plumbaginaceae	-	Plumbagin	Cholorofom	15, 30	≥15	28	Streptozotocin	Albino Wistar rats	[92]
Plumeria alba	White frangipani or nosegay	Apocynaceae	-	-	Alcoholic	250	250	14	Streptozotocin	Male Sprague Dawley rats	[93]
Potentilla fulgens L	Bajradanti	Rosaceae	-	-	Ethanolic	100	-	30	Streptozotocin	Male Sprague Dawley rats	[94]
Premna corymbosa (Burm. F.) Rottl	Buas-buas	Verbenaceae	-	-	Ethanolic	200, 400	≥200	0.3	Alloxan	Albino Wister rats	[95]
Quercus infectoria Olivier	Aleppo oak	Fagaceae	-	-	Methanolic	250, 500	≥250	0.3	Alloxan	Albino rats	[96]
Rauwolfia serpentina	Indian snakeroot or devil pepper	Apocynaceae	Alkaloids, glycosides, cardiac glycosides, tannins, resins, saponins, phytosteroids, triterpenoids	-	Methanolic	10, 30, 60	≥10	14	Alloxan	Male Wister mice	[97]
Rehmannia glutinosa (Di Huang)	Chinese foxglove	Scrophulariaceae		-	-	5, 10, 20, 50	≥10	14	Streptozotocin	Male Wistar rats	[98]
Rheum emodi	Rhubarb	Polygonaceae	Anthraquinones	Emodin							
	-	2	2 mg.kg of pure Emodin	0.1	Streptozotocin	Male albino Wister rats	[99]				

Table 1 (continued)

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 ribes 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]
Rhus mysorensis Heyne	Mysore sumac	Anacardiaceae	Terpenoids, phytosteroids,tannins, flavonoids, Cardiac glycosides,saponins	-	Alcoholic	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	Wistar rats	[103]
Rubia cordifolia L	Madder	Rubiaceae	-	-	Aqueous	1000	100	56	Streptozotocin	Male albino Wistar rats	[104]
Salacia chinensis	Saptarangi	Hippocrateaceae	Xanthonoid, phenols	Mangiferin	Isloated 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]
					Ethyl acetate	29	-				
					Methanolic	350	350				
					Aqueous	500	-				
					Tolbutamide	15	-				
					Methanolic	175		120			
Salvadora persica	Miswak, toothbrush tree or mustard tree	Salvadoraceae	-	-	Hydroalcoholic	200, 400	400	21	Streptozotocin	Wister albino rats	[82]
Sansevieria roxburghiana	Indian bowstring heamp	Asparagaceae	Phenols, phytosteroids, fatty acids	Ferulic acid, caffeic acid, heptadecanoic acid, sinapyl alcohol, gallic acid, 4-hydroxycinnamic acid, 4-hydroxy-3-methoxybenzoic acid, protocatechuic acid, oleic acid, vanillin, hydroquinone, 4-hydroxybenzaldehyde, ergosterol, stigmasterol	Aqueous	50, 100	≥50	28	Streptozotocin	Wistar 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 moranensis M	Cocolmecatl	Smilacaceae	-	3-*O*-caffeoyl-quinic acid, 5-*O*-caffeoyl-quinic acid & trans-resveratrol	Ethanolic	80	80	42	Streptozotocin	Wistar rats	[111]

Table 1 (continued)

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 Wister rats	[113]
Terminalia superba	Limba or afara	Combretaceae	-	Methyl gallate	Methanolic	200	200	14	Alloxan	Wistar rats	[114]
Tetrapleura tetraptera	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	Streptozotocin-nicotinamide	Mice	[117]
Trichosanthes tricuspidata	Indrayan	Cucurbitaceae	Glycosides, terpenoids	-	Ethanolic	200, 400	≥100	21	Alloxan	Male albino Wister rats	[118]
Triticum repens L. or *Agropyron repens*	Couch grass, N'jm L'bouri or outara	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]
Xeromphis uliginosa Retz	Bherani or pindalu	Rubiaceae	-	-	Methanolic	500	-	7	Alloxan	Evan's Rats	[121]
Zaleya decandra L. N. Burm. F	Horse purslane	Aizoaceae	Flavonoids, alkaloids, phytosterol, cardic glycosides, terpenoids, tannins, phenols	-	Ethanolic	200	200	15	Alloxan	Albino Wistar rat	[122]
Zingiber officinale	Ginger	Zingiberaceae	-	-	Ethanolic	50,100,200,400,800	≥50	0.3	Treptozotocin	Wistar rats	[123]
Ziziphus mucronata Willd	Buffalo thorn	Rhamnaceae	-	-	Butanolic	150 or 300	300	28	Streptozotocin	Male Sprague–Dawley rats	[124]

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].

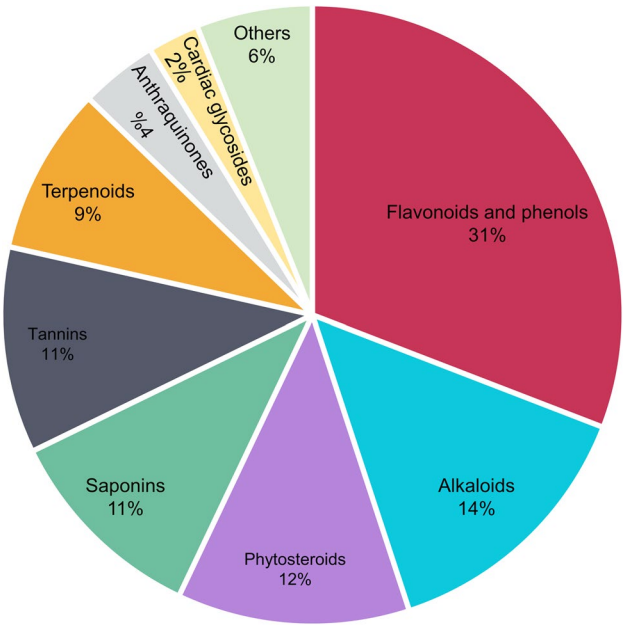

Fig. 1 The class of compounds with antidiabetic bioactivity in plant roots and rhizomes

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 isoquinoline alkaloids isolated from *Coptis japonica* showed strong antidiabetic activity as aldose reductase inhibitors in an in vivo study [141]. Chen et al. 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

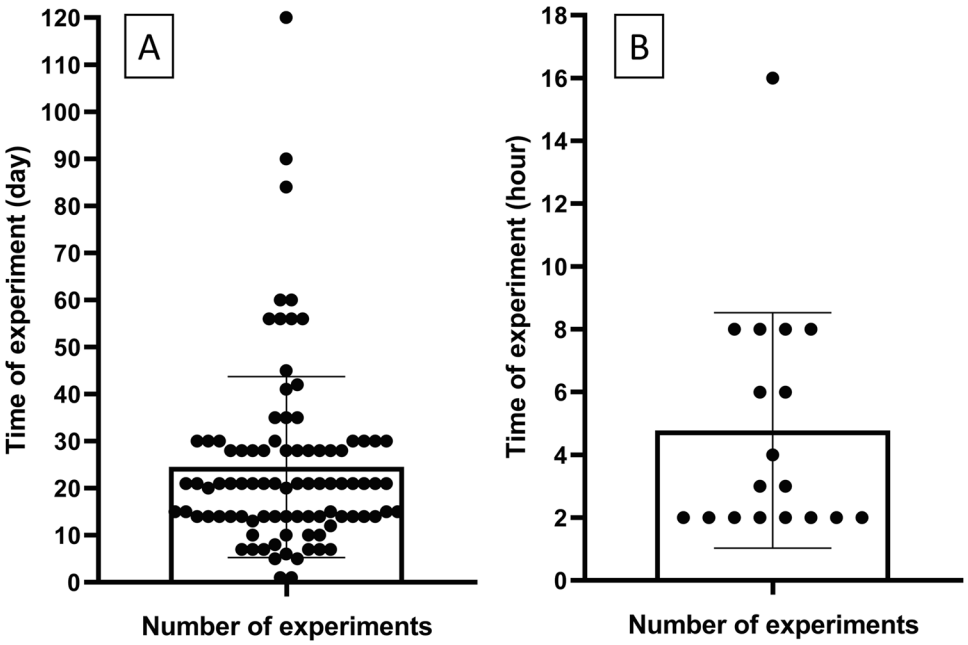

Fig. 2 The time of experiments in the reviewed in vivo studies. A: long-time (more than one day, n: 90), B: short-time (less than one day, n: 18)

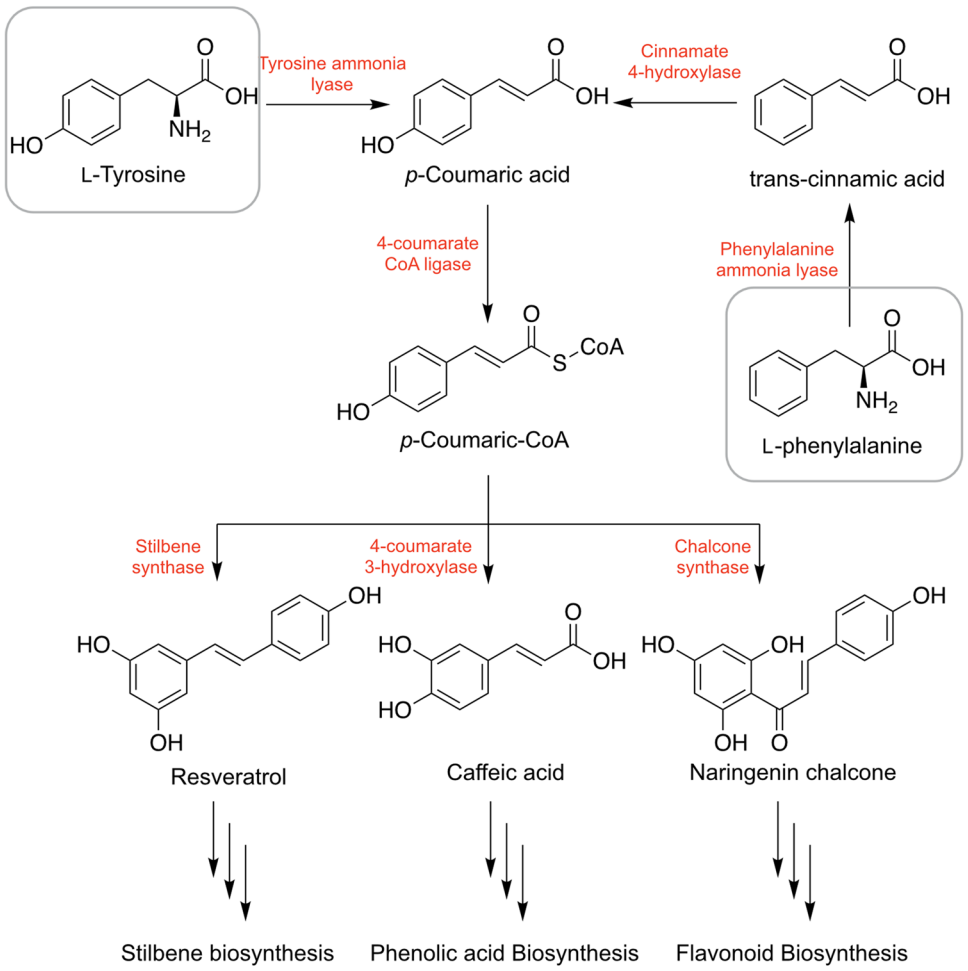

Fig. 3 Biosynthesis pathway of phenols and flavonoids in the plant root system

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 (C_5H_8) 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 (C_5H_8) with additional isoprene units leading to the monoterpenoids ($C_{10}H_{16}$), sesquiterpenoids ($C_{15}H_{24}$), diterpenoids ($C_{20}H_{32}$), sesterterpenoids ($C_{25}H_{40}$), triterpenoids ($C_{30}H_{48}$), tetraterpenoids ($C_{40}H_{64}$), and polyterpenoids ($[C_5H_8]_n$). 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].

Anthraquinones

Anthraquinones structurally consist of two aromatic rings joined together by two carbonyl groups, creating a planar, aromatic structure. In plants, anthraquinones 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 anthraquinones 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 anthraquinones 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

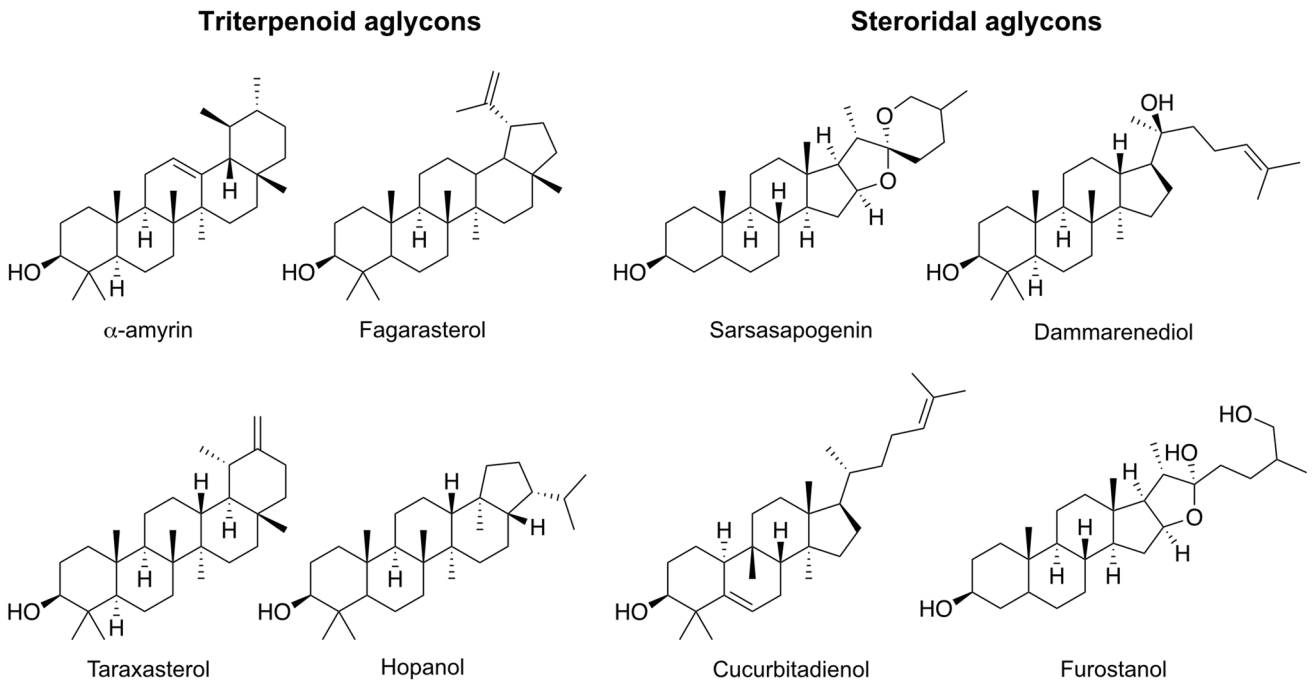

Fig. 4 Chemical structure of selected triterpenoid and steroidal aglycones of saponins present in the plant root system

the biological activity of these molecules. 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].

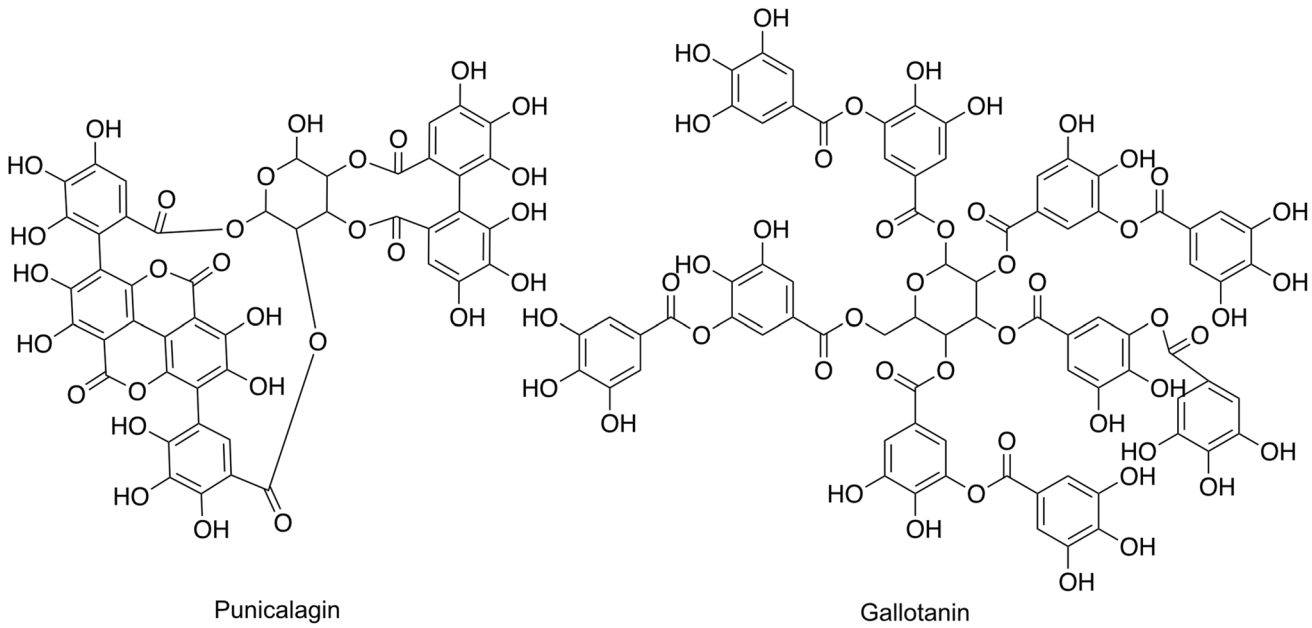

Fig. 5 Chemical structure of hydrolyzable (punicalagin) and non-hydrolyzable (Gallotannin) tannins

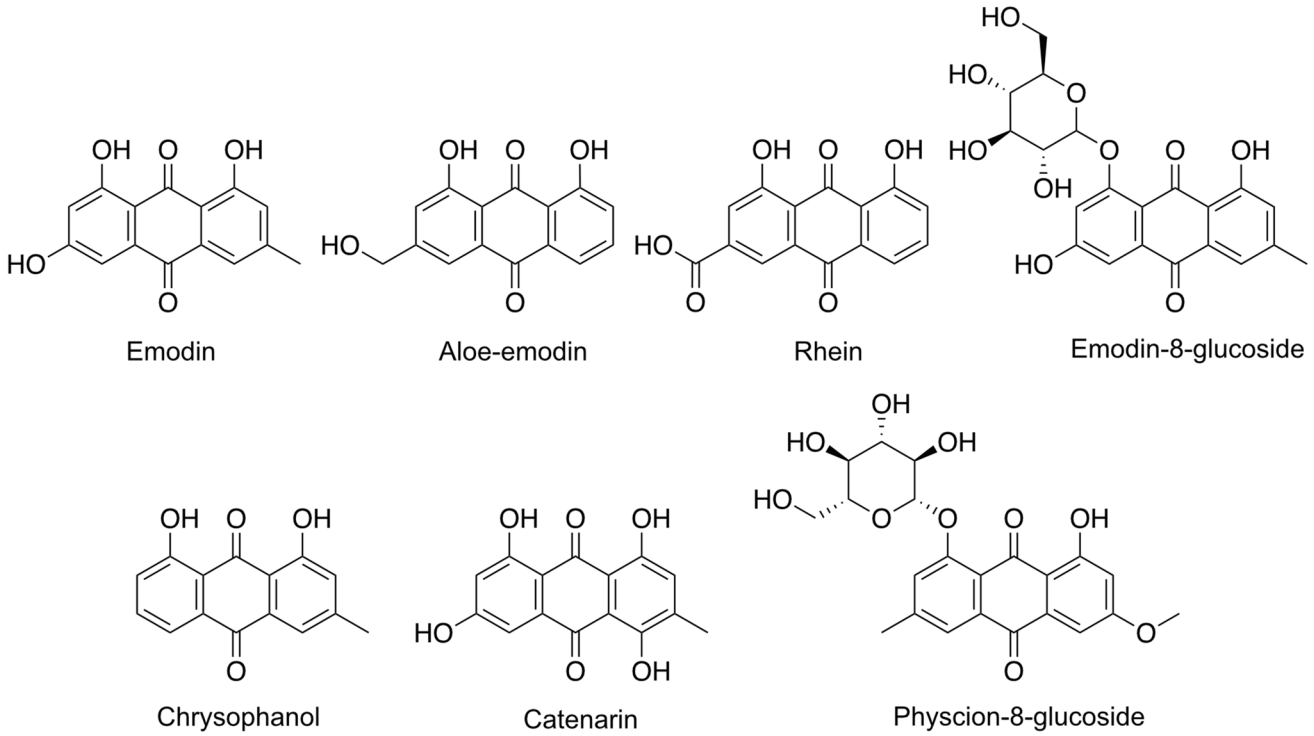

Fig. 6 Chemical structure of the most frequent anthraquinones in the root system with α-amylase and α-glucosidase inhibitory activities

Conclusion

This review focuses on the literature survey of in vivo antidiabetic 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.

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Declarations

Conflict of interest None.

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