Natural Products for the Treatment of Type 2 Diabetes Mellitus*

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Key words
- diabetes
- antidiabetic
- medicinal plants
- clinical trials

Abstract

Type 2 diabetes mellitus is a metabolic disease characterized by persistent hyperglycemia. High blood sugar can produce long-term complications such as cardiovascular and renal disorders, retinopathy, and poor blood flow. Its development can be prevented or delayed in people with impaired glucose tolerance by implementing lifestyle changes or the use of therapeutic agents. Some of these drugs have been obtained from plants or have a microbial origin, such as galegine isolated from *Galega officinalis*, which has a great similarity to the antidiabetic drug metformin. Picnogenol, acarbose, miglitol, and voglibose are other antidiabetic products of natural origin. This review compiles the principal articles on medicinal plants used for treating diabetes and its comorbidities, as well as mechanisms of natural products as antidiabetic agents. Inhibition of α-glucosidase and α-amylase, effects on glucose uptake and glucose transporters, modification of mechanisms mediated by the peroxisome proliferator-activated receptor, inhibition of protein tyrosine phosphatase 1B activity, modification of gene expression, and activities of hormones involved in glucose homeostasis such as adiponectin, resistin, and incretin, and reduction of oxidative stress are some of the mechanisms in which natural products are involved. We also review the most relevant clinical trials performed with medicinal plants and natural products such as aloe, banaba, bitter melon, caper, cinnamon, cocoa, coffee, fenugreek, garlic, guava, gymnema, nettle, sage, soybean, green and black tea, turmeric, walnut, and yerba mate. Compounds of high interest as potential antidiabetics are: fukugetin, palmatine, berberine, honokiol, amorfrutins, trigonelline, gymnemic acids, gurmarin, and phlorizin.

Abbreviations

AMPK:	AMP-activated protein kinase
CAP:	c-Cbl-associated protein
DDP-4:	dipeptidyl peptidase-4
GIP:	glucose-dependent insulinotropic polypeptide
GLP-1:	glucagon-like peptide-1
GLUT4:	glucose transporter-4
GSH:	glutathione
HOMA-IR:	homeostasis model assessment-insulin resistance
IL:	interleukin
iNOS:	inducible nitric oxide synthase
IRS:	insulin receptor substrate
LXRα:	liver X receptor α
MAPK:	mitogen-activated protein kinases
MDA:	malondialdehyde
NF-κB:	nuclear factor-κB
PPAR:	peroxisome proliferator-activated receptor
PTP1B:	protein tyrosine phosphatase 1B
SGLT2:	sodium-glucose cotransporter-2
T2DM:	type 2 diabetes mellitus
TGF:	transforming growth factor
TNF-α:	tumor necrosis factor-α

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Introduction

Diabetes is a chronic disease, which if not treated properly, generates serious complications that reduce patients' quality of life and raises the cost of their care [1]. Its prevalence is increasing steadily worldwide, and it is estimated that by 2025, 300 million people in the world will be affected by this

* Dedicated to Professor Dr. Dr. h.c. mult. Adolf Nahrstedt on the occasion of his 75th birthday.

illness. It is a disease strongly associated with both microvascular and macrovascular complications, whose pathophysiological mechanisms are diverse and sometimes unclear [2].

T2DM, a metabolic disease characterized by a persistent increase in blood glucose above normal values (hyperglycemia) due to a progressive insulin secretory defect on the background of insulin resistance [3], is the most common form of the disease. In Western countries, it accounts for 90–95% of all cases of diabetes. T2DM incidence increases from the third decade of age [4]. Chronic hyperglycemia is associated with long-term dysfunction and failure of different organs (eyes, kidneys, nerves, heart, and blood vessels) and is usually associated with other cardiovascular risk factors such as hypertension, overweight/obesity, dyslipidemia, and unhealthy lifestyles (e.g., inadequate diet and sedentarism) [5,6].

Worldwide, the care of T2DM patients consumes between 5 and 10% of the budget allocated to the health system due to the higher frequency of consultations and hospitalizations, and longer rehospitalizations and more complex treatments [7]. The development of chronic complications also increases the costs of patient care [8]. Several studies have shown that actions aimed at preventing these complications are cost effective [9]. Development of T2DM can be prevented or at least delayed in patients with impaired glucose tolerance by implementing lifestyle changes [10] or the use of therapeutic agents [11–13]. In this sense, changes in lifestyle have shown to be the most convenient cost-effective prevention and the lowest incidence of adverse side effects.

T2DM includes individuals who have insulin resistance, as mentioned above, and usually relative insulin deficiency. Its development shows a gradual transition in which alterations of the pancreatic β cell mass and function are preceded by a decreased response of peripheral tissues to insulin (insulin resistance). These individuals, at least initially, do not need insulin treatment to survive and, in some cases, adequate glycemic control can be achieved with weight loss, exercise, and/or oral glucose-lowering agents [14]. However, patients with severe β cell destruction, and therefore no residual insulin secretion, require insulin for survival.

The onset of T2DM is preceded by impaired glucose tolerance, in which the changes described in T2DM are already present, though to a lesser degree [15,16]. T2DM usually remains undiagnosed for many years because hyperglycemia increases gradually and at earlier stages it is often insufficient for the patient to notice any classic symptoms of the illness.

It is now clear that the paramount condition for developing T2DM is β cell failure. Although several pathogenic processes are involved in the development of T2DM (aside from the autoimmune destruction of β cells, which does not occur), two basic conditions for abnormalities in carbohydrate, fat, and protein metabolism in target tissues of the diabetic patient normally coexist in the same person: insulin resistance and decreased function and mass of pancreatic β cells.

Following a meal, insulin promotes carbohydrate uptake at storage sites and drives the conversion of carbohydrates into lipids, a more efficient means of storage for calories. Interaction between insulin and its receptor triggers a downstream signalling pathway that is ultimately responsible for the metabolic effects, including those mentioned above, of the hormone on target tissues. In insulin resistance, this transduction pathway becomes impaired, thereby resulting in hampered insulin action. Several mechanisms have been proposed to explain the pathogenesis of insulin resistance: ectopic lipid accumulation, endoplasmic reticulum stress, and activation of unfolded protein response and systemic inflammation. These mechanisms, which reflect the failure of different aspects of metabolic control, may crosstalk to regulate insulin action [17].

A decreased function of pancreatic β cells must be considered when secretion of insulin in response to a rise in blood glucose is insufficient to meet the demand (a relative rather than an absolute deficiency) [18].

Impaired β cell function involves three features: decreased sensitivity to glucose, loss of pulsatility and the biphasic nature of insulin secretion, and a decrease in β cell mass. In the first case, although the normal sensitivity threshold has wide individual variations not affecting their ability to maintain glucose homeostasis, sensitivity of β cells to glucose decreases progressively from impaired glucose tolerance to T2DM [19]. In the second case, biphasic profile and pulsatility are characteristic features of insulin secretion altered early in T2DM, thus resulting in good indicators of a progressive decline in β cell function. Secretory dysfunction of β cells occurs before the onset of clinical manifestations, and other factors such as dyslipidemia, changes in hormone levels and cytokine function, and impairment of endothelial cells and vascular flow, contribute to its development [20]. In the third case, maintenance of an adequate β cell mass is essential for controlling blood glucose homeostasis and preventing the development of diabetes. Clinical studies clearly show that an inadequate β cell mass due to an imbalance between the rate of cell renewal and apoptosis is observed in T2DM, with autopsies of individuals with diabetes having shown a 50–60% decrease of β cell mass, which is already evident at the stage of impaired glucose tolerance [16]. These results demonstrate that a decrease in β mass is a progressive process that starts early in the pathogenesis of T2DM.

Characteristic diabetic hyperglycemia plays an important role in impairing insulin secretion and β cell mass, a phenomenon called glucotoxicity that triggers glycooxidation processes. As demonstrated by Sakura et al., there is a negative correlation between β cell mass and expression of oxidative stress-related DNA damage in the islet of patients with T2DM [21]. Another mechanism involved in β cell failure is insular amyloid deposition. Fibrillary degeneration of amylin in β granules is a process that increases with age and is markedly increased in people with diabetes [16]. Glycooxidative stress and amyloid deposition can explain the decrease in β cell function and mass in diabetic hyperglycemia associated with increased endoplasmic reticulum stress in the impaired glucose tolerance state. Functional overload of β cells due to increased demand for the hormone in insulin-resistant states could be responsible for the activation of endoplasmic reticulum stress and a consequently increased rate of apoptosis [22].

The aim of this review is to present new findings in phytotherapy for T2DM, with the objectives focused on novel ethnopharmacological approaches, recent research on selected plants and isolated compounds, and, especially, recent contributions from clinical trials.

Antidiabetics of Plant Origin

Throughout history, different remedies and drugs have been used to treat T2DM, including insulin before knowledge of its mechanism of action. Some of them have been included in the therapeutic arsenal of medicine, and others are used as complementary therapy in patients with hyperglycemia. Several of these com-

pounds have been obtained from plants or from microbes. Classic examples are galegine, phenolics compounds and pycnogenol derived from plants, and acarbose, miglitol, and voglibose from microbes.

The first medicinal plant described with a clear antidiabetic effect was *Galega officinalis* L. (Fabaceae), which has been prescribed since the Middle Age to treat diabetes mellitus. From this plant, also called goat's rue, French lilac, or Italian fitch, a guanidine derivative, galegine, was isolated. This compound, whose chemical structure is quite similar to the antidiabetic drug metformin, is responsible for the lowering of blood glucose produced by the plant extract. The structure of both compounds is shown in **Fig. 1** [23,24].

Different phenolic compounds such as flavonoids and antocyanins have positive effects on diabetes [25]. For example, different anthocyanins from *Ipomoea batatas* (L.) Poir. (Convolvulaceae) and *Pharbitis nil* (L.) Choisy (Convolvulaceae) are effective inhibitors of intestinal α-glucosidase/maltase activity [26] and can reduce glycemia after starch-rich meals. Inhibitory effects of anthocyanins depend on their structure, as their potency as α-glucosidase inhibitors is higher in acylated anthocyanins than in deacylated derivatives [23].

A third example of a natural product with antidiabetic properties is pycnogenol, a patented water extract obtained from French maritime pine bark (*Pinus pinaster* Aiton, Pinaceae) rich in polyphenols [23]. Antidiabetic properties of pycnogenol are due to its digestive enzyme inhibitory activity, especially against α-glucosidase [27]. Of the compounds present in the mixture, only (+)-catechin and procyanidins are able to inhibit α-glucosidase. Pycnogenol also competitively inhibited α-amylases from the human salivary glands and the porcine pancreas [28]. Pycnogenol (100 mg/day for 3 months) in addition to conventional treatment with oral antidiabetic drugs reduced blood glucose levels and improved endothelial function in patients with T2DM. Moreover, this reduction in glycemia was dose dependent without increasing insulin secretion [29,30].

In addition to antidiabetic plant compounds, three examples of microbial origin may be mentioned. Acarbose (from *Actinoplanes* sp.) is probably the most widely used digestive enzyme inhibitor for the treatment of T2DM, acting on α-glucosidase, α-amylase, sucrase, and maltase, but without insulinotropic properties [23, 31,32]. Miglitol is a second-generation α-glucosidase inhibitor structurally similar to glucose. Originally obtained from various *Bacillus* and *Streptomyces* strains, it is now obtained by the oxidation of 1-amino-D-sorbitol to 6-amino-L-sorbose by fermentation using *Gluconobacter oxydans* [23]. Voglibose is synthesized from valiolamine, which is isolated from a fermentation broth of *Streptomyces hydroscopicus subsp. limoneus* [33]. It is also an α-glucosidase inhibitor, which competitively and reversibly inhibits glucoamylase, sucrase, and isomaltase but has no activity on α-amylases. It also reduces plasma glucose levels and insulin in a dose-dependent manner [23,34].

An interesting point to consider is herbal drug standardization. In-depth analysis of each step during the preparation of samples is necessary in order to ensure quality, safety, and reproducibility. With this objective, Chawla et al. [35] proposed a model for developing these challenges in clinical studies, and suggested further studies to guarantee effective herbal drug standardization methodology, as well as a regulatory standard guide for future research.

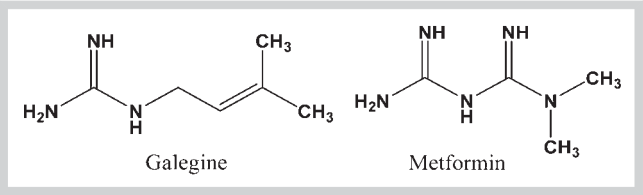


Fig. 1 Chemical structures of galegine and metformin.

Recent Reviews on Antidiabetic Medicinal Plants

In recent years, many reviews focusing on natural products and medicinal plants with antidiabetic potential have been published. For example, Hays et al. [36] reviewed the role of natural products and pharmacological interventions in the prevention and treatment of T2DM. Nahas and Moher [37] reviewed some relevant medicinal plants and their potential as antidiabetics, including clinical trials. Bedekar et al. [23] compiled data on natural products for T2DM treatment. Patel et al. analyzed pharmacological aspects of antidiabetic properties and compiled data concerning 37 species in a first study [38] and 68 species in a second revision [39]. Chang et al. [40] reviewed mechanisms of antidiabetic action and herbal therapies for T2DM and their potential applications. El-Abhar and Schaalan [41] analyzed potential mechanisms in phytotherapy and their possible clinical applications. Finally, Eddouks et al. [42] compiled 111 antidiabetic medicinal plants that can improve insulin sensitivity, selecting 31 with a high potential for future studies due to their important role in controlling insulin resistance associated with diabetes mellitus.

In other types of reviews, the authors focused their efforts on compiling antidiabetic medicinal plants from different parts of the world in function of their ethnopharmacogical use (**Table 1**).

This review will focus on recent studies, especially relevant contributions that involved clinical trials.

Mechanisms of Natural Products as Antidiabetic Agents

Different authors have focused their studies on the mechanism of action of principles isolated from medicinal plants with antidiabetic properties. For example, Tabatabaei-Malazy et al. [66] reviewed the effects of the main component of antidiabetic plants with direct action on insulin secretion from the pancreas. They established that improvement of β cell function and insulin secretion is possible with antioxidant compounds via suppression of oxidative stress, although other mechanisms are also important such as cytokine-induced impairment, suppression of NF-κB, activation of uncoupling protein 2, insulin-like activity, and increasing intracellular calcium. These authors compiled the effects of different agents but did not establish the mechanism of each compound. El-Abhar and Schaalan [41] also reviewed the potential mechanisms of natural products as antidiabetic agents. They established different points with potential such as inhibition of glucose absorption in the gut, enhancement of glucose uptake and upregulation of glucose transports, activation of nuclear receptors, increasing adiponectin release, modification of glycogen metabolism, insulinomimetic and insulinotropic effects, ele-

Ethnopharmacological criteria used	Country	Ref.
Antidiabetic herbal drugs officially approved	China	[43]
Antidiabetic plants	Iran	[44–46]
Antidiabetic plants with α-glucosidase activity	Mexico	[47,48]
Medicinal plants with antidiabetic potential	India	[49,50]
Antidiabetic interventions in Ayurvedic medicine	India	[51]
Antidiabetic medicinal	Pakistan	[52]
Medicinal plants used for management of T2DM	Bangladesh	[53,54]
Plant species used as antidiabetics	India, Pakistan, Sri Lanka	[55]
Medicinal plants used in diabetes	Guinea	[56]
Antidiabetic plants with α-glucosidase activity	Philippines	[57]
Plants used against diabetes in Kisangani City	DR Congo	[58]
Ethnomedicinal native remedies used in diabetes	Mauritius	[59,60]
Traditional medicinal plants used in diabetes	Nigeria	[61]
Plants with antidiabetic potential used in African	Africa	[62]
Medicinal plants used in diabetes	Morocco	[63]
Antidiabetic medicinal plants	Jordan	[64]
Antidiabetic remedies from Lima market	Peru	[65]

Table 1 Relevant reviews on antidiabetic medicinal plants from different parts of the world in function of their ethnopharmacogical use.

vation of D-*chiro*-inositol, incretin mimetic and incretin enhancers, roles of endogenous opioids on glucose homeostasis, and antioxidants. New types of antidiabetic drugs have been introduced in treatments in recent years, such as DDP-4 inhibitors, GLP-1 analogs, and cannabinoid receptor type 1 antagonists. Several studies reported that some natural products could act by these mechanisms.

Inhibition of α-glucosidase and α-amylase in the digestive tract

As mentioned above in the Antidiabetics of Plant Origin section, inhibition of α-glucosidase activity was demonstrated as a good strategy for controlling glycemia and in consequence, glucosidase inhibitors have been used in medicine for diabetes treatment. Even though the use of acarbose, the principal drug of this group, is now restricted due to its low efficacy in decreasing glycemia and unpleasant side effects, neither of which are well accepted by both patients and physicians, various researchers focused their studies on different plant extracts containing glucosidase inhibitors without these side effects. For example, Ramírez et al. [47] screened the inhibitory effect of hydroethanolic extracts from 23 medicinal plants used in Mexico as antidiabetics on glucosidase obtained from rat intestinal mucosa. *Camellia sinensis* (L.) Kuntze (Theaceae) displayed the highest inhibitory activity (85%, IC_{50} 299 µg/mL), followed by *Ludwigia octovalvis* (Jacq.) P.H. Raven (Onagraceae) and *Iostephane heterophylla* (Cav.) Benth. Ex Hemsl. (Asteraceae) (83%, IC_{50} 202 µg/mL and 61%, CI_{50} 509 µg/mL, respectively). Although the authors confirmed that the major compounds in the active species are catechins, flavonols, flavones, and caffeoyl derivatives, they proposed more phytochemical assays to detect other active principles.

El-Abhar and Schaalan [41] reviewed and compiled different species with effects on glucose absorption in the gut. Some well-known species, such as *Adathoda vasica* Nees (Acanthaceae), have sucrose inhibitory activity, with vasicine and vasicinol (**Fig. 2**) as potential active phytochemicals, which may be of interest for the future development of new α-glucosidase inhibitory agents. Andrographolide (**Fig. 2**) from *Andrographis paniculata* (Burn. f.) Nees (Acanthaceae) could be another interesting active principle as was demonstrated *in vitro* using porcine α-amylase (IC_{50} = 11.3 ± 0.29 mg/mL) and *in vivo* (10 mg/kg) using diabetic rats as well as pycnogenol from *P. pinaster*. Fenugreek seeds (*Trigonella foenum-graecum* L., Fabaceae) inhibit intestinal glucosidase in diabetic rats (standard laboratory chow supplemented with 20% fenugreek), and have a positive effect on glucolytic and gluconeogenic enzymes to restore glucose homeostasis [41].

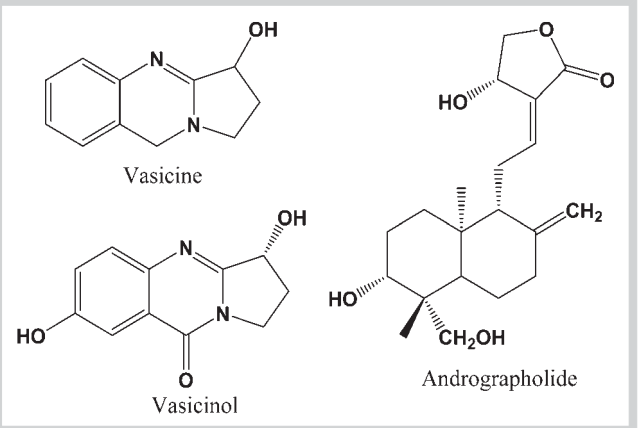


Fig. 2 Chemical structures of vasicine, vasicinol, and andrographolide.

Inhibition of α-amylase is a possibility for treating T2DM by phytotherapy. Amylase inhibitors retard the liberation of glucose from carbohydrates, delaying its intestinal absorption and consequently postprandial glycemia, thus reducing hyperglycemia [67]. In this sense, Melzig and Funke [68] studied the possible use of α-amylase inhibitors from medicinal plants in a supplementary treatment of diabetes. They suggest a rational therapy with traditional herbal preparations and clinical studies, and propose the use of blueberry (leaves), tamarind, lemon balm, rosemary, white kidney beans (hulls), and green tea. Rahimzadeh et al. [69] tested two aqueous leaf extracts from *Urtica dioica* L. (Urticaceae) and *Juglans regia* L. (Juglandaceae) for α-amylase inhibition *in vitro* using acarbose as the standard inhibitor. Both plant extracts showed time- and concentration-dependent competitive inhibition of α-amylase, with the extract from *J. regia* (0.4 mg/mL) being more active than *U. dioica* (2 mg/mL). In the same sense, Picot et al. [60] tested five medicinal plants as potential inhibitors of α-amylase *in vitro*, but only three of them showed activity: *Erythroxylum laurifolium* Lam. (Erythroxylaceae), *Elaeodendron orientale* Jacq. (Celastraceae), and *Antidesma madagascariensis* Lam. (Euphorbiaceae), with IC_{50} values of 7.5,

1.7, and 2.2 mg/mL, respectively. Another interesting study focused on the search for new inhibitions of α-amylase contained endophytic actinomycetes from leaves and stems of medicinal plants such as *Leucas ciliata* Benth. (Lamiaceae) and *Rauwolfia densiflora* (Wall) Benth. ex HK.f (Apocynaceae) [67]. The authors justified their experiments as a good model for finding new sources of antidiabetic agents.

For the same purpose, Li et al. [70] recently investigated and established a ligand screening method based on enzyme-immobilized magnetic nanoparticles integrated with HPLC for studying new α-amylase inhibitors of plant origin. The authors isolated three potential agents from extracts of *Garcinia xanthochymus* Hook.f. (Clusiaceae), which were identified as the bioflavonoids fukugetin, GB2a, and GB2a glucoside. Fukugetin and GB2a gave IC_{50} values of 0.97 µg/mL and 3.46 µg/mL, respectively, whereas the antidiabetic standard drug used, acarbose, showed an IC_{50} value of 9.04 µg/mL. The potency of the GB2a glucoside was clearly lower than the aglycones tested.

Effects on glucose uptake and glucose transporters

In a physiological process in myocytes and adipocytes, insulin induces the activation of the insulin receptor, which leads to the recruitment of IRS proteins followed by activation of phosphatidyl inositol 3 kinase and subsequent translocation of GLUT4 to the plasma membrane and glucose uptake [71]. Different agents targeted this process. For example, a 70% ethanol extract (10 µg/mL) from *Tinospora cordifolia* (Willd.) Miers ex Hook.f. & Thomson (Menispermaceae) and its major compound palmatine (625 nM) (**Fig. 3**) induced overexpression of GLUT-4 up to 5- and 4-fold, respectively. On account of these results, the authors hypothesize that these medicinal plants and palmatine activity are majorly mediated through the insulin pathway [72].

Kadan et al. [73] screened eight medicinal plants used for treating diabetes and tested the effects of the 50% ethanol plant extract on a GLUT4 translocation assay. The extracts were added to L6-GLUT4myc cells in the presence or absence of insulin. Their results indicate that four of the eight plants, *T. foenum-graecum, U. dioica, Atriplex halimus* Ritter ex Moq. (Chenopodiaceae), and *Cinnamomum verum* J.Presl (Lauraceae), induce a significant increase in GLUT translocation, thus suggesting that the antidiabetic properties of these plants are mediated, at least partially, through regulation of this process. However, these results should be taken with caution since the study involved muscle cells overexpressing GLUT4.

El-Abhar and Schaalan [41] described different medicinal plants that upregulate GLUT4 expression or increase its translocation. As relevant antidiabetic plants with active principles, they cited *Cecropia obtusifolia* Bertrol (Cecropiaceae) and chlorogenic acid, *Momordica charantia* L. (Cucurbitaceae), *Lagerstroemia speciosa* (L.) Pers. (Lythraceae) and corosolic acid, *A. paniculata* and andrographolide, and *Panax ginseng* C. A.Meyer (Araliaceae) and ginsenoside Rh2.

Some of these mechanisms are mediated by PPAR. PPARs are a group of three nuclear receptor isoforms (PPARγ, PPARα, and PPARδ) encoded by different genes (*PPAR*G and others). Ligand-regulated transcription factors, they control gene expression (such as *CAP* and *GLUT4*) by binding to specific response elements within promoters [74].

Human PPARα is expressed in several metabolically active tissues including liver, kidney, heart, skeletal muscle, and brown fat. It is also present in monocytic, vascular endothelial, and vascular smooth muscle cells. PPARα plays a critical role in the regulation of cellular uptake, activation, and oxidation of fatty acids, and induces expression of two proteins that transport fatty acids across cell membranes. Thus, an increase in PPARα expression can prevent some risk factors and have a net benefit to improve metabolic outcomes.

PPARγ plays a relevant role in controlling cellular energy homeostasis. Induced during the differentiation of preadipocytes into adipocytes, it plays an important role in lipid metabolism, but al-

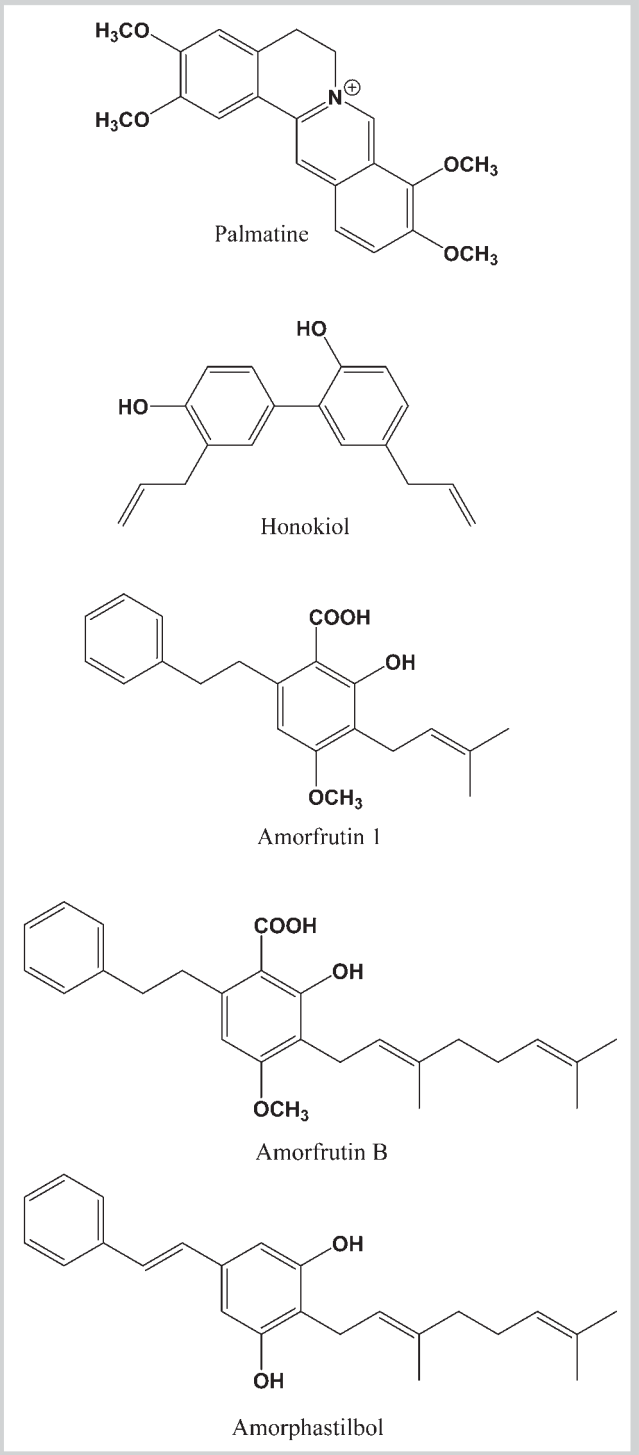


Fig. 3 Chemical structures of palmatine, honokiol, amorfrutin 1, amorfrutin B, and amorphastilbol.

so in other pathways such as inflammation, immunity, and glucose homeostasis. Specifically, PPARγ controls the expression of several factors secreted from adipose tissue that influence insulin sensitivity positively, such as adiponectin and leptin, or negatively, such as resistin and TNF-α. Also, in differentiated adipocytes, PPARγ can directly modulate the expression of genes involved in glucose homeostasis, e.g., it upregulates GLUT4 and CAP, which are encoded by *GLUT4* and *c-CAP* genes, respectively [75]. Some previous reports established that this could be the mechanism of antidiabetic action of plants such as pomegranate (*Punica granatum* L., Lythraceae), which is used in traditional folk medicines of India. The authors cited the possible involvement of oleanolic, ursolic, and gallic acids in this mechanism [76]. In addition, Wang et al. [75] extensively reviewed medicinal plants and their isolated compounds with effects on PPARγ activation and cited 45 medicinal plants and 20 natural products, such as honokiol, amorfrutin 1, amorfrutin B, and amorphastilbol (**Fig. 3**), as potential therapeutic agents to counteract metabolic syndrome and T2DM [75]. For example, honokiol binds to purified human PPARγ (*Ki* = 22.9 mM), activating PPARγ-dependent reporter gene expression as a partial agonist (EC_{50} = 3.9 µM) and induces glucose uptake but not adipogenesis in 3 T3-L1 cells (at 1–10 µM). In *in vivo* experiments, honokiol decreased blood glucose levels in diabetic KKAy mice with simultaneous suppression of weight gain. For the other three compounds, *Ki* values of binding to purified human PPARγ were 0.24 µM, 0.019 µM, and 0.85 µM, respectively [76].

Sangeetha et al. [72] studied the effects of *T. cordifolia* and one of its major compounds, palmatine, on the expression of PPARα and PPARγ. Whereas the first transcription factor is upregulated by both the extract and alkaloid, the second is downregulated by *T. cordifolia* and palmatine, 0.67- and 0.38-fold, respectively. The moderate upregulation of PPARα expression could in part justify medicinal use of this plant.

Green tea (*C. sinensis*) and its epigallocatechin gallate-enriched extract (**Fig. 4**) improved glucose homeostasis and increased the expression of PPARγ in a fructose fed insulin-resistant hamster model. *Clematis pickeringii* A.Gray (Ranunculaceae) activated the expression of both PPARα and PPARγ in HepG2 cells. Honokiol, the active principle of *Magnolia officinalis* Rehder & E. H.Wilson (Magnoliaceae), stimulated basal glucose uptake and acted as a partial agonist of PPARγ (*in silico* and *in vitro* studies). In a fusion receptor of the yeast Gal4-DNA binding study, rosemary (*Rosmarinus officinalis* L., Lamiaceae) and sage (*Salvia officinalis* L., Lamiaceae) are activators of human PPARγ. Their active principles could be carnosol and carnosic acid, which gave EC_{50} values of 41.2 ± 5.9 µM and 19.6 ± 2.0 µM, respectively [41].

Isoliquiritigenin and liquiritigenin isolated from *Glycyrrhiza glabra* L. (Fabaceae) rhizomes and nine derivatives were screened in an oral glucose tolerance test in normal Swiss albino male mice. Seven out of eleven tested compounds showed a significant blood glucose-lowering effect. The structure-activity relationship indicated that ether and ester groups present in these compounds are relevant for this activity. Isoliquiritigenin, 2′,4′-dimethoxy-4-hydroxychalcone and liquiritigenin-7,4′-dibenzoate (**Fig. 4**) were selected to evaluate their *in vivo* antidiabetic activities at 200, 50, and 50 mg/kg bw, respectively, and were found to be potential candidates for treating diabetes. A previous study demonstrated that chalcone derivative antidiabetic activity is mediated via stimulation of PPARγ, and that flavonoids modify activity of intracellular enzymes such as glucosidases [77].

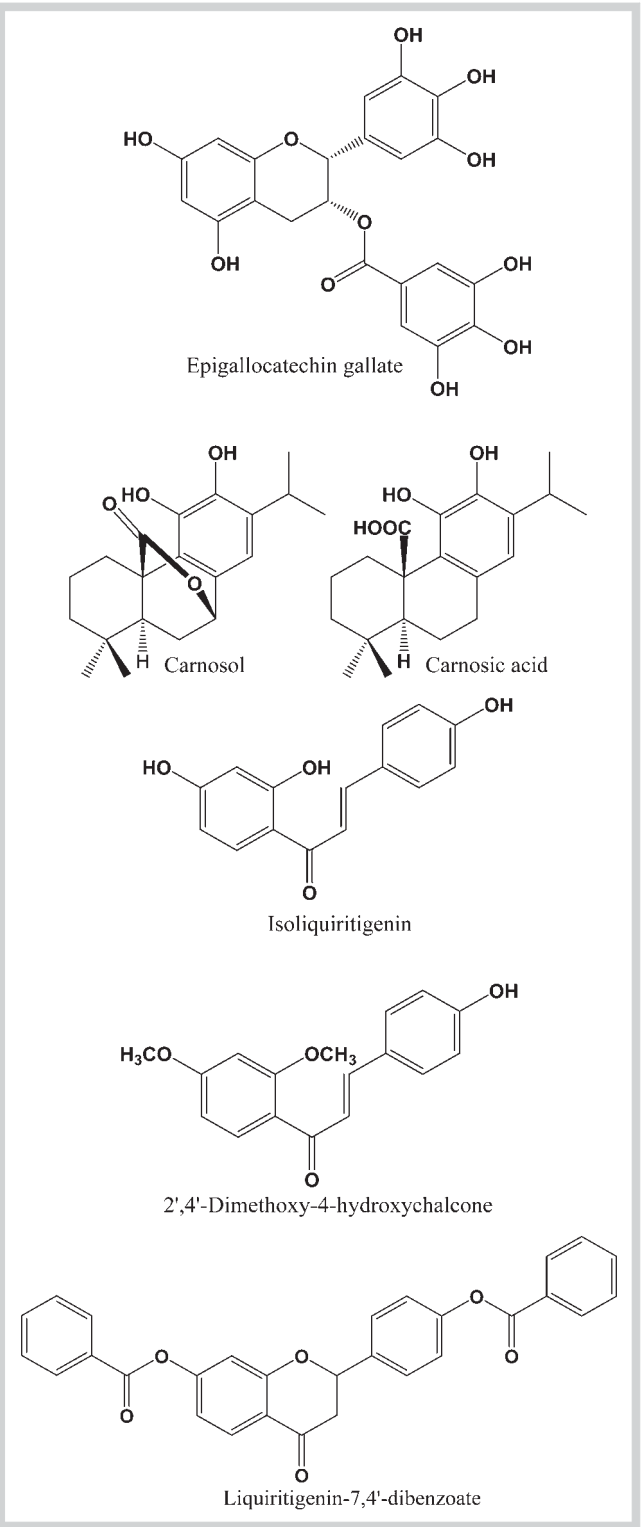


Fig. 4 Chemical structures of epigallocatechin gallate, carnosol, carnosic acid, isoliquiritigenin, 2′,4′-dimethoxy-4-hydroxychalcone, and liquiritigenin-7,4′-dibenzoate.

Adiponectin is a protein exclusively secreted by adipocytes (collectively called adipokines). Epidemiological studies revealed that patients with diabetes have a lower circulating level of adiponectin compared with nondiabetic subjects, thus a low level of this adipokine can be an excellent predictor of developing

T2DM [41]. Some antidiabetic compounds from medicinal plants, such as *I. batatas, Aronia melanocarpa* (Michx.) M.Roem (Rosaceae), and *Salacia reticulata* Wight (Celastraceae), as well as from the mushroom *Agaricus blazei* Murill (Agaricaceae), act to increase adiponectin release.

PPARγ also controls expression of resistin from adipose tissue, which influences insulin sensitivity negatively. Different plant extracts and natural products could modify the expression of this hormone. Studies with *Rehmannia glutinosa* Steud. (Scrophulariaceae) [78], *Lysimachia foenum-graecum* Hance (Primulaceae) [79], and *Garcinia cambogia* Roxb. (Clusiaceae) [80] demonstrated significant reductions in glucose intolerance and the plasma resistin level in treated diabetic mice. However, in this last study, an increase in hepatic collagen accumulation, lipid peroxidation, and cytokine expression was observed. These changes could cause liver inflammation and, in consequence, a potential nondesirable effect. In the case of isolated compounds, trigonelline [81] and oleanolic acid [82] attenuated resistin expression via the downregulation of its gene expression (*ADIPOQ*).

Another point to be considered in the research of antidiabetic medicinal plants in the near future is the study of new antidiabetic agents and new targets for these compounds. For example, the potential effects of the bark of apple trees was reported for the treatment of T2DM as SGLT2 inhibitors, because inhibition of this system could be as efficient as other oral hypoglycemic drugs [83]. However, more highly interesting seems to be the studies of Makarova et al. [84] who analyzed health-promoting properties of apples (*Malus domestica* Borkh., Rosaceae) and phlorizin-enriched powder derived from unripe apples as potential antihyperglycemic agents in healthy volunteers. The unripe apple preparations have 12.6 g/kg of phlorizin. Acute ingestion of the apple preparation improved glucose metabolism in the oral glucose tolerance test by reducing the postprandial glucose response approximately two-fold after 15 to 30 min and by increasing urinary glucose excretion fivefold during the 2 to 4 h interval of the test [84]. Because phlorizin is a competitive inhibitor of SGLT1 (which contributes to renal glucose reabsorption in the small intestine) and SGLT2 (which contributes to glucose reabsorption in the small intestine and nephron), it reduces renal glucose transport, thus lowering glycemia. Some semisynthetic analogs have been introduced in therapeutic treatments as potential antidiabetic agents, as is the case of sergliflozin, remogliflozin, canagliflozin, and dapagliflozin [85], thus illustrating an excellent way for discovering new active compounds, especially in the field of antidiabetic drugs (**Fig. 5**).

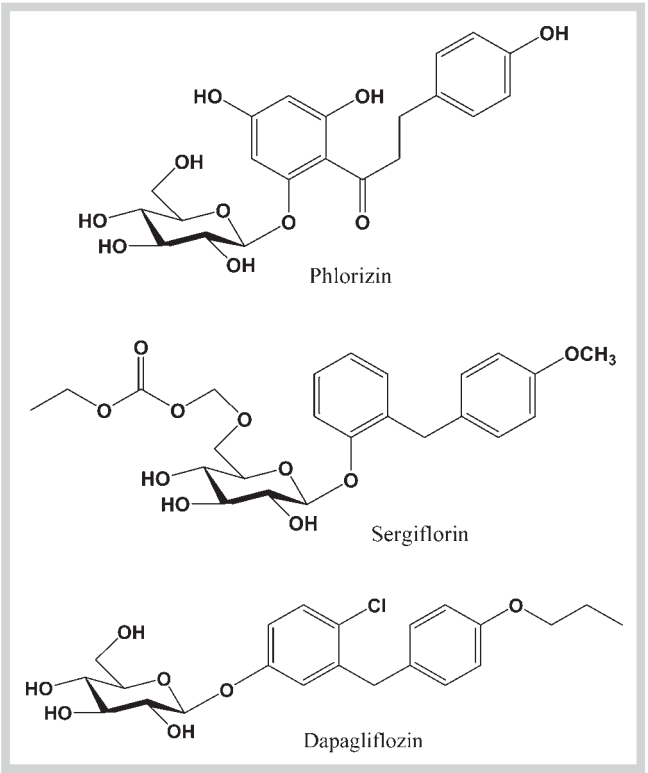


Fig. 5 Chemical structures of phlorizin, sergliflozin, and dapagliflozin.

Enhancers of insulin secretion and pancreatic β cell proliferation

Incretins are gut-derived hormones released in response to nutrient ingestion, principally glucose and fat [86]. They are members of the glucagon superfamily and stimulate pancreatic insulin secretion in a glucose-dependent manner. There are two gut hormones with an incretin effect, the GIP secreted by L-cells of the distal ileum and colon, and GLP-1 secreted by K-cells in the duodenum and jejunum. Both GLP-1 and GIP are rapidly inactivated by the enzyme DPP-4 [87]. In consequence, inhibition of DPP-4 to extend GLP-1 half-life or usage of GLP-1 analogs resitant to DDP-4 degradation are two very well-recognized strategies to find antidiabetic compounds. Different inulin-type fructans (**Fig. 6**), such as those obtained from *Cichorium intybus* L. (Asteraceae) and *Agave tequilana* F. A. C. Weber (Agavaceae), enhance colon production of GLP-1 [41], whereas *Pterocarpus marsupium* Roxb. (Leguminosae), *Eugenia jambolana* Lam. (Myrtaceae), *Agonia cretica* L. (Zygophyllaceae), and *Hedera nepalensis* K.Koch (Araliaceae) inhibit DPP-4.

Kosaraju et al. [88] tested three antidiabetic plants and demonstrated that *P. marsupium* and *E. jambolana* inhibited DPP-4. The third species, *Gymnema sylvestre* (Retz.) R.Br. ex Sm. (Asclepiadaceae), showed a limited effect in this test. Active extracts significantly increased GLP-1 levels with a peak at 2 h. However, Saleem et al. [89] with *Fagonia cretica* L. (Zygophyllaceae) and *H. nepalensis* showed a greater effect as DDP-4 inhibitors, with IC_{50} values in the range of 17.2 to 34.4 µg/mL versus 273.7 to 773.2 µg/m, respectively, values higher than those obtained in the case of plants studied by Kosaraju et al. [88]. Four compounds were identified, three from *F. cretica* (quinovic acid glycosides, **Fig. 6**), which inhibited DPP-4 activity (IC_{50} 30.7–57.9 µM), and one from *H. nepalensis*, the triterpene lupeol (IC_{50} 31.6 µM) [89].

Harmine is the major alkaloid from *Peganum harmala* L. (Zygophyllaceae). It is a competitive inhibitor of ATP binding to the kinase pocket of dual-specificity tyrosine-regulated kinase-1a (DYRK1A) and it likely acts as a mediator of human β cell proliferation and differentiation, but harmine can also inhibit other DYRK family members, monoamine oxidases (MAO), and cdc-like kinases (CLK). In order to avoid these secondary effects, Wang et al. [90] studied different harmine analogs with therapeutic interest, and obtained that INDY, a chemical compound that inhibits DYRK1A but not MAO, activated proliferation in human β cells, whereas harmaline and harmane are inhibitors of MAO but not DYRK1A and did not induce proliferation. The authors concluded that harmine analogs could be a good source of DYRK1A inhibitors with interest for obtaining new antidiabetic agents.

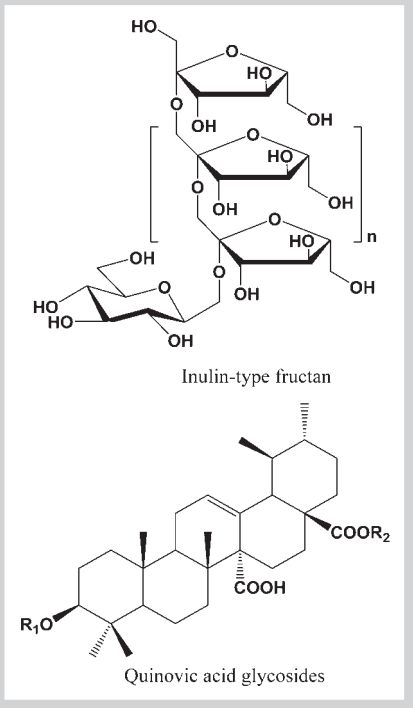


Fig. 6 Chemical structures of inulin-type fructans and quinovic acid glycosides.

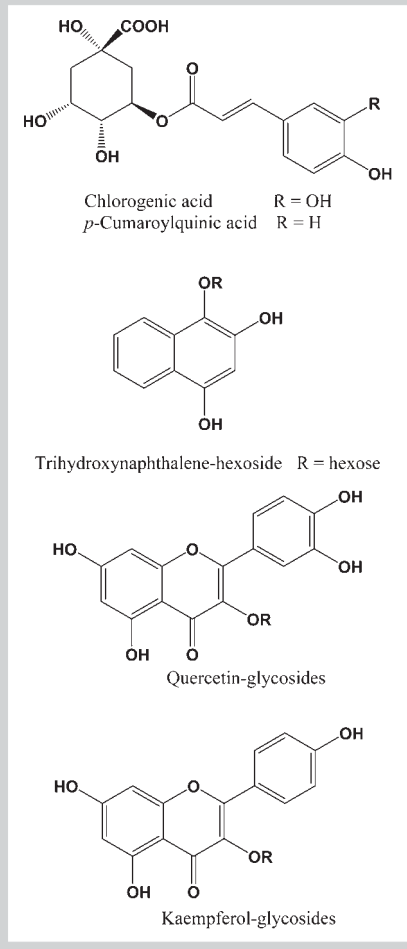


Fig. 7 Chemical structures of chlorogenic acid, 3-*p*-coumaroylquinic acid, trihydroxynaphthalene-hexoside, kaempferol-glycosides, and quercetin-glycosides.

Inhibition of protein tyrosine phosphatase 1B activity

PTP1B negatively regulates the insulin-signaling pathway. This enzyme could be a promising therapeutic target for T2DM treatment [91].

Uddin et al. [92] studied the effects of an ethyl acetate-soluble extract of *Camellia japonica* Wall. (Theaceae) fruit peels together with ten triterpenoids isolated from this plant. Although the study focused on potential anticancer agents in human breast cancer cell lines, the effects of these compounds as PTP1B inhibitors and their chemical structure-activity relationship were established. The PTP1B inhibitory activity range (IC_{50} values) was from 3.77 to 6.40 µM.

The air-dried green leaves of walnut (*J. regia*) are used to treat diabetic symptoms in folk medicine. Their leaf methanolic extract enhanced glucose uptake in myocytes by inhibition of PTP1B but had no effect as a PPARγ agonist. The main compounds identified in this extract were chlorogenic acid, 3-*p*-coumaroylquinic acid, and a trihydroxynaphthalene-hexoside as well as eight flavonoid glycosides derived from kaempferol and quercetin (**Fig. 7**) [93].

Oxidative stress, diabetes, and antioxidants

The metabolic abnormalities of diabetes cause mitochondrial superoxide over-production in several tissues including the endocrine pancreas, which in turn activates pathways involved in the pathogenesis of complications and a further increase in intracellular reactive oxygen species (ROS) [94]. Therefore, ROS seem to be causal agents in the pathogenesis of diabetes by damaging *β* cells. However, the removal of too many ROS may itself lead to metabolic dysfunction and predisposition to diabetes [95]. Consequently, since oxidative stress plays a key role in insulin resistance and *β* cell dysfunction, administration of antioxidants could help to reduce diabetic complications, but it should be considered that a drastic reduction of radicals such as NO after an antioxidant therapy could be implicated in future cardiovascular diseases associated with diabetes. Therefore, different studies were oriented towards this goal. Some examples of species with positive effects are compiled in **Table 2** [41].

Palma et al. [96] evaluated the effects of curcumin (**Fig. 8**) and insulin on antioxidant enzyme activity in blood, liver, and kidney as well as on lipid peroxidation in rats. Histopathological analysis showed that treatment with insulin improved renal and hepatic lesions from both the diabetic insulin-treated group and the diabetic insulin/curcumin-treated group, as well as thiobarbituric acid reactive substance levels in serum, liver, and kidney of the treated groups. Rats treated with curcumin and insulin presented an increase in catalase activity, revealing a positive interaction between both substances. This treatment also prevented the oxidative stress in blood, which was reduced through the modulation of enzymatic antioxidant defenses [96].

Otostegia persica Boiss (Lamiaceae) significantly decreased glycemia in diabetic rats 1–4 h after treatment, parallel to an increase in the serum insulin level. This extract also significantly decreased MDA and increased GSH levels in the liver of diabetic rats. The authors identified thymol (**Fig. 8**) as the major compound in the active extract [97].

Cyanidin-3-*O*-*β*-D-glucopyranoside (**Fig. 8**) from mulberry (*Morus alba* L., Moraceae) fruits has protective effects against oxidative damage in streptozotocin-induced diabetic rat bladder [98]. *Achyranthes aspera* Duss (Amaranthaceae) ethanolic extracts showed antioxidant activity and significantly reduced blood glucose levels in alloxan-induced diabetic mice. This extract also prevented lipid peroxidation and hydroperoxides, increased catalase activity, and reduced nitric oxide levels in the

Table 2 Plants with positive effects in experimental diabetes mellitus through their antioxidant properties [41].

Plant species	Family
Acanthopanax senticosus Harms	Araliaceae
Albizia lebbeck (L.) Benth.	Mimosaceae
Allium sativum L.	Alliaceae
Amaranthus esculentus Besser	Amaranthaceae
Aralia taibaiensis Z. Z.Wang & H. C.Zheng	Araliaceae
Azadirachta indica A.Juss.	Meliaceae
Camellia sinensis (L.) Kuntze	Theaceae
Capparis decidua Edgew.	Capparaceae
Emblica officinalis Gaertn.	Euphorbiaceae
Ficus carica L.	Moraceae
Ficus bengalensis L.	Moraceae
Gentiana olivieri Griseb	Gentianaceae
Lycium barbarum Lam.	Solanaceae
Momordica charantia L.	Cucurbitaceae
Morinda officinalis F. C.How	Rubiaceae
Musa × *sapientum* L.	Musaceae
Ocimum sanctum L.	Lamiaceae
Panax ginseng C. A.Meyer	Araliaceae
Phyllanthus amarus Schumach.	Euphorbiaceae
Plantago depressa Willd.	Plantaginaceae
Pueraria lobata (Willd.) Ohwi	Fabaceae
Punica granatum L.	Lythraceae
Scutellaria baicalensis Georgi	Lamiaceae
Silybum marianum (L.) Gaertn.	Asteraceae
Strobilanthes crispa T. Anderson	Acanthaceae
Vaccinium arctostaphylos L.	Ericaceae

same experiments. The authors conclude that antihyperglycemic activity of *A. aspera* extracts could be mediated by oxidative stress reduction [99]. The methanolic extract of *Picralima nitida* Th. & H.Dur. (Apocynaceae) and the hydroethanolic extract of *Sonchus oleraceus* Wall. (Asteraceae) showed significant antidiabetic activities, with a 39% reduction in glycemia, a significant reduction in MDA and hydrogen peroxide levels, and a substantial increase in catalase activity [100]. *Murraya koenigii* Spreng. (Rutaceae) and *Olea europaea* L. (Oleaceae) reduced serum glucose levels by 56% and 67%, respectively, compared to the metformin group (63%). The authors hypothesized that antioxidants such as carbazole alkaloids and polyphenols in the extract could be responsible for this activity [101].

Berberine (**Fig. 8**) is an alkaloid found in different medicinal plants such as *Berberis vulgaris* L. (Berberidaceae), *Coptis chinensis* Franch. (Ranunculaceae), and *Hydrastis canadensis*. Poir. (Ranunculaceae). It showed antioxidant activity due to its scavenger properties against superoxide free radicals, an increase of sirtuin 1 expression, and attenuation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase expression. Activation of NADPH oxidase is associated with diabetes, and is now considered a potential target to treat the illness and related complications. Therefore, inhibition of NADPH oxidase could partially explain the beneficial effects of berberine on diabetic complications. Inflammation is also critical for the pathogenesis of T2DM, and berberine has shown anti-inflammatory properties, probably due to its capacity to inhibit mediators and transcription factors such as TNF-α, IL-6, IL-1β, matrix metalloproteinase-9, cyclooxygenase-2, iNOS, AMPK, MAPK, nuclear factor erythroid 2-related factor 2 pathway, and NF-κB pathway, which reduced the inflammatory response in T2DM. In conclusion, berberine anti-

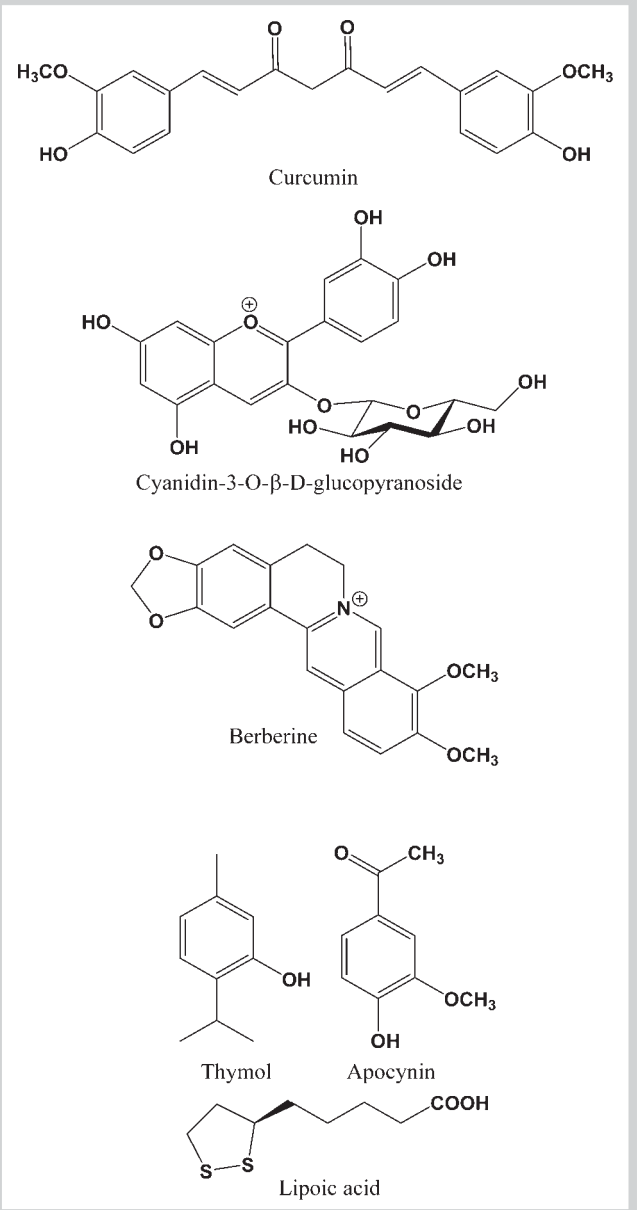


Fig. 8 Chemical structures of curcumin, thymol, cyanidin-3-*O*-*β*-D-glucopyranoside, berberine, apocynin, and lipoic acid.

oxidant and anti-inflammatory activities could contribute to its therapeutic efficacy against T2DM and insulin resistance [102].

Apocynin and lipoic acid (**Fig. 8**) are compounds with high potential as antidiabetic agents. Both compounds are widely distributed in the plant kingdom, and could be the active principles in studied or not yet investigated medicinal plants. Lipoic acid is common in plants of the Brassicaceae family (broccoli and watercress) but also in spinach and potatoes, whereas apocynin is common in *Picrorhiza kurroa* Royle ex Benth. (Scrophulariaceae) but also in other medicinal plants such as *Jatropha multifida* L. (Euphorbiaceae) and *Apocynum cannabinum* L. (Apocynaceae). Castro et al. [103] demonstrated that lipoic acid prevented hyperinsulinemia, hypertriglyceridemia, and insulin resistance, and improved hepatic insulin sensitivity and glucose tolerance. In the case of apocynin, these authors [104] also demonstrated the role of NADPH oxidase in fructose-rich diet-induced hepatic oxidative

stress and metabolic changes, and their prevention by apocynin coadministration. They concluded that inhibition of NADPH oxidase by apocynin prevents changes in plasma and liver functionality, and might become a useful tool for the prevention and treatment of T2DM.

Relevant Clinical Trials with Medicinal Plants and Natural Products

The number of clinical trials carried out with medicinal plants as antidiabetic agents are quite limited and some of them are developed with herbal formulation [105–110]. Other studies include specific medicinal plants or extracts, and measure some characteristic parameter, such as glycated hemoglobin (HbA1c) in patients with T2DM [108]. However, all of these studies were of poor quality with unclear methods of randomization, threats to blinding, and lack of baseline demographics.

In recent years, some interesting articles on natural antidiabetics, including medicinal plants used in folk medicine and phytotherapy, have been reported. Among these plants, bitter melon (*M. charantia*), nettle (*U. dioica*), sage (*S. officinalis*), and walnut tree (*J. regia*) are widely used in folk medicine and some clinical studies were also developed.

Aloe

Vogler and Ernst [109] reviewed antidiabetic properties of *Aloe barbadensis* Mill., syn: *Aloe vera* (L.) Burm.f., (Aloaceae) and selected a study with 72 diabetic women without drug therapy, divided into two groups. They received *A. vera* gel (15 g) or placebo for 42 days. Blood glucose levels subsequently decreased from 250 mg to 141 mg/dL in the experimental group. The same research team investigated the effects of *A. vera* gel in combination with a standard oral antidiabetic therapy (2 × 5 mg oral glibenclamide) and the subjects received either *Aloe* or placebo as above. Results showed similar decreases in blood glucose in the actively treated group as described in the first trial. However, these studies were neither randomized nor blinded to patient or investigator.

Devaraj et al. [110] designed a double-blind, placebo-controlled pilot study of two *Aloe* products (UP780 and AC952) in patients with prediabetes over an 8-week period. A group of 45 subjects with impaired fasting glucose or impaired glucose tolerance was recruited. Parameters such as fasting glucose, insulin, homeostasis model assessment (HOMA), HbA1c, fructosamine, oral glucose tolerance test, and oxidative stress (urinary F2-isoprostanes) were measured along with lipid profile and high-sensitivity C-reactive protein levels before and after supplementation. Compared to the placebo, only the AC952 *A. vera* inner leaf gel powder resulted in a significant reduction in glucose and fructosamine. In the UP780 *A. vera* inner leaf gel powder standardized with 2% aloesin group (**Fig. 9**), there were significant reductions in HbA1c, fructosamine, fasting glucose, insulin, and HOMA. Only the UP780 aloe group had a significant reduction in F2-isoprostanes compared to placebo group. After evaluation of these results, the authors considered that standardized aloe preparations offer an attractive adjunctive strategy to revert impaired fasting glucose and impaired glucose tolerance observed in conditions of prediabetes/metabolic syndrome.

Choi et al. [111] studied the metabolic effects of an *A. vera* gel complex (*Aloe* QDM complex, composed of processed *A. vera* gel 147 mg and aloesin powder 3 mg) on subjects with prediabetes or early T2DM. They determined the effects of the *Aloe* QDM complex on fasting blood glucose, fasting serum insulin, and HOMA-IR in obese individuals (n = 136) with prediabetes or early diabetes mellitus without medical treatment. After 4 weeks, the serum insulin level and HOMA-IR were lower in the intervention group. They also were lower after 8 weeks, but with borderline significance. They concluded that in obese individuals with prediabetes or early-untreated T2DM, *Aloe* QDM complex reduced insulin resistance as well as other parameters such as body weight and body fat mass.

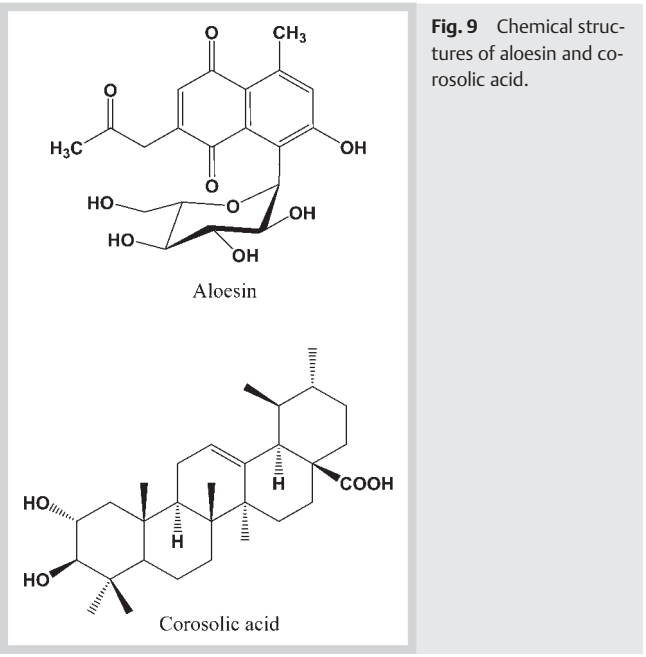


Fig. 9 Chemical structures of aloesin and corosolic acid.

Banaba

The hypoglycemic effects of banaba (*L. speciosa*) have been attributed to both corosolic acid (**Fig. 9**) and ellagitannins [112]. To ratify these properties and active principles, different studies were run *in vitro* in animal models and in human beings using water-soluble banaba leaf extracts (100 mg), corosolic acid-standardized extracts (60 mg containing 10 mg corosolic acid/2 weeks), and purified corosolic acid (10 mg/30 days). Stohs et al. concluded that banaba extract and corosolic acid could improve symptoms associated with metabolic syndrome as well as offering other health benefits. In fact, patients treated with pure corosolic acid (10 mg/30 days) had decreased blood sugar levels within 60 min. The authors also hypothesize that beneficial effects of banaba and corosolic acid with respect to glucose metabolism appear to involve multiple mechanisms, including enhanced cellular uptake of glucose, impaired hydrolysis of sucrose and starches, and decreased gluconeogenesis. These effects could be mediated by PPAR, MAPK, and NF-κB [112].

Bitter melon

M. charantia is a climbing perennial plant that produces elongated fruits with a pronounced bitter taste, which is known as bitter melon or bitter gourd [113]. This species has been studied *in vitro* and *in vivo* for its potential antidiabetic properties, with different parts of this plant (seeds, fruit pulp, leaves, and whole plant) and different doses (from 400 mg to 6 g/day) being assayed. In experiments using rats, *M. charantia* improves glucose

tolerance, suppresses postprandial hyperglycemia, and enhances insulin sensitivity. Several mechanisms of action have been proposed such as induction of glucose uptake and increased adiponectin secretion [41], activation of the AMPK system, and PPARα and PPARγ receptor activation. PPARα and PPARγ are pivotal in lipid and glucose hemostasis and may mitigate insulin resistance [106]. Different compounds have been isolated and some of them have been implicated as potential active principles such as α-eleostearic acid (9-*cis*, 11-*trans*, 13-*trans* octadecatrienoic acid) as a PPARα activator [114]. However, a Zn-free protein bearing insulinomimetic activities has been isolated from the fruit of this plant [115], which could be related to the protein called "vegetable insulin" reported 30 years ago [113].

Nahas and Moher [37] reviewed previous clinical trials and cited one with 40 and a second with 51 patients in which no effects on HbA1c or fasting blood glucose were reported. Leung et al. [113] compiled ten clinical studies performed until 2008, but only five were relevant and only four were designed as clinical trials. Some of these reported significant results in the reduction of both fasting and postprandial sugar levels. However, the different size of the trials, forms of administration (methanol extract, dried powder, fresh fruit or enriched fraction), dosage (timing and dose), and outcome measures (HbA1c, postprandial sugar levels or oral glucose tolerance test), use of the same subjects as controls and trials, different reports on adverse effects, etc., render these studies only relatively interesting for the use of this medicinal plant as an antidiabetic.

Ooi et al. [116,117] compiled randomized, controlled trials that compared *M. charantia* for T2DM with a placebo or a control intervention, with or without pharmacological or non-pharmacological interventions. Four randomized, controlled trials with up to three months' duration and studying 479 participants met the inclusion criteria. The results showed no statistically significant difference in glycemic control with *M. charantia* preparations compared to the placebo or reference drugs metformin and glibenclamide. No serious adverse effects were reported in any trial.

Medagama and Bandara [118] reviewed the clinical trial of bitter melon and cited several objections to establishing its clinical efficacy: heterogeneity of patients, doses (0.5 to 6 g/day), method of preparation, dosage, and primary outcome measures in the different studies. A relevant point was that two studies used dried fruit and another used a commercially available preparation. However, when fresh juice was used in a case series, there was a significant reduction of fasting plasma glucose and postprandial plasma glucose. These effects could indicate the importance of the type of fruit and method of preparation for future studies.

Caper

Caper bush, *Capparis spinosa* L. (Capparaceae), is a perennial plant with edible flower buds (capers) and fruit (caper berries). The fruits are traditionally used as antihyperglycemic food by Iranian diabetic patients. Huseini et al. [119] conducted a randomized clinical trial with 54 patients (40–65 years of age) with established T2DM and standard antidiabetic therapy. For 2 months the treated group (n = 28) received 400 mg extract × 3 each day vs. placebo (n = 26). The results showed a significant decrease in fasting blood glucose levels (11.2%) and HbA1c (4.8%) in caper-treated patients compared to the control, whereas the placebo group also had a clear reduction when compared with controls, 4.2% and 2.0%, respectively, in fasting blood glucose levels and glycosylated hemoglobin at the end of the study. However, other parameters showed a higher reduction, such as triglyceride level (24%) in the caper-treated group vs. control (16%). The authors concluded that caper fruits could be used as an adjuvant agent for the treatment of diabetic patients. However, these authors specify some deficiencies of their study, such as the small sample size and lack of identification of active constituents.

Cinnamon

Cinnamon, *Cinnamomum cassia* Siebold (Lauraceae), is a spice with high global consumption. It was claimed to be a natural insulin sensitizer in adipocytes and in different animal models [120–124]. In these studies, different active compounds were isolated and identified, such as a methylhydroxychalcone polymer with insulin-mimetic effects [123,124], but the study was not confirmed by Anderson et al. [125] who suggested that the active compounds had been likely misidentified.

In 2003, Khan et al. [126] published the first study on cinnamon supplementation in humans, which reported a clear reduction in fasting glycemia (18–29%) after 40 days of daily supplementation with only 1, 3, or 6 g of cinnamon in patients with T2DM. However, this study did not report any dietary standardization during the intervention, and the authors did not include potential changes in blood insulin and/or HbA1c concentrations. More recently, Vanschoonbeek et al. [127] designed a similar study but with 25 postmenopausal patients with T2DM that were supplemented with either cinnamon (1.5 g/day) or a placebo, concluding that cinnamon supplementation does not improve whole-body insulin sensitivity or oral glucose tolerance in these patients.

Pham et al. [128] reviewed clinical trials and found two prospective, randomized, double-blind, placebo-controlled, peer-reviewed clinical trials and one prospective, placebo-controlled, peer-reviewed clinical trial that evaluated the efficacy of cinnamon supplementation (1 to 6 g/day) in patients with T2DM, with a total of 164 patients involved in these trials. Two of these trials reported modest improvements of glycemia, suggesting that cinnamon has a quite modest effect on glycemia in patients with poorly controlled T2DM.

Kirkham et al. [129] reviewed the therapeutic potential of *C. verum* and *C. cassia* in patients with diabetes and insulin resistance, particularly their ability to reduce blood glucose levels and inhibit protein glycation. Two of the studies showed significant fasting blood glucose reductions (between 10 and 29%), one of them reported an 8.4% reduction vs. the placebo, and another reported a significant reduction in glucose response using oral glucose tolerance tests. Doses varied from 1 to 10 g/daily, and 1 to 3 months. Three diabetic studies selected reported no significant results.

Two years later, Davis and Yokoyama [130] made a meta-analysis of clinical studies, including three new clinical trials along with five trials used in previous meta-analyses, using a literature search of randomized, placebo-controlled trials reporting data on cinnamon and/or cinnamon extract effects on fasting blood glucose in T2DM or prediabetic patients. They reported that the intake of cinnamon or its extract results in a significant lowering in fasting glycemia of about − 0.5 mmol/L in these patients [124].

In 2012, Leach and Kumar [131] reviewed randomized, controlled trials comparing the effects of orally administered cinnamon (2 g/day for a period ranging from 4 to 16 weeks) vs. a placebo, active medication, or no treatment. After identifying ten prospective, parallel-group designs, randomized controlled trials, involving 577 participants, the authors concluded that the effect of cinnamon on fasting blood glucose level is not conclusive. However, the same year, Akilen et al. [132] reported a sys-

tematic review and meta-analysis on the effect of cinnamon on glycemic control in patients with T2DM (six clinical trials with a total of 435 patients, 40 days to 4 months, 1 to 6 g per day). The results showed a significant decrease in mean HbA1c and fasting plasma glucose, concluding that the use of cinnamon could be beneficial for glycemic control and that the short-term (< 4 months) effects of its use look promising.

In conclusion, although cinnamon clearly possesses antihyperglycemic properties and the potential to reduce postprandial blood glucose levels, no definitive conclusions can be established for its use in antidiabetic therapy.

Cocoa

Cocoa, *Theobroma cacao* L. (Sterculiaceae), and its derivatives are of interest in the prevention of cardiovascular disease [133, 134]. In a clinical trial, Grassi et al. [135] studied the effect of flavanols from chocolate on different cardiovascular risk factors in hypertensive patients, including insulin sensitivity and β cell function. They used two groups of hypertensive patients, randomized to receive either flavanol-rich dark chocolate or flavanol-free white chocolate (100 g/day for 15 days). The results showed that the first group but not the second decreased insulin resistance and increased insulin sensitivity and β cell function. Some years later, Hooper et al. [136] realized a systematic review on the effects of cocoa, chocolate, and flavan-3-ols (**Fig. 10**) on the classic risk factors, and also considered the reciprocal relation between insulin resistance and endothelial dysfunction [137] as well as other independent predictors such as fasting glucose, insulin, and HbA1c. The review, including 42 acute or short-term, randomized controlled trials with 1297 patients, showed that chocolate or cocoa induced a significant reduction in serum insulin without negative effects, thus suggesting insulin resistance improvement [136].

Coffee

Seeds of coffee, *Coffea arabica* L. (Rubiaceae), intake is associated with a reduced risk of T2DM. To confirm this property, Salazar-Martínez et al. [138] examined the long-term relationship between the consumption of coffee and other caffeinated beverages and the incidence of T2DM in a prospective cohort study (The Nurses' Health Study and Health Professionals' Follow-up Study). They followed up 41 934 men (1986 to 1998) and 84 276 women (1980 to 1998) without diabetes, and 1333 new cases of T2DM in men and 4085 new cases in women were documented. They found an inverse association between coffee intake and T2DM, thus suggesting that long-term coffee consumption is associated with a significantly lower risk for the disease [138]. This effect was associated with mineral and antioxidant contents, but the role of caffeine was not specified until the Pereira et al. study [139]. These authors demonstrated in a prospective analysis with a cohort of 28 812 postmenopausal women free of diabetes of the Iowa Women's Health Study (1986–1997) that coffee intake, especially decaffeinated, was inversely associated with a risk of T2DM.

Fenugreek

Seeds of fenugreek (*T. foenum-graecum*) are used to enhance flavor, color, and texture of food, and are also used for medicinal purposes. Different epidemiological and laboratory studies have ratified their medicinal properties [140–143]. Studies in humans demonstrated that fenugreek exerts hypoglycemic effects by stimulating glucose-dependent insulin secretion from pancreatic

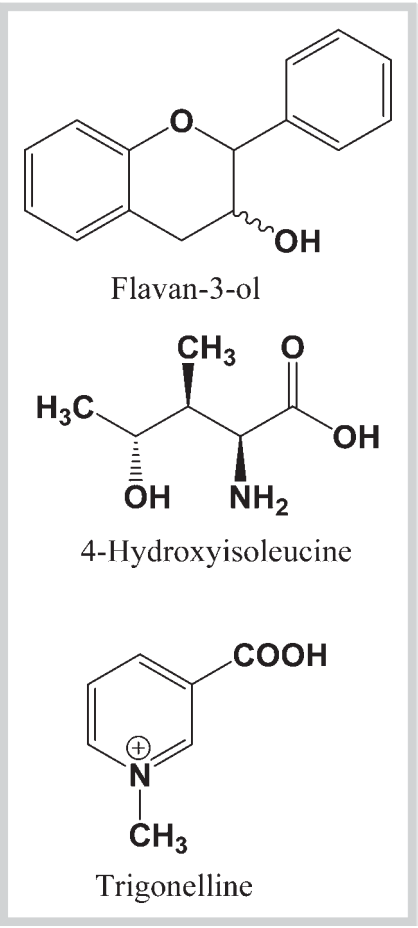


Fig. 10 Chemical structures of flavan-3-ols, 4-hydroxyisoleucine, and trigonelline.

β cells and increasing the number of insulin receptors as well as by inhibiting the activity of α-amylase and sucrase [140]. Previous clinical trials were run with weak methodology and lacked an adequate description of blinding, randomization, baseline patients' characteristics, statistical analysis, and standardization data for the therapy used [140].

Recently, Neelakantan et al. [144] reviewed clinical trials on the effect of fenugreek intake on markers of glucose homeostasis. Ten trials were identified in which fenugreek significantly changed fasting blood glucose, post-load glucose, and HbA1c compared to control interventions. Heterogeneity of results was partly justified by the diabetes status of the patients, study design (parallel or crossover), study duration (< 30 days or ≥ 30 days), and dose employed (< 5 g, 5–10 g, or > 10 g) since significant effects on fasting and 2 h glucose were found only in studies performed in diabetic patients that received medium or high doses of fenugreek. In conclusion, clinical trials support beneficial effects of fenugreek seeds on glycemic control in persons with diabetes.

Several studies identified different compounds responsible for the abovementioned effects. Basch et al. [140] established that the amino acid 4-hydroxyisoleucine (**Fig. 10**) is responsible for the increase in glucose-induced insulin release in humans, acting on pancreatic β cells. Another potential active principle is trigonelline (**Fig. 10**), the major alkaloid component of fenugreek, which has hypoglycemic activity, reduces diabetic auditory neuropathy, and affects β cell regeneration, insulin secretion, and activities of enzymes related to glucose metabolism as well as antioxidant capacity [145]. Swaroop et al. [143] cited the furostanolic

saponins as active compounds, whereas Perla and Jayanty [24] established that biguanide-related compounds could be, in part, the active principles given that fenugreek seeds contain a relevant amount of these compounds (18.98 µg/g).

Garlic

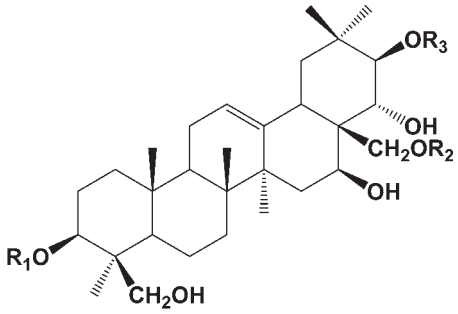
Garlic, *Allium sativum* L. (Alliaceae), has been used in India for its antidiabetic properties since ancient times [49]. In recent years, different *in vitro* and *in vivo* studies demonstrated garlic's antihyperglycemic effects. Ackermann et al. [146] reviewed the effects of garlic on several cardiovascular-related factors and its adverse effects; after analyzing 45 randomized trials, they observed no effects on glycemic-related outcomes. In their conclusions, the authors recommend future studies with clear definitions of constituents and preparations, because in these clinical trials there are great variations of samples (oil macerate, aged garlic, and different kinds of extracts) and doses (from 10 mg to 10 g). Some years later, Mohammadi and Oshaghi [147], working with mice, observed that garlic extract antagonized LXRα, an important regulator of cholesterol, triglycerides, and glucose homeostasis, and increased LXRα expression in the intestine. These effects could have an important role in the reduction of the lipid profile by garlic, which would justify the potential for this treatment of diabetes, but it should be demonstrated in humans.

Guava

Psidium guajava L. (Myrtaceae) or guava, also known as guayaba (Spanish), is a food crop and medicinal plant from tropical countries whose leaves (water extract) are used to reduce hyperglycemia in diabetic patients in Mexico. Many papers describing its pharmacological activities have been published, and Gutiérrez et al. reported two clinical assays [148]. In one paper in China, a multicentric, randomized, controlled trial evaluated the efficacy of guava in diabetes management. After oral administration of 500 mg of aqueous leaf extract to 50 diabetic patients, they considered that guava could be used as a complementary therapy for preventing and treating diabetes mellitus, but not as a principal agent, since it is less effective than standard drugs. In the second trial, oral administration of 500 mg (fruit) to 40 patients decreased glycemia after 3 weeks of treatment compared to the diabetic control group.

Gymnema

The leaf of *G. sylvestre* is a reputed herb in both Ayurvedic and Western medicines. It shows positive effects on blood sugar homeostasis and controls sugar cravings [149]. It acts through the stimulation of insulin secretion from pancreatic β cells, and some active compounds have been cited such as gymnemic acids and gurmarin, a 35-amino-acid peptide (4209 MW) (**Fig. 11**). Kosaraju et al. [88] demonstrated that *Gymnema* showed a limited effect on GLP-1 levels, although other effects, such as the interaction with glyceraldehyde-3-phosphate dehydrogenase, a key enzyme in glycolysis pathway, have been described [149]. Complementary mechanisms were described for this species, such as the modulation of the enzymes responsible for glucose utilization (increased phosphorylase activity and decreased activity of gluconeogenic enzymes and sorbitol dehydrogenase) and inhibition of glucose absorption in the bowel [150]. Other effects of *Gymnema* extract include a prolonged hypoglycemic action of exogenous insulin in dogs without a pancreas, intensification of effects of insulin, and extended duration of reduced glucose levels. These effects were observed after administration of the extract, the saponin fraction, or isolated triterpene glycosides [150, 151]. Some of these properties have been confirmed in different clinical trials conducted in the US with a patented preparation based on a standardized extract (400 mg/day), but 27 patients with type 1 diabetes mellitus with insulin therapy were studied, and it was concluded that *Gymnema* increases the endogenous levels of insulin, possibly due to pancreatic regeneration [150]. However, two small, open-label trials have also yielded promising results after administration of *Gymnema* to patients with T2DM. In the first trial, patients that received 200 mg daily for 18 to 20 months of an ethanolic extract significantly improved fasting blood glucose and HbA1c levels. The second trial was uncontrolled, and patients that received 800 mg daily of a similar extract for 3 months reduced fasting blood glucose and HbA1c levels; however, they used a mixed population of 65 patients with type 1 and type 2 diabetes. In conclusion, *Gymnema* reduced HbA1c levels and appears to improve glycemic control, although complementary studies are necessary [37]. In a later study, T2DM patients received 500 mg herb/day for 3 months and the treated group reduced both fasting and postprandial blood glucose and HbA1c [152]. All together, these findings suggest that *Gymnema* extract could be beneficial for the management of diabetes mellitus.



Gymnemic acids

<1Glu-Gln-Cys-Val-5Lys-Lys-Asp-Glu-Leu-10Cys-Ile-Pro-Tyr-Tyr-15Leu-Asp-Cys-Cys-Glu-20Pro-Leu-Glu- Cys-Lys-25Lys-Val-Asn-Trp-Trp-30Asp-His-Lys-Cys-Ile-35Gly>
(Glu = pyroglutamic-acid residue)

Gurmarin

Fig. 11 Chemical structures of gymnemic acids and gurmarin.

Nettle

U. dioica is a herbaceous perennial flowering plant with many hollow stinging hairs on the leaves and stems, which break off to leave a sharp, needle-like tube that pierces the skin and injects histamine and acetylcholine, causing itching and burning. Its roots are used against benign prostatic hyperplasia and its leaves are used in traditional medicine as an antihyperglycemic agent to treat diabetes mellitus [153]. Studies in animals demonstrated that nettle leaves have insulin secretagogue, PPARγ agonistic, and α-glucosidase inhibitory effects [69, 154]. Kianbakht et al. [155] ran a randomized, double-blind, placebo-controlled clinical trial to evaluate the effects of nettle leaf extract (500 mg/8 h, 3 months) combined with conventional oral antihyperglycemic drugs. The clinical trial included 46 treated patients vs. 46 in the placebo group. At the endpoint, the extract significantly lowered

the blood levels of fasting glucose, 2 h postprandial glucose, and HbA1c, without significant effects on other hepatic or cardiovascular parameters vs. the placebo. All considered, these results demonstrated that nettle is safe and may have a beneficial effect on glycemic control in patients with advanced T2DM needing insulin therapy. Nettle may also improve efficacy of conventional oral antihyperglycemic drugs to control glycemia, although the authors consider that further trials with a larger number of patients to assess the efficacy and safety of nettle as well as more studies addressing mechanisms and bioactivity involved in its antidiabetic effects are necessary [155].

Sage

Leaves of *S. officinalis* are used to treat digestive and metabolic disorders including T2DM [156]. Their antihyperglycemic effect has been studied in different animal model of diabetes [157, 158] and in a crossover trial with six healthy female volunteers [159] as well as a 2-month randomized, double-blind, placebo controlled trial [160], but no glycemia was assayed. However, two years later, the last authors evaluated the efficacy and safety of a sage leaf extract in the treatment of 86 hyperlipidemic T2DM patients using a randomized, placebo-controlled, parallel group study with 42 treated patients treated with leaf hydroethanolic extract (500 mg/8 h for 3 months) and 44 as placebo groups. In this case, fasting glucose and HbA1c values were determined, together with the lipidemic profile. They described that the leaf extract lowered fasting glucose and HbA1c compared to the baseline at the endpoint with no adverse effects reported. Therefore, they concluded that sage leaves might be safe and have antihyperglycemic effects in hyperlipidemic T2DM patients since the lipidemic profile also improved [156].

Soybean

Estrogens have been reported to be beneficial for the prevention and treatment of T2DM by attenuating insulin resistance, improving insulin secretion, and increasing the β cell mass [161]. As a result, there are some studies on the potential of isoflavonoids derived from *Glycine max* (L.) Merr. (Fabaceae) as antidiabetic agents since they may improve glucose homeostasis through estrogenic action. Other authors also reported that, although the lack of testing with human subjects does not permit definitive conclusions, evidence suggests that fermented soy products may be better for preventing or delaying the progression of T2DM compared to nonfermented soybeans [162].

Some years later, Zhang et al. [163] conducted a systematic review and meta-analysis to confirm the effects of soy isoflavone supplementation on body weight and fasting glucose and insulin levels in non-Asian postmenopausal women. They analyzed three groups: a) nine studies with 528 participants for body weight, b) eleven studies with 1182 participants for fasting glucose, and c) eleven studies with 1142 participants for fasting insulin. The dose of treatment varied from 40 to 160 mg, and the duration varied from 8 weeks to 1 year. They observed significant reductions in body weight and glucose and fasting insulin levels with soy isoflavone supplementation compared to the placebo control group. Isoflavones could also significantly reduce blood glucose in longer treatments (> 6 months) in postmenopausal women. The authors concluded that soy isoflavones could be beneficial for glucose and insulin control as well as body weight reduction, but they recommended larger and well-designed studies to confirm these data.

Tea

Various studies report that polyphenolic compounds present in green and black tea (*C. sinensis*) are associated with beneficial effects in the prevention of cardiovascular disease and antidiabetic properties [164]. In this direction, different studies have been designed in order to identify the effects of tea on glucose metabolism and insulin signaling as well as possible positive effects on patients with established diabetes. The Women's Health Study described that tea drinkers (drinking ≥ 4 cups of tea/day) had a 30% lower risk for developing T2DM vs. non-tea consuming women [165]. In the Japanese, who consume ≥ 4 cups of green tea daily, there is a 33% reduced risk for diabetes, but no reduction was observed for red or black teas [166]. However, Neyestani et al. [167] reported the positive effect of black tea intake on different biomarkers in the serum of patients with T2DM (total antioxidant capacity, MDA, C-reactive protein, and GSH levels). The positive effect of green tea was correlated with the continuous ingestion of catechin-rich beverages. In effect, in a double-blind, controlled study, patients with T2DM without insulin therapy received green tea (582.8 mg catechins or 96.3 mg of catechins/day for 12 weeks) and at the end of the trial, there was an increase in insulin and a decrease in HbA1c levels in the catechin group vs. the control [168].

Turmeric

The dried powder of the rhizome of *Curcuma longa* L. (Zingiberaceae) has been used for centuries as a medicinal agent and specifically as an antidiabetic drug. Both the rhizome extract and its principal component, curcumin (**Fig. 8**), have been extensively studied. However, studies over the past decade have indicated that curcumin-free turmeric components also possess antidiabetic properties [169]. Gupta et al. [170] compiled data from clinical trials on turmeric, including diabetes. One study examined the effects of turmeric on postprandial plasma glucose and insulin levels and the glycemic index in 14 healthy subjects in a crossover trial. Ingestion of turmeric increased postprandial serum insulin levels without affecting glycemia or the glycemic index, thereby suggesting an effect on insulin secretion [171]. In a complementary study, Khajehdehi et al. [172] investigated the effects of turmeric on serum and urinary TGF-β, IL-8, and TNF-α as well as proteinuria on 40 patients with overt T2DM nephropathy. They were randomly assigned to either a trial group (500 mg of turmeric, 3 times/day, 2 months) or the control group. The results showed that serum concentrations of the parameters studied (TGF-β, IL-8, and TNF-α) decreased significantly with no adverse effects related to turmeric supplementation. Because TGF-β plays a key role in the pathogenesis of diabetic nephropathy, and elevated concentrations of serum TNF-α and urinary levels of IL-8 are associated with a decline in renal function in type 1 diabetic nephropathy, turmeric supplementation in a diet could be a promising approach as a safe and effective alternative therapy for T2DM nephropathy [172].

Other studies on diabetic retinopathy established that the therapeutic potential of curcumin for delaying this damage is exerted through its antioxidant and anti-inflammatory properties as well as inhibition of vascular endothelial growth factor, stromal cell-derived factor 1, and PPARγ [173]. However, since the digestive system poorly absorbs dietary curcumin, this fraction becomes inactive by glucuronidation and is instead excreted. In consequence, it is unclear how dietary curcumin exerts its beneficial effects in T2DM and associated diseases. Therefore, Maradana et al. [174] reviewed new methods of delivering curcumin, including

nanoparticles and lipid/liposome formulations that increase intestinal absorption and bioavailability of curcumin. For example, a curcumin-phosphatidylcholine complex (Meriva, 1 g/day, 4 weeks) increases bioavailability of oral curcumin and is safe for human use. These preliminary findings suggested the usefulness of this and other curcumin formulations for the management of diabetic microangiopathy, although further studies are necessary to determinate whether curcumin/lipid complexes increase the efficacy of oral curcumin alone.

Walnut

J. regia is known as the common walnut tree and its fruits as walnuts. The leaves of this tree are traditionally used for the treatment of diabetes in different Asiatic and Mediterranean countries [175]. Different *in vitro* and *in vivo* studies in animals determined its potential value as an antidiabetic medicinal plant [176–181]. In order to determine the effects on humans, Hosseini et al. [176,179] studied the effects of an aqueous leaf extract on 58 Iranian T2DM patients. Male and female patients were randomly divided into two groups. One group (n = 30) received 100 mg of leaf extract twice per day for 3 months, and the other a placebo (n = 28). HbA1c, blood glucose, insulin, serum glutamic oxaloacetic transaminase, serum glutamate-pyruvate transaminase, and alkaline phosphate levels were evaluated at the beginning and after 2 months of the trial. Serum fasting HbA1c and blood glucose levels significantly decreased, and the insulin level increased in the group treated with walnut leaf extract. In a complementary study, the same authors studied 61 T2DM patients (40–60 years of age) with a fasting blood glucose between 150 and 200 mg/dL and HbA1c between 7 and 9%, and randomly divided them into two groups. The treatment group received 100 mg of leaf extract, twice per day for 3 months. The standard antidiabetic therapy (metformin and glibenclamide) as well as nutritional diet were followed in both groups. After three months, the glucose and HbA1c levels of the treated patients had significantly decreased compared to the placebo group, and no relevant side effects were observed [175,179]. *In vitro* studies proposed that the inhibition of α-amylase [69], the inhibition of glycation and oxidation reactions [180], and the inhibition of PTP1B [93] were possible mechanisms of action.

Yerba mate

Ilex paraguariensis A. St.-Hil. (Aquifoliaceae), commonly known as "yerba mate" or "té del Paraguay", was originally used to prepare psychostimulant beverages, but was subsequently included in phytotherapy worldwide [181–183]. In addition to its effects on the nervous system, other effects such as vasodilator, hypolipidemic associated with weight reduction, and antidiabetic, mainly by virtue of its antioxidant capacity, have been described. Some *in vivo* studies have also been done in recent years. Oliveira et al. [184] evaluated the antidiabetic properties of yerba mate extract in alloxan-induced diabetic Wistar rats and demonstrated that yerba mate interfered with glucose absorption in the gut by decreasing SGLT1 expression. However, no significant differences in serum glucose, insulin, and hepatic glucose-6-phosphatase activity vs. the control were observed. Yerba mate extract also affects food intake, lipid metabolism, and glucose concentrations [185], and ameliorates insulin resistance in mice with high-fat diet-induced obesity [186]. In this last study, the authors demonstrated a restoration of hepatic, IRS-1, and protein kinase B (Akt) phosphorylation. In addition, the high-fat diet caused the upregulation of TNF-α, IL-6, and iNOS gene expression and a reduction of NF-κB nuclear translocation. It is known that the TNF-α receptor results in the serine phosphorylation of IRS-1, which attenuates its ability to transduce insulin-mediated cellular events [186]. In a complementary study, Pereira et al. [187] demonstrated that the polar fractions (polyphenols) from yerba mate induced insulin secretion, inhibited *in vitro* disaccharidase activities with a maximum inhibitory effect on maltase activity of 35%, and reduced protein glycation by glucose or fructose by around 50% and 90%, respectively. They concluded that yerba mate has a potential antihyperglycemic role that may be able to improve diabetic status and could be a source of multiple hypoglycemic compounds.

As mentioned in the introduction, obesity is associated with an increased risk of developing insulin resistance and T2DM. It is well known that adipose tissue of obese individuals releases increased amounts of non-esterified fatty acids, glycerol, hormones, and pro-inflammatory cytokines (adipokines) involved in the development of insulin resistance and T2DM [188]. De Morais et al. [189] showed that yerba mate intake by dyslipidemic individuals had antiobesity activity (330 mL of green or roasted yerba mate infusions, 3 times per day for 40 days). A 60-day intervention pilot study evaluated the effects of roasted mate tea consumption (330 mL, 3 times per day), with or without dietary counseling, on glycemic and lipid profiles of individuals with T2DM or prediabetes [190]. Mate tea consumption significantly decreased the levels of fasting glucose, glycated HbA1c, and LDL-c in T2DM subjects, and in prediabetic individuals, LDL-c, non-HDL-c, and triglycerides diminished significantly. More recently, in another pilot study, the effects of yerba mate were also studied in 11 T2DM and 11 prediabetic volunteers (1 L/day of mate tea) [191]. T2DM subjects showed a significant reduction in fasting plasma glucose and HbA1c after 60 days of mate tea consumption; however, normal values were not achieved. In prediabetic individuals, mate tea intake did not promote a decrease in fasting plasma glucose, but did significantly lower the HbA1c concentration after 40 days of treatment.

Future Perspectives and Conclusions

Varied and interesting approaches have been proposed for treating T2DM. There are many preclinical studies in animals as well as screening of medicinal plants used for treating diabetes in different parts of the world. However, the major interest could be the increasing number of systematic reviews on clinical trials developed in recent times. They open new possibilities with a high level of credibility in the field of medicinal plants and natural products. Some new aspects in research are introduced and some points of view could be of high interest, such as genomic, metabolomics, or *in silico* studies. For example, Anuradha [192] reviewed the nutrigenomic approaches based on ethnopharmacology and phytotherapy concepts and their relation to T2DM. Indeed, the interaction between bioactive food components and the genome may influence cell processes and modulate the onset and progression of T2DM, the disease being susceptible to dietary intervention. The authors identified many phytochemicals from traditional medicinal plants that can target diabetogenic genes, and established a future application of nutritional therapy for the modification of genes relevant for diabetes. Other authors propose the use of a structure-based design of compounds from natural sources for diabetes. From the literature, they selected three targets: α-glucosidase, aldose reductase and PTP1B en-

zymes, and carried out a high throughput virtual screening followed by induced fit docking studies. They applied this study to a number of natural products, and concluded that some of the natural inhibitors successively satisfied all the *in silico* parameters and could be of interest as antidiabetic agents [193].

In the near future, some interesting new sources should be tested and their active principles studied. For example, Melzig and Funke [68] proposed blueberry (leaves), tamarind, lemon balm, rosemary, white kidney beans (hulls) and green tea as medicinal plants with high interest for clinical trials. Other aspect to be considered for future research is the potential effect on specific or new targets implicated in T2DM. As a proof of concept the study of the bark of apple trees as SGLT2 inhibitor drove to the isolation of phlorizin, and then several semisynthetic derivatives were obtained and used as antidiabetic drugs, such as sergliflozin, remogliflozin, canagliflozin and dapagliflozin [84,85].

Other aspect of interest is the potential interaction and posibles incompatibilities of antidiabetic plants with drugs used in human medicine as was described by the European Medicines Agency (EMA) and The European Scientific Cooperative on Phytotherapy (ESCOP), and reviewed and summarized by Vanaclocha et al. [194]. Some of them are the negative effect on digestive absorption of drugs in presence of fenugreek due to its mucilages, or the case of plants with caffeine, such as mate and green tea, that can interfere with sedative and adrenergic drugs. Other described interactions are garlic with anticoagulants, as well as many plants with hypogliycemic medications, such as gymnema or fenugreek [195,196]. There are also potential interaction between medicinal plants with dual effects and medicines. For example, olive leaves have antidiabetic and antihypertensive effects, and people that use extracts from that as antidiabetic some time can have hypotensive crisis and vice versa [197].

In conclusion, natural products, especially those of plant origin, are important sources of compounds with different chemical structures which, acting through diverse mechanisms, could offer a therapeutic alternative to treat T2DM. Since results with several of these compounds are preliminary or inadequately documented, it is necessary to continue working on their research and development before using them as new antidiabetic drugs.

Conflict of Interest

The authors declare no conflicts of interest.

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References

1 *Klonoff DC, Schwartz DM.* An economic analysis of interventions for diabetes. Diabetes Care 2000; 23: 390–404
2 *King H, Aubert RE, Herman WH.* Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes Care 1998; 21: 1414–1431
3 *ADA, American Diabetes Association.* Standards of medical care in diabetes – 2014. Diabetes Care 2014; 37: S14–S80
4 *ADA, American Diabetes Association.* Clinical practice recommendations 2007. Diabetes Care 2007; 30: S3
5 *LADA, Latin American Diabetes Association.* Guías ALAD de diagnóstico control y tratamiento de la diabetes mellitus tipo 2. Ver Asoc Latinoam Diabetes 2006; 14: 3–4
6 *Fall CH.* Non-industrialised countries and affluence. Br Med Bull 2001; 60: 33–50
7 *Gagliardino JJ, Martella A, Etchegoyen GS, Caporale JE, Guidi ML, Olivera EM, González C.* Hospitalization and re-hospitalization of people with and without diabetes in La Plata, Argentina: comparison of their clinical characteristics and costs. Diabetes Res Clin Pract 2004; 65: 51–59
8 *Williams R, Van Gaal L, Lucioni C; CODE-2 Advisory Board.* Assessing the impact of complications on the costs of type II diabetes. Diabetologia 2002; 45: S13–S17
9 *CDC Diabetes Cost-effectiveness Group.* Cost-effectiveness of intensive glycemic control, intensified hypertension control, and serum cholesterol level reduction for type 2 diabetes. JAMA 2002; 287: 2542–2551
10 *Tuomilehto J, Lindström J, Eriksson JG, Valle TT, Hämäläinen H, Ilanne-Parikka P, Keinänen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M; Finnish Diabetes Prevention Study Group.* Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001; 344: 1343–1350
11 *Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM; Diabetes Prevention Program Research Group.* Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346: 393–403
12 *Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trail Research Group.* Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. Lancet 2002; 15: 2072–2077
13 *DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators, Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, Hanefeld M, Hoogwerf B, Laakso M, Mohan V, Shaw J, Zinman B, Holman RR.* Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet 2006; 368: 1096–1105
14 *ADA, American Diabetes Association.* Diagnosis and classification of diabetes mellitus. Diabetes Care 2013; 36: S67–S74
15 *ADA, American Diabetes Association.* Clinical practice recommendations 2005. Diabetes Care 2005; 28: S1–S79
16 *Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC.* β-Cell deficit and increased β-cell apoptosis in humans with type 2 diabetes. Diabetes 2003; 52: 102–110
17 *Samuel VT, Shulman GI.* Mechanisms for insulin resistance: common threads and missing links. Cell 2012; 148: 852–887
18 *Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, Neifing JL, Ward WK, Beard JC, Palmer JP.* Quantification of the relationship between insulin sensitivity and β-cell function in human subjects. Evidence for a hyperbolic function. Diabetes 1993; 42: 1663–1672
19 *Ferrannini E, Gastaldelli A, Miyazaki Y, Matsuda M, Mari A, DeFronzo RA.* β-Cell function in subjects spanning the range from normal glucose tolerance to overt diabetes: a new analysis. J Clin Endocrinol Metab 2005; 90: 493–500
20 *Weyer C, Bogardus C, Mott DM, Pratley RE.* The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest 1999; 104: 787–794
21 *Sakura H, Mizukami H, Yagihashi N, Wada R, Hanyu C, Yagihashi S.* Reduced β-cell mass and expression of oxidative stress-related DNA damage in the islet of Japanese type II diabetic patients. Diabetologia 2002; 45: 85–96
22 *Araki E, Oyadomari S, Mori M.* Impact of endoplasmic reticulum stress pathway on pancreatic β-cells and diabetes mellitus. Exp Biol Med 2003; 228: 1213–1217
23 *Bedekar A, Shah K, Koffas M.* Natural products for type II diabetes treatment. Adv Appl Microbiol 2010; 71: 21–73
24 *Perla V, Jayanty SS.* Biguanide related compounds in traditional antidiabetic functional foods. Food Chem 2013; 138: 1574–1580
25 *Nelson-Dooley C, Della-Fera MA, Hamrick M, Baile CA.* Novel treatments for obesity and osteoporosis: targeting apoptotic pathways in adipocytes. Curr Med Chem 2005; 12: 2215–2225
26 *Matsui T, Ueda T, Oki T, Sugita K, Terahara N, Matsumoto K.* α-Glucosidase inhibitory action of natural acylated anthocyanins. 1. Survey of

natural pigments with potent inhibitory activity. J Agric Food Chem 2001; 49: 1948–1951
27 *Schafer A, Hogger P.* Oligomeric procyanidins of French maritime pine bark extract (Pycnogenol) effectively inhibit α-glucosidase. Diabetes Res Clin Pract 2007; 77: 41–46
28 *Kim YM, Jeong YK, Wang MH, Lee WY, Rhee HI.* Inhibitory effect of pine extract on α-glucosidase activity and postprandial hyperglycemia. Nutrition 2005; 21: 756–761
29 *Liu X, Wei J, Tan F, Zhou S, Würthwein G, Rohdewald P.* Antidiabetic effect of Pycnogenol French maritime pine bark extract in patients with diabetes type II. Life Sci 2004; 75: 2505–2513
30 *Liu X, Wei J, Tan F, Zhou S, Würthwein G, Rohdewald P.* Pycnogenol, French maritime pine bark extract, improves endothelial function of hypertensive patients. Life Sci 2004; 74: 855–862
31 *Wehmeier UF.* The biosynthesis and metabolism of acarbose in Actinoplanes sp. SE50/110: A progress report. Biocatal Biotransformation 2003; 21: 279–284
32 *Wehmeier UF, Piepersberg W.* Biotechnology and molecular biology of the α-glucosidase inhibitor acarbose. Appl Microbiol Biotechnol 2004; 63: 613–625
33 *Matsuo T, Odaka H, Ikeda H.* Effect of an intestinal disaccharidase inhibitor (AO-128) on obesity and diabetes. Am J Clin Nutr 1992; 55: 314S-317S
34 *Chen X, Zheng Y, Shen Y.* Voglibose (Basen, AO-128), one of the most important α-glucosidase inhibitors. Curr Med Chem 2006; 13: 109–116
35 *Chawla R, Thakur P, Chowdhry A, Jaiswal S, Sharma A, Goel R, Sharma J, Priyadarshi SS, Kumar V, Sharma RK, Arora R.* Evidence based herbal drug standardization approach in coping with challenges of holistic management of diabetes: a dreadful lifestyle disorder of 21st century. J Diabetes Metab Disord 2013; 12: 35
36 *Hays NP, Galassetti PR, Coker RH.* Prevention and treatment of type 2 diabetes: current role of lifestyle, natural product, and pharmacological interventions. Pharmacol Ther 2008; 118: 181–191
37 *Nahas R, Moher M.* Complementary and alternative medicine for the treatment of type 2 diabetes. Can Fam Physician 2009; 55: 591–596
38 *Patel DK, Kumar R, Laloo D, Hemalatha S.* Diabetes mellitus: an overview on its pharmacological aspects and reported medicinal plants having antidiabetic activity. Asian Pac J Trop Biomed 2012; 2: 411–420
39 *Patel DK, Prasad SK, Kumar R, Hemalatha S.* An overview on antidiabetic medicinal plants having insulin mimetic property. Asian Pac J Trop Biomed 2012; 2: 320–330
40 *Chang CL, Lin Y, Bartolome AP, Chen YC, Chiu SC, Yang WC.* Herbal therapies for type 2 diabetes mellitus: chemistry, biology, and potential application of selected plants and compounds. Evid Based Complement Alternat Med 2013; 2013: 378657
41 *El-Abhar HS, Schaalan MF.* Phytotherapy in diabetes: Review on potential mechanistic perspectives. World J Diabetes 2014; 5: 176–197
42 *Eddouks M, Bidi A, El Bouhali B, Hajji L, Zeggwagh NA.* Antidiabetic plants improving insulin sensitivity. J Pharm Pharmacol 2014; 66: 1197–1214
43 *Jia W, Gao W, Tang L.* Antidiabetic herbal drugs officially approved in China. Phytother Res 2003; 17: 1127–1134
44 *Shojaii A, Dabaghian FH, Goushegir A, Fard MA.* Antidiabetic plants of Iran. Acta Med Iran 2011; 49: 637–642
45 *Rashidi AA, Mirhashemi SM, Taghizadeh M, Sarkhail P.* Iranian medicinal plants for diabetes mellitus: a systematic review. Pak J Biol Sci 2013; 16: 401–411
46 *Zarshenas MM, Khademian S, Moein M.* Diabetes and related remedies in medieval Persian medicine. Indian J Endocrinol Metab 2014; 18: 142–149
47 *Ramírez G, Zavala M, Pérez J, Zamilpa A. In vitro* screening of medicinal plants used in Mexico as antidiabetics with glucosidase and lipase inhibitory activities. Evid Based Complement Alternat Med 2012; 2012: 701261
48 *Mata R, Cristians S, Escandón-Rivera S, Juárez-Reyes K, Rivero-Cruz I.* Mexican antidiabetic herbs: valuable sources of inhibitors of α-glucosidases. J Nat Prod 2013; 76: 468–483
49 *Grover JK, Yadav S, Vats V.* Medicinal plants of India with anti-diabetic potential. J Ethnopharmacol 2002; 81: 81–100
50 *Mukherjee PK, Maiti K, Mukherjee K, Houghton PJ.* Leads from Indian medicinal plants with hypoglycemic potentials. J Ethnopharmacol 2006; 106: 1–28
51 *Hardy ML, Coulter I, Venuturupalli S, Roth EA, Favreau J, Morton SC, Shekelle P.* Ayurvedic interventions for diabetes mellitus: a systematic review. Evid Rep Technol Assess (Summ) 2001; 41: 2 p
52 *Zia-ur-rehman M, Mirajab K, Mushtaq A.* Potential for Pakistani traditional medicinal plants to combat diabetes. J Tradit Chin Med 2014; 34: 488–490
53 *Kadir MF, Bin Sayeed MS, Shams T, Mia MM.* Ethnobotanical survey of medicinal plants used by Bangladeshi traditional health practitioners in the management of diabetes mellitus. J Ethnopharmacol 2012; 144: 605–611
54 *Kabir MH, Hasan N, Rahman MM, Rahman MA, Khan JA, Hoque NT, Bhuiyan MR, Mou SM, Jahan R, Rahmatullah M.* A survey of medicinal plants used by the Deb barma clan of the Tripura tribe of Moulvibazar district, Bangladesh. J Ethnobiol Ethnomed 2014; 10: 19
55 *Marwat SK, Rehman F, Khan EA, Khakwani AA, Ullah I, Khan KU, Khan IU.* Useful ethnophytomedicinal recipes of angiosperms used against diabetes in South East Asian Countries (India, Pakistan & Sri Lanka). Pak J Pharm Sci 2014; 27: 1338–1358
56 *Diallo A, Traore MS, Keita SM, Balde MA, Keita A, Camara M, Van Miert S, Pieters L, Balde AM.* Management of diabetes in Guinean traditional medicine: an ethnobotanical investigation in the coastal lowlands. J Ethnopharmacol 2012; 144: 353–361
57 *Lawag IL, Aguinaldo AM, Naheed S, Mosihuzzaman M.* α-Glucosidase inhibitory activity of selected Philippine plants. J Ethnopharmacol 2012; 144: 217–219
58 *Katemo M, Mpiana PT, Mbala BM, Mihigo SO, Ngbolua KN, Tshibangu DS, Koyange PR.* Ethnopharmacological survey of plants used against diabetes in Kisangani City (DR Congo). J Ethnopharmacol 2012; 144: 39–43
59 *Mootoosamy A, Mahomoodally MF.* Ethnomedicinal application of native remedies used against diabetes and related complications in Mauritius. J Ethnopharmacol 2014; 151: 413–444
60 *Picot CM, Subratty AH, Mahomoodally MF.* Inhibitory potential of five traditionally used native antidiabetic medicinal plants on α-amylase, α-glucosidase, glucose entrapment, and amylolysis kinetics *in vitro*. Adv Pharmacol Sci 2014; 2014: 739834
61 *Ezuruike UF, Prieto JM.* The use of plants in the traditional management of diabetes in Nigeria: pharmacological and toxicological considerations. J Ethnopharmacol 2014; 155: 857–924
62 *Mohammed A, Ibrahim MA, Islam MS.* African medicinal plants with antidiabetic potentials: a review. Planta Med 2014; 80: 354–377
63 *Jamila F, Mostafa E.* Ethnobotanical survey of medicinal plants used by people in Oriental Morocco to manage various ailments. J Ethnopharmacol 2014; 154: 76–87
64 *Afifi FU, Kasabri V.* Pharmacological and phytochemical appraisal of selected medicinal plants from Jordan with claimed antidiabetic activities. Sci Pharm 2013; 81: 889–932
65 *Bussmann RW, Paniagua-Zambrana N, Chamorro MR, Moreira NM, del Rosario Cuadros Negri ML, Olivera J.* Peril in the market-classification and dosage of species used as anti-diabetics in Lima, Peru. J Ethnobiol Ethnomed 2013; 9: 37
66 *Tabatabaei-Malazy O, Larijani B, Abdollahi M.* A systematic review of *in vitro* studies conducted on effect of herbal products on secretion of insulin from Langerhans islets. J Pharm Pharm Sci 2012; 15: 447–466
67 *Akshatha VJ, Nalini MS, D'Souza C, Prakash HS.* Streptomycete endophytes from anti-diabetic medicinal plants of the Western Ghats inhibit α-amylase and promote glucose uptake. Lett Appl Microbiol 2014; 58: 433–439
68 *Melzig MF, Funke I.* Pflanzliche Alpha-Amylasehemmer – eine Möglichkeit zur Phytotherapie bei Diabetes Mellitus Typ II? Wien Med Wochenschr 2007; 157: 320–324
69 *Rahimzadeh M, Jahanshahi S, Moein S, Moein MR.* Evaluation of alpha-amylase inhibition by *Urtica dioica* and *Juglans regia* extracts. Iran J Basic Med Sci 2014; 17: 465–469
70 *Li Y, Chen Y, Xiao C, Chen D, Xiao Y, Mei Z.* Rapid screening and identification of α-amylase inhibitors from *Garcinia xanthochymus* using enzyme-immobilized magnetic nanoparticles coupled with HPLC and MS. J Chromatogr B Analyt Technol Biomed Life Sci 2014; 960: 166–173
71 *Wilcox G.* Review article insulin and insulin resistance. Clin Biochem Rev 2005; 26: 19–39
72 *Sangeetha MK, Priya CD, Vasanthi HR.* Anti-diabetic property of *Tinospora cordifolia* and its active compound is mediated through the expression of Glut-4 in L6 myotubes. Phytomedicine 2013; 20: 246–248
73 *Kadan S, Saad B, Sasson Y, Zaid H. In vitro* evaluations of cytotoxicity of eight antidiabetic medicinal plants and their effect on GLUT4 Translocation. Evid Based Complement Alternat Med 2013; 2013: 549345

74 *Berger J, Moller DE.* The mechanisms of action of PPARs. Annu Rev Med 2002; 53: 409–435
75 *Wang L, Waltenberger B, Pferschy-Wenzig EM, Blunder M, Liu X, Malainer C, Blazevic T, Schwaiger S, Rollinger JM, Heiss EH, Schuster D, Kopp B, Bauer R, Stuppner H, Dirsch VM, Atanasov AG.* Natural product agonists of peroxisome proliferator-activated receptor gamma (PPARγ): a review. Biochem Pharmacol 2014; 92: 73–89
76 *Katz SR, Newman RA, Lansky EP. Punica granatum*: heuristic treatment for diabetes mellitus. J Med Food 2007; 10: 213–217
77 *Gaur R, Yadav KS, Verma RK, Yadav NP, Bhakuni RS. In vivo* anti-diabetic activity of derivatives of isoliquiritigenin and liquiritigenin. Phytomedicine 2014; 21: 415–422
78 *Lv XF, Meng QY, Guo XM.* Effect of *Rehmannia glutinosa* water extraction on insulin resistance and gene expression of resistin in type 2 diabetes mellitus rats. Zhongguo Zhong Yao Za Zhi 2007; 32: 2182–2184
79 *Seo JB, Choe SS, Jeong HW, Park SW, Shin HJ, Choi SM, Park JY, Choi EW, Kim JB, Seen DS, Jeong JY, Lee TG.* Anti-obesity effects of *Lysimachia foenum-graecum* characterized by decreased adipogenesis and regulated lipid metabolism. Exp Mol Med 2011; 43: 205–215
80 *Kim YJ, Choi MS, Park YB, Kim SR, Lee MK, Jung UJ. Garcinia cambogia* attenuates diet-induced adiposity but exacerbates hepatic collagen accumulation and inflammation. World J Gastroenterol 2013; 19: 4689–4701
81 *Ilavenil S, Arasu MV, Lee JC, Kim da H, Roh SG, Park HS, Choi GJ, Mayakrishnan V, Choi KC.* Trigonelline attenuates the adipocyte differentiation and lipid accumulation in 3T3-L1 cells. Phytomedicine 2014; 21: 758–765
82 *Kim HS, Sung HY, Kim MS, Kim JL, Kang MK, Gong JH, Park HS, Kang YH.* Oleanolic acid suppresses resistin induction in adipocytes by modulating Tyk-STAT signaling. Nutr Res 2013; 33: 144–153
83 *Mauricio D.* Inhibidores SGLT-2: de la corteza del manzano y la glucosuria familiar al tratamiento de la diabetes mellitus tipo 2. Med Clin (Barc) 2013; 141 (Suppl. 2): S31–S35
84 *Makarova E, Górnaś P, Konrade I, Tirzite D, Cirule H, Gulbe A, Pugajeva I, Seglina D, Dambrova M.* Acute anti-hyperglycaemic effects of an unripe apple preparation containing phlorizin in healthy volunteers: a preliminary study. J Sci Food Agric 2015; 95: 560–568
85 *Chao EC, Henry RR.* SGLT2 inhibition–a novel strategy for diabetes treatment. Nat Rev Drug Discov 2010; 9: 551–559
86 *Yabe D, Seino Y.* Two incretin hormones GLP-1 and GIP: comparison of their actions in insulin secretion and *β* cell preservation. Prog Biophys Mol Biol 2011; 107: 248–256
87 *Cernea S, Raz I.* Therapy in the early stage: incretins. Diabetes Care 2011; 34 (Suppl. 2): S264–S271
88 *Kosaraju J, Dubala A, Chinni S, Khatwal RB, Satish Kumar MN, Basavan D.* A molecular connection of *Pterocarpus marsupium, Eugenia jambolana* and *Gymnema sylvestre* with dipeptidyl peptidase-4 in the treatment of diabetes. Pharm Biol 2014; 52: 268–271
89 *Saleem S, Jafri L, Haq IU, Chee Chang L, Calderwood D, Green BD, Mirza B.* Plants *Fagonia cretica* L. and *Hedera nepalensis* K. Koch contain natural compounds with potent dipeptidyl peptidase-4 (DPP-4) inhibitory activity. J Ethnopharmacol 2014; 1156: 26–36
90 *Wang P, Alvarez-Perez JC, Felsenfeld DP, Liu H, Sivendran S, Bender A, Kumar A, Sanchez R, Scott DK, Garcia-Ocaña A, Stewart AF.* A high-throughput chemical screen reveals that harmine-mediated inhibition of DYRK1A increases human pancreatic beta cell replication. Nat Med 2015; 21: 383–388
91 *Combs AP.* Recent advances in the discovery of competitive protein tyrosine phosphatase 1B inhibitors for the treatment of diabetes, obesity, and cancer. J Med Chem 2010; 53: 2333–2344
92 *Uddin MN, Sharma G, Yang JL, Choi HS, Lim SI, Kang KW, Oh WK.* Oleanane triterpenes as protein tyrosine phosphatase 1B (PTP1B) inhibitors from *Camellia japonica*. Phytochemistry 2014; 103: 99–106
93 *Pitschmann A, Zehl M, Atanasov AG, Dirsch VM, Heiss E, Glasl S.* Walnut leaf extract inhibits PTP1B and enhances glucose-uptake *in vitro*. J Ethnopharmacol 2014; 152: 599–602
94 *Giacco F, Brownlee M.* Oxidative stress and diabetic complications. Circ Res 2010; 107: 1058–1070
95 *Halliwell B.* Free radicals and antioxidants: updating a personal view. Nutr Rev 2012; 70: 257–265
96 *Palma HE, Wolkmer P, Gallio M, Corrêa MM, Schmatz R, Thomé GR, Pereira LB, Castro VS, Pereira AB, Bueno A, de Oliveira LS, Rosolen D, Mann TR, de Cecco BS, Graça DL, Lopes ST, Mazzanti CM.* Oxidative stress parameters in blood, liver, and kidney of diabetic rats treated with curcumin and/or insulin. Mol Cell Biochem 2014; 386: 199–210
97 *Manzari-Tavakoli A, Pouraboli I, Yaghoobi MM, Mehrabani M, Mirtadzadini SM.* Antihyperglycemic, antilipid peroxidation, and insulin secretory activities of *Otostegia persica* shoot extract in streptozotocin-induced diabetic rats and *in vitro* C187 pancreatic *β*-cells. Pharm Biol 2013; 51: 253–259
98 *Ha US, Bae WJ, Kim SJ, Yoon BI, Jang H, Hong SH, Lee JY, Hwang SY, Kim SW.* Protective effect of cyanidin-3-O-*β*-D-glucopyranoside fraction from mulberry fruit pigment against oxidative damage in streptozotocin-induced diabetic rat bladder. Neurourol Urodyn 2013; 32: 493–499
99 *Talukder FZ, Khan KA, Uddin R, Jahan N, Alam MA. In vitro* free radical scavenging and anti-hyperglycemic activities of *Achyranthes aspera* extract in alloxan-induced diabetic mice. Drug Discov Ther 2012; 6: 298–305
100 *Teugwa CM, Mejiato PC, Zofou D, Tchinda BT, Boyom FF.* Antioxidant and antidiabetic profiles of two African medicinal plants: *Picralima nitida* (Apocynaceae) and *Sonchus oleraceus* (Asteraceae). BMC Complement Altern Med 2013; 13: 175
101 *El-Amin M, Virk P, Elobeid MA, Almarhoon ZM, Hassan ZK, Omer SA, Merghani NM, Daghestani MH, Al-Olayan EM.* Anti-diabetic effect of *Murraya koenigii* (L) and *Olea europaea* (L) leaf extracts on streptozotocin induced diabetic rats. Pak J Pharm Sci 2013; 26: 359–365
102 *Li Z, Geng YN, Jiang JD, Kong WJ.* Antioxidant and anti-inflammatory activities of berberine in the treatment of diabetes mellitus. Evid Based Complement Alternat Med 2014; 2014: 289264
103 *Castro MC, Massa ML, Schinella G, Gagliardino JJ, Francini F.* Lipoic acid prevents liver metabolic changes induced by administration of a fructose-rich diet. Biochim Biophys Acta 2013; 1830: 2226–2232
104 *Castro MC, Francini F, Schinella G, Caldiz CI, Zubiria MG, Gagliardino JJ, Massa ML.* Apocynin administration prevents the changes induced by a fructose-rich diet on rat liver metabolism and the antioxidant system. Clin Sci (Lond) 2012; 123: 681–692
105 *Li ZQ, Chang HJ, Sang WF.* Clinical efficacy of special effect san xiao decoction on type 2 diabetes mellitus. Zhong Yao Cai 2013; 36: 163–166
106 *Sengupta K, Mishra AT, Rao MK, Sarma KV, Krishnaraju AV, Trimurtulu G.* Efficacy and tolerability of a novel herbal formulation for weight management in obese subjects: a randomized double blind placebo controlled clinical study. Lipids Health Dis 2012; 11: 122
107 *Ghorbani A.* Clinical and experimental studies on polyherbal formulations for diabetes: current status and future prospective. J Integr Med 2014; 12: 336–345
108 *Moona MM, Smits R, Kertesz J, Meyer A, Mackler L.* Clinical inquiry: do complementary agents lower HbA1c when used with standard type 2 diabetes therapy? J Fam Pract 2014; 63: 336–338
109 *Vogler BK, Ernst E. Aloe vera*: a systematic review of its clinical effectiveness. Br J Gen Pract 1999; 49: 823–828
110 *Devaraj S, Yimam M, Brownell LA, Jialal I, Singh S, Jia Q.* Effects of *Aloe vera* supplementation in subjects with prediabetes/metabolic syndrome. Metab Syndr Relat Disord 2013; 11: 35–40
111 *Choi HC, Kim SJ, Son KY, Oh BJ, Cho BL.* Metabolic effects of *Aloe vera* gel complex in obese prediabetes and early non-treated diabetic patients: randomized controlled trial. Nutrition 2013; 29: 1110–1114
112 *Stohs SJ, Miller H, Kaats GR.* A review of the efficacy and safety of banaba (*Lagerstroemia speciosa* L.) and corosolic acid. Phytother Res 2012; 26: 317–324
113 *Leung L, Birtwhistle R, Kotecha J, Hannah S, Cuthbertson S.* Anti-diabetic and hypoglycaemic effects of *Momordica charantia* (bitter melon): a mini review. Br J Nutr 2009; 102: 1703–1708
114 *Chuang CY, Hsu C, Chao CY, Wein YS, Kuo YH, Huang CJ.* Fractionation and identification of 9c,11 t,13 t-conjugated linolenic acid as an activator of PPARα in bitter gourd (*Momordica charantia* L.). J Biomed Sci 2006; 13: 763–772
115 *Yibchok-Anun S, Adisakwattana S, Yao CY, Sangvanich P, Roengsumran S, Hsu WH.* Slow acting protein extract from fruit pulp of *Momordica charantia* with insulin secretagogue and insulinomimetic activities. Biol Pharm Bull 2006; 29: 1126–1131
116 *Ooi CP, Yassin Z, Hamid TA. Momordica charantia* for type 2 diabetes mellitus. Cochrane Database Syst Rev 2010; 2: CD007845
117 *Ooi CP, Yassin Z, Hamid TA. Momordica charantia* for type 2 diabetes mellitus. Cochrane Database Syst Rev 2012; 8: CD007845
118 *Medagama AB, Bandara R.* The use of complementary and alternative medicines (CAMs) in the treatment of diabetes mellitus: is continued use safe and effective? Nutr J 2014; 13: 102
119 *Huseini HF, Hasani-Rnjbar S, Nayebi N, Heshmat R, Sigaroodi FK, Ahvazi M, Alaei BA, Kianbakht S. Capparis spinosa* L. (Caper) fruit extract in

treatment of type 2 diabetic patients: a randomized double-blind placebo-controlled clinical trial. Complement Ther Med 2013; 21: 447–452
120 *Khan A, Bryden NA, Polansky MM, Anderson RA.* Insulin potentiating factor and chromium content of selected foods and spices. Biol Trace Elem Res 1990; 24: 183–188
121 *Broadhurst CL, Polansky MM, Anderson RA.* Insulin-like biological activity of culinary and medicinal plant aqueous extracts *in vitro*. J Agric Food Chem 2000; 48: 849–852
122 *Jarvill-Taylor KJ, Anderson RA, Graves DJ.* A hydroxychalcone derived from cinnamon functions as a mimetic for insulin in 3T3–L1 adipocytes. J Am Coll Nutr 2001; 20: 327–336
123 *Qin B, Nagasaki M, Ren M, Bajotto G, Oshida Y, Sato Y.* Cinnamon extract (traditional herb) potentiates *in vivo* insulin-regulated glucose utilization via enhancing insulin signaling in rats. Diabetes Res Clin Pract 2003; 62: 139–148
124 *Gruenwald J, Freder J, Armbruester N.* Cinnamon and health. Crit Rev Food Sci Nutr 2010; 50: 822–834
125 *Anderson RA, Broadhurst CL, Polansky MM, Schmidt WF, Khan A, Flanagan VP, Schoene NW, Graves DJ.* Isolation and characterization of polyphenol type-A polymers from cinnamon with insulin-like biological activity. J Agric Food Chem 2004; 52: 65–70
126 *Khan A, Safdar M, Ali Khan MM, Khattak KN, Anderson RA.* Cinnamon improves glucose and lipids of people with type 2 diabetes. Diabetes Care 2003; 26: 3215–3218
127 *Vanschoonbeek K, Thomassen BJ, Senden JM, Wodzig WK, van Loon LJ.* Cinnamon supplementation does not improve glycemic control in postmenopausal type 2 diabetes patients. J Nutr 2006; 136: 977–980
128 *Pham AQ, Kourlas H, Pham DQ.* Cinnamon supplementation in patients with type 2 diabetes mellitus. Pharmacotherapy 2007; 27: 595–599
129 *Kirkham S, Akilen R, Sharma S, Tsiami A.* The potential of cinnamon to reduce blood glucose levels in patients with type 2 diabetes and insulin resistance. Diabetes Obes Metab 2009; 11: 1100–1113
130 *Davis PA, Yokoyama W.* Cinnamon intake lowers fasting blood glucose: meta-analysis. J Med Food 2011; 14: 884–889
131 *Leach MJ, Kumar S.* Cinnamon for diabetes mellitus. Cochrane Database Syst Rev 2012; 9: CD007170
132 *Akilen R, Tsiami A, Devendra D, Robinson N.* Cinnamon in glycaemic control: Systematic review and meta analysis. Clin Nutr 2012; 31: 609–615
133 *Andújar I, Recio MC, Giner RM, Ríos JL.* Cocoa polyphenols and their potential benefits for human health. Oxid Med Cell Longev 2012; 2012: 906252
134 *Latif R.* Chocolate/cocoa and human health: a review. Neth J Med 2013; 71: 63–68
135 *Grassi D, Desideri G, Necozione S, Lippi C, Casale R, Properzi G, Blumberg JB, Ferri C.* Blood pressure is reduced and insulin sensitivity increased in glucose-intolerant, hypertensive subjects after 15 days of consuming high-polyphenol dark chocolate. J Nutr 2008; 138: 1671–1676
136 *Hooper L, Kay C, Abdelhamid A, Kroon PA, Cohn JS, Rimm EB, Cassidy A.* Effects of chocolate, cocoa, and flavan-3-ols on cardiovascular health: a systematic review and meta-analysis of randomized trials. Am J Clin Nutr 2012; 95: 740–751
137 *Kim JA, Montagnani M, Koh KK, Quon MJ.* Reciprocal relationships between insulin resistance and endothelial dysfunction: molecular and pathophysiological mechanisms. Circulation 2006; 113: 1888–1904
138 *Salazar-Martínez E, Willett WC, Ascherio A, Manson JE, Leitzmann MF, Stampfer MJ, Hu FB.* Coffee consumption and risk for type 2 diabetes mellitus. Ann Intern Med 2004; 140: 1–8
139 *Pereira MA, Parker ED, Folsom AR.* Coffee consumption and risk of type 2 diabetes mellitus: an 11-year prospective study of 28812 postmenopausal women. Arch Intern Med 2006; 166: 1311–1316
140 *Basch E, Ulbricht C, Kuo G, Szapary P, Smith M.* Therapeutic applications of fenugreek. Altern Med Rev 2003; 8: 20–27
141 *Haber SL, Keonavong J.* Fenugreek use in patients with diabetes mellitus. Am J Health Syst Pharm 2013; 70: 1196–1203
142 *Yadav UC, Baquer NZ.* Pharmacological effects of *Trigonella foenum-graecum* L. in health and disease. Pharm Biol 2014; 52: 243–254
143 *Swaroop A, Bagchi M, Kumar P, Preuss HG, Tiwari K, Marone PA, Bagchi D.* Safety, efficacy and toxicological evaluation of a novel, patented anti-diabetic extract of *Trigonella foenum-fraecum* seed extract (Fenfuro). Toxicol Mech Methods 2014; 24: 495–503
144 *Neelakantan N, Narayanan M, de Souza RJ, van Dam RM.* Effect of fenugreek (*Trigonella foenum-graecum* L.) intake on glycemia: a meta-analysis of clinical trials. Nutr J 2014; 13: 7
145 *Zhou J, Chan L, Zhou S.* Trigonelline: a plant alkaloid with therapeutic potential for diabetes and central nervous system disease. Curr Med Chem 2012; 19: 3523–3531
146 *Ackermann RT, Mulrow CD, Ramirez G, Gardner CD, Morbidoni L, Lawrence VA.* Garlic shows promise for improving some cardiovascular risk factors. Arch Intern Med 2001; 161: 813–824
147 *Mohammadi A, Oshaghi EA.* Effect of garlic on lipid profile and expression of LXR alpha in intestine and liver of hypercholesterolemic mice. J Diabetes Metab Disord 2014; 13: 20
148 *Gutiérrez RM, Mitchell S, Solis RV. Psidium guajava*: a review of its traditional uses, phytochemistry and pharmacology. J Ethnopharmacol 2008; 117: 1–27
149 *Tiwari P, Mishra BN, Sangwan NS.* Phytochemical and pharmacological properties of *Gymnema sylvestre*: an important medicinal plant. Biomed Res Int 2014; 2014: 830285
150 *Di Fabio G, Romanucci V, Zarrelli M, Giordano M, Zarrelli A.* C-4 gem-dimethylated oleanes of *Gymnema sylvestre* and their pharmacological activities. Molecules 2013; 18: 14892–14919
151 *Alqahtani A, Hamid K, Kam A, Wong KH, Abdelhak Z, Razmovski-Naumovski V, Chan K, Li KM, Groundwater PW, Li GQ.* The pentacyclic triterpenoids in herbal medicines and their pharmacological activities in diabetes and diabetic complications. Curr Med Chem 2013; 20: 908–931
152 *Kumar SN, Mani UV, Mani I.* An open label study on the supplementation of *Gymnema sylvestre* in type 2 diabetics. J Diet Suppl 2010; 7: 273–282
153 *Dar SA, Ganai FA, Yousuf AR, Balkhi MU, Bhat TM, Sharma P.* Pharmacological and toxicological evaluation of *Urtica dioica*. Pharm Biol 2013; 51: 170–180
154 *Rau O, Wurglics M, Dingermann T, Abdel-Tawab M, Schubert-Zsilavecz M.* Screening of herbal extracts for activation of the human peroxisome proliferator-activated receptor. Pharmazie 2006; 61: 952–956
155 *Kianbakht S, Khalighi-Sigaroodi F, Dabaghian FH.* Improved glycemic control in patients with advanced type 2 diabetes mellitus taking *Urtica dioica* leaf extract: a randomized double-blind placebo-controlled clinical trial. Clin Lab 2013; 59: 1071–1076
156 *Kianbakht S, Dabaghian FH.* Improved glycemic control and lipid profile in hyperlipidemic type 2 diabetic patients consuming *Salvia officinalis* L. leaf extract: a randomized placebo. Controlled clinical trial. Complement Ther Med 2013; 21: 441–446
157 *Eidi M, Eidi A, Zamanizadeh H.* Effect of *Salvia officinalis* L. leaves on serum glucose and insulin in healthy and streptozocin-induced diabetic rats. J Ethnopharmacol 2005; 100: 310–313
158 *Lima CF, Azevedo MF, Araujo R, Fernandes-Ferreira M, Pereira-Wilson C.* Metformine-like effect of *Salvia officinalis* (common sage): is it useful in diabetes prevention? Br J Nutr 2006; 96: 326–333
159 *Sa CM, Ramos AA, Azevedo MF, Lima CF, Fernandes-Ferreira M, Pereira-Wilson C.* Sage tea drinking improves lipid profile and antioxidant defenses in humans. Int J Mol Sci 2009; 10: 3937–3950
160 *Kianbakht S, Abasi B, Perham M, Hashem Dabaghian F.* Antihyperlipidemic effects of *Salvia officinalis* L. leaf extract in patients with hyperlipidemia: a randomized double blind placebo-controlled clinical trial. Phytother Res 2011; 25: 1849–1853
161 *Choi SB, Jang JS, Park S.* Estrogen and exercise may enhance beta-cell function and mass via insulin receptor substrate 2 induction in ovariectomized diabetic rats. Endocrinology 2005; 146: 4786–4794
162 *Kwon DY, Daily JW 3rd, Kim HJ, Park S.* Antidiabetic effects of fermented soybean products on type 2 diabetes. Nutr Res 2010; 30: 1–13
163 *Zhang YB, Chen WH, Guo JJ, Fu ZH, Yi C, Zhang M, Na XL.* Soy isoflavone supplementation could reduce body weight and improve glucose metabolism in non-Asian postmenopausal women–a meta-analysis. Nutrition 2013; 29: 8–14
164 *Khan N, Mukhtar H.* Tea and health: studies in humans. Curr Pharm Des 2013; 19: 6141–6147
165 *Song Y, Manson JE, Buring JE, Sesso HD, Liu S.* Associations of dietary flavonoids with risk of type 2 diabetes, and markers of insulin resistance and systemic inflammation in women: a prospective study and cross-sectional analysis. J Am Coll Nutr 2005; 24: 376–384
166 *Iso H, Date C, Wakai K, Fukui M, Tamakoshi A.* The relationship between green tea and total caffeine intake and risk for self-reported type 2 diabetes among Japanese adults. Ann Intern Med 2006; 144: 554–562
167 *Neyestani TR, Shariatzade N, Kalayi A, Gharavi A, Khalaji N, Dadkhah M, Zowghi T, Haidari H, Shab-bidar S.* Regular daily intake of black tea improves oxidative stress biomarkers and decreases serum C-reactive

protein levels in type 2 diabetic patients. Ann Nutr Metabol 2010; 57: 40–49
168 *Nagao T, Meguro S, Hase T, Otsuka K, Komikado M, Tokimitsu I, Yamamoto T, Yamamoto K.* A catechin-rich beverage improves obesity and blood glucose control in patients with type 2 diabetes. Obesity (Silver Spring) 2009; 17: 310–317
169 *Aggarwal BB, Yuan W, Li S, Gupta SC.* Curcumin-free turmeric exhibits anti-inflammatory and anticancer activities: Identification of novel components of turmeric. Mol Nutr Food Res 2013; 57: 1529–1542
170 *Gupta SC, Sung B, Kim JH, Prasad S, Li S, Aggarwal BB.* Multitargeting by turmeric, the golden spice: From kitchen to clinic. Mol Nutr Food Res 2013; 57: 1510–1528
171 *Wickenberg J, Ingemansson SL, Hlebowicz J.* Effects of *Curcuma longa* (turmeric) on postprandial plasma glucose and insulin in healthy subjects. Nutr J 2010; 9: 43
172 *Khajehdehi P, Pakfetrat M, Javidnia K, Azad F, Malekmakan L, Nasab MH, Dehghanzadeh G.* Oral supplementation of turmeric attenuates proteinuria, transforming growth factor-β and interleukin-8 levels in patients with overt type 2 diabetic nephropathy: a randomized, double-blind and placebo-controlled study. Scand J Urol Nephrol 2011; 45: 365–370
173 *Aldebasi YH, Aly SM, Rahmani AH.* Therapeutic implications of curcumin in the prevention of diabetic retinopathy via modulation of antioxidant activity and genetic pathways. Int J Physiol Pathophysiol Pharmacol 2013; 5: 194–202
174 *Maradana MR, Thomas R, O'Sullivan BJ.* Targeted delivery of curcumin for treating type 2 diabetes. Mol Nutr Food Res 2013; 57: 1550–1556
175 *Hosseini S, Huseini HF, Larijani B, Mohammad K, Najmizadeh A, Nourijelyani K, Jamshidi L.* The hypoglycemic effect of *Juglans regia* leaves aqueous extract in diabetic patients: A first human trial. Daru 2014; 22: 19
176 *Jelodar G, Mohsen M, Shahram S.* Effect of walnut leaf, coriander and pomegranate on blood glucose and histopathology of pancreas of alloxan induced diabetic rats. Afr J Tradit Complement Altern Med 2007; 43: 299–305
177 *Asgary S, Parkhideh S, Solhpour A, Madani H, Mahzouni P, Rahimi P.* Effect of ethanolic extract of *Juglans regia* L. on blood sugar in diabetes-induced rats. J Med Food 2008; 11: 533–538
178 *Mohammadi J, Sadeqpour K, Delaviz H, Mohammadi B.* Anti-diabetic effects of an alcoholic extract of *Juglans regia* in an animal model. Turk J Med Sci 2011; 41: 685–691
179 *Hosseini S, Jamshidi L, Mehrzadi S, Mohammad K, Najmizadeh AR, Alimoradi H, Huseini HF.* Effects of *Juglans regia* L. leaf extract on hyperglycemia and lipid profiles in type two diabetic patients: a randomized double-blind, placebo-controlled clinical trial. J Ethnopharmacol 2014; 152: 451–456
180 *Ahmad H, Khan I, Wahid A.* Antiglycation and antioxidation properties of *Juglans regia* and *Calendula officinalis*: possible role in reducing diabetic complications and slowing down ageing. J Tradit Chin Med 2012; 32: 411–414
181 *Heck CI, de Mejia EG.* Yerba Mate Tea (*Ilex paraguariensis*): a comprehensive review on chemistry, health implications, and technological considerations. J Food Sci 2007; 72: R138–R151
182 *Bracesco N, Sánchez AG, Contreras V, Menini T, Gugliucci A.* Recent advances on *Ilex paraguariensis* research: minireview. J Ethnopharmacol 2011; 136: 378–384
183 *Schinella G, Neyret E, Cónsole G, Tournier H, Prieto JM, Ríos JL, Giner RM.* An aqueous extract of *Ilex paraguariensis* reduces carrageenan-induced edema and inhibits the expression of cyclooxygenase-2 and inducible nitric oxide synthase in animal models of inflammation. Planta Med 2014; 80: 961–968
184 *Oliveira DM, Freitas HS, Souza MF, Arçari DP, Ribeiro ML, Carvalho PO, Bastos DH.* Yerba Maté (*Ilex paraguariensis*) aqueous extract decreases intestinal SGLT1 gene expression but does not affect other biochemical parameters in alloxan-diabetic Wistar rats. J Agric Food Chem 2008; 56: 10527–10532
185 *Kang YR, Lee HY, Kim JH, Moon DI, Seo MY, Park SH, Choi KH, Kim CR, Kim SH, Oh JH, Cho SW, Kim SY, Kim MG, Chae SW, Kim O, Oh HG.* Anti-obesity and anti-diabetic effects of Yerba Mate (*Ilex paraguariensis*) in C57BL/6J mice fed a high-fat diet. Lab Anim Res 2012; 28: 23–29
186 *Arçari DP, Bartchewsky W jr., dos Santos TW, Oliveira KA, DeOliveira CC, Gotardo ÉM, Pedrazzoli J jr., Gambero A, Ferraz LF, Carvalho Pde O, Ribeiro ML.* Anti-inflammatory effects of yerba maté extract (*Ilex paraguariensis*) ameliorate insulin resistance in mice with high fat diet-induced obesity. Mol Cell Endocrinol 2011; 335: 110–115
187 *Pereira DF, Kappel VD, Cazarolli LH, Boligon AA, Athayde ML, Guesser SM, Da Silva EL, Silva FR.* Influence of the traditional Brazilian drink *Ilex paraguariensis* tea on glucose homeostasis. Phytomedicine 2012; 19: 868–877
188 *Kahn SE, Hull RL, Utzschneider KM.* Review article mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature 2006; 444: 840–846
189 *De Morais EC, Stefanuto A, Klein GA, Boaventura BC, de Andrade F, Wazlawik E, Di Pietro PF, Maraschin M, da Silva EL.* Consumption of yerba mate (*Ilex paraguariensis*) improves serum lipid parameters in healthy dyslipidemic subjects and provides an additional LDL-cholesterol reduction in individuals on statin therapy. J Agric Food Chem 2009; 57: 8316–8324
190 *Klein GA, Stefanuto A, Boaventura BC, de Morais EC, Cavalcante Lda S, de Andrade F, Wazlawik E, Di Pietro PF, Maraschin M, da Silva EL.* Mate tea (*Ilex paraguariensis*) improves glycemic and lipid profiles of type 2 diabetes and pre-diabetes individuals: a pilot study. J Am Coll Nutr 2011; 30: 320–332
191 *Bremer Boaventura C, Faria Di Pietro P, Klein GA, Stefanuto A, de Morais EC, de Andrade F, Wazlawika E, da Silva EL.* Antioxidant potential of mate tea (*Ilex paraguariensis*) in type 2 diabetic mellitus and pre-diabetic individuals. J Funct Foods 2013; 5: 1057–1064
192 *Anuradha CV.* Phytochemicals targeting genes relevant for type 2 diabetes. Can J Physiol Pharmacol 2013; 91: 397–411
193 *Suhitha S, Gunasekaran K, Velmurugan D.* Structure based design of compounds from natural sources for diabetes and inflammation. Bioinformation 2012; 8: 1125–1131
194 *Vanaclocha B, Risco E, Cañigueral S.* Interacciones entre preparados vegetales y fármaos de sínteis: revisión de las monografías de la EMA y ESCOP. Rev Fitoter 2014; 14: 5–36
195 *Bratman S, Girman AM.* Mosby's handbook of herbs and supplements and their therapeutic uses. St. Louis: Mosby Health Gate; 2003
196 *Harkness R, Bratman S.* Mosby's handbook of drug-herb and drug-supplement interactions. St. Louis: Mosby Health Gate; 2003
197 *Ríos JL.* Fitoterapia. Valencia (Spain): Publicaciones Universitat de Valencia; 2009