Antidiabetic Potential of Medicinal Plants

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Diabetes mellitus is one of the major health problems in the world, the incidence and associated mortality are increasing. Inadequate regulation of the blood sugar imposes serious consequences for health. Conventional antidiabetic drugs are effective, however, also with unavoidable side effects. On the other hand, medicinal plants may act as an alternative source of antidiabetic agents.

Keywords: Diabetes mellitus ; medicinal plants ; antidiabetic ; hypoglycemic ; antihyperglycemic

1. Introduction

Diabetes mellitus (DM) is a serious, chronic, and complex metabolic disorder of multiple aetiologies with profound consequences, both acute and chronic [1]. Also known only as diabetes, DM and its complications affect people both in the developing and developed countries, leading to a major socioeconomic challenge. It is estimated that 25% of the world population is affected by this disease [2]. Genetic and environmental factors contribute significantly to the development of diabetes [3]. During the development of diabetes, the cells of the body cannot metabolize sugar properly due to deficient action of insulin on target tissues resulting from insensitivity or lack of insulin (a peptide hormone that regulates blood glucose). The inability of insulin to metabolize sugar occurs when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. This triggers the body to break down its own fat, protein, and glycogen to produce sugar, leading to the presence of high sugar levels in the blood with excess by-products called ketones being produced by the liver [4][5]. Diabetes is distinguished by chronic hyperglycemia with disturbances in the macromolecules' metabolism as a result of impairments in insulin secretion, insulin action, or both. Diabetes causes long-term damage, dysfunction, and failure of various organ systems (heart, blood vessels, eyes, kidneys, and nerves), leading to disability and premature death [6]. The severity of damage triggered by hyperglycemia on the respective organ systems may be related to how long the disease has been present and how well it has been controlled. Several symptoms such as thirst, polyuria, blurring of vision, and weight loss also accompany diabetes [7].

2. Medicinal Plants as an Alternative Source of Antidiabetic Agents

Natural products, particularly of plant origin, are the main quarry for discovering promising lead candidates and play an imperative role in the upcoming drug development programs [8][9][10]. Ease of availability, low cost, and least side effects make plant-based preparations the main key player of all available therapies, especially in rural areas [11]. Moreover, many plants provide a rich source of bioactive chemicals, which are free from undesirable side effects and possess powerful pharmacological actions [12][13][14][15][16][17][18]. Plants also have always been an exemplary source of drugs with many of the currently available drugs being obtained directly or indirectly from them [2][13][14][15]. The recent review of Durazzo et al. [19] gives a current snapshot of the strict interaction between the main biologically active compounds in plants and botanicals by giving a mini overview of botanicals features, a definition of the study, and examples of innovative (i.e., an assessment of the interaction of bioactive compounds, chemometrics, and the new goal of biorefineries) and a description of existing databases (i.e., plant metabolic pathways, food composition, bioactive compounds, dietary supplements, and dietary markers); in this regard, the authors marked the need for categorization of botanicals as useful tools for health research [19].

For centuries, many plants have been considered a fundamental source of potent antidiabetic drugs. In developing countries, particularly, medicinal plants are used to treat diabetes to overcome the burden of the cost of conventional medicines to the population [2]. Nowadays, treatments of diseases including diabetes using medicinal plants are recommended [20] because these plants contain various phytoconstituents such as flavonoids, terpenoids, saponins, carotenoids, alkaloids, and glycosides, which may possess antidiabetic activities [21]. Also marked by Durazzo et al. [19], the combined action of biologically active compounds (i.e., polyphenols, carotenoids, lignans, coumarins, glucosinolates, etc.) leads to the potential beneficial properties of each plant matrix, and this can represent the first step for understanding

their biological actions and beneficial activities. Generally, the main current approaches of study [22][23] of the interactions of phytochemicals can be classified: (i) model system development of interactions [24][25][26]; (ii) study of extractable and nonextractablecompounds [27][28]; or (iii) characterization of biologically active compound-rich extracts [29][30].

The antihyperglycemic effects resulting from treatment with plants are usually attributed to their ability to improve the performance of pancreatic tissue, which is done by increasing insulin secretions or by reducing the intestinal absorption of glucose [2].

The number of people with diabetes today has been growing and causing increasing concerns in the medical community and the public. Despite the presence of antidiabetic drugs in the pharmaceutical market, the treatment of diabetes with medicinal plants is often successful. Herbal medicines and plant components with insignificant toxicity and no side effects are notable therapeutic options for the treatment of diabetes around the world [31]. Most tests have demonstrated the benefits of medicinal plants containing hypoglycemic properties in diabetes management. Ríos et al. [32] described medicinal plants (i.e., aloe, banaba, bitter melon, caper, cinnamon, cocoa, coffee, fenugreek, garlic, guava, gymnema, nettle, sage, soybean, green and black tea, turmeric, walnut, and yerba mate) used for treating diabetes and its comorbidities and the mechanisms of natural products as antidiabetic agents, with attention to compounds of high interest such as fukugetin, palmatine, berberine, honokiol, amorfrutins, trigonelline, gymnemic acids, gurmarin, and phlorizin. The current review of Bindu and Narendhirakannan [33] has categorized and described from literature 81 plants native to Asian countries with antidiabetic, antihyperglycemic, hypoglycemic, anti-lipidemic, and insulin-mimetic properties.

In the *Artemisia* genus, *Artemisia absinthium* is one of the traditional medicinal plant used for diabetes treatment [34]. *Artemisia afra* is one of the popular herbal medicines used in the southern part of Africa [35]. *Artemisia herba-alba* is a traditional medicinal plant [36], and its aqueous extract of the leaves and barks reduces blood glucose levels [37]. *Solanum americanum* is a traditional medicine used in Guatemala [38], while *Solanum viarum* is used in India [39]. *Terminalia arjuna* is a plant used in India and Bangladesh [40] and exhibits amylase inhibition (IC_{50} value of 302 µg/mL) [41]. *Terminalia chebula* is a medicinal plant used in India [42], Bangladesh [43], Thailand [44], and Iran [45]. *Euphorbia ligularia* [46], *Euphorbia neriifolia* [47], and *Euphorbia caducifolia* [48] are some of the plants traditionally used in India. Similarly, *Euphorbia thymifolia* and *Euphorbia hirta* are used in Bangladesh [49][50], and *Euphorbia kansui* is a Korean traditional medicinal plant used for diabetes treatment [51]. *Allium cepa*, *Mangifera indica*, *Murraya koenigii*, and *Phyllanthus amarus* reduce triglycerides (TG), total cholesterol (TC), and very low-density lipoproteins (VLDL) levels and exhibit antidiabetic and hypolipidemic effects [52].

3. Medicinal Plants with Antidiabetic Potential

3.1. Preclinical In Vitro/In Vivo (Animal) Studies

Several plant species having hypoglycemic activity have been available in the literature; most of these plants contain bioactive compounds such glycosides, alkaloids, terpenoids, flavonoids, carotenoids, etc., that are frequently implicated as having an antidiabetic effect. In this section, plant species with antidiabetic potential will be organized in alphabetical order (**Table 1**).

Table 1. Plant extracts with antidiabetic potential.

Species	Extract	Part of the Plant	Dosage (mg/kg)	Experimental Model	Induction of Diabetes	Reference
Acacia arabica	**chloroform**	**bark**	**250, 500**	**male Wistar rats and albino mice**	**alloxan**	**[53]**
	chloroform	**bark**	**100, 200**	**female albino rats**	**streptozotocin**	**[54]**
Achyranthes rubrofusca	**aqueous and ethanolic**	**leaves**	**200**	**rats**	**alloxan**	**[55]**
Albizzia lebbeck	**methanol/dichloro-methane**	**stem bark**	**100, 200, 300, 400**	**male albino Wistar rats**	**streptozotocin**	**[56]**
	methanolic	**bark**	**200, 350, 620**	**female Sprague–Dawley rats**	**streptozotocin-nicotinamide**	**[57]**
Aloe vera	**aqueous**	**leaves**	**130**	**swiss albino mice**	**streptozotocin**	**[58]**
	ethanolic	**leaves**	**300**	**male albino Wistar rats**	**streptozotocin**	**[59]**

Species	Extract	Part of the Plant	Dosage (mg/kg)	Experimental Model	Induction of Diabetes	Reference
Amaranthus tricolor	methanolic	whole plant	50, 100, 200, 400	male swiss albino mice	glucose-induced hyperglycemia	[60]
Anacardium occidentale	aqueous	leaves	175	male albino Wistar rats	streptozotocin	[61]
	methanolic	leaves	100	female albino mice	streptozotocin	[62]
Azadirachta indica	ethanolic	leaves	200	adult rabbits	alloxan	[63]
Barleria prionitis	ethanolic	leaves and root	200	adult albino rats	alloxan	[64]
Bauhinia thoningii	aqueous	leaves	500	Wistar albino rats	alloxan	[65]
Caesalpinia ferrea	aqueous	stem bark	300, 450	male Wistar rats	streptozotocin	[66]
Camellia sinensis	crude tea	leaves	0.5 mL/day	male albino mice	streptozotocin	[67]
Casearia esculenta Roxb	aqueous	root	200, 300	male albino Wistar rats	streptozotocin	[68]
Cassia fistula	ethanolic	stem bark	250, 500	Wistar rats	alloxan	[69]
Cassia grandis	aqueous and ethanolic	stem	150	male albino Wistar rats	alloxan	[70]
Catharanthus roseus	dichloromethane-methanol	leaves and twigs	500	male Sprague–Dawley rats	streptozotocin	[71]
	ethanolic	leaves	100, 200	male Wistar rats	streptozotocin	[72]
Cecropia pachystachya	methanolic	leaves	80	male Wistar rats	alloxan	[73]
Ceriops decandra	ethanolic	leaves	30, 60, 120	male albino Wistar rats	alloxan	[74]
Chiliadenus iphionoides	ethanolic	aerial parts	1000	male and female diabetes-prone *Psammomys obesus*	-	[75]
Cinnamomum cassia	ethanolic	bark	200, 300	male Kunming mice	streptozotocin	[76]
Cinnamomum japonica	ethanolic	bark	200, 300	male Kunming mice	streptozotocin	[76]
Citrullus colocynthis	aqueous	root	2000	male and female Wistar rats and Swiss albino mice	alloxan	[77]
	aqueous	seed	1, 2 mL/kg	male Wistar albino rats	alloxan	[78]
Coscinium fenestratum	ethanolic	stem	250	male albino Wistar rats	streptozotocin-nicotinamide	[79]
Eucalyptus citriodora	aqueous	leaves	250, 500	albino rats	alloxan	[80]
Gymnema sylvestre	ethanolic	leaves	100	male Sprague–Dawley rats	streptozotocin	[81]
Heinsia crinata	ethanolic	leaves	450–1350	rats	alloxan	[82]
Helicteres isora	butanol and aqueous ethanol	roots	250	male Wistar rats	alloxan	[83]

Species	Extract	Part of the Plant	Dosage (mg/kg)	Experimental Model	Induction of Diabetes	Reference
Momordica charantia	aqueous	pulp	13.33 g pulp/kg	male albino Wistar rats	alloxan	[84]
	ethanolic	fruit	200	adult rabbits	alloxan	[63]
	ethanolic	fruit	400	male Sprague–Dawley rats	streptozotocin	[85]
Moringa oleifera	methanolic	pod	150, 300	Wistar albino rats	streptozotocin	[86]
	-	leaves	50	male Sprague–Dawley rats	alloxan	[87]
Murraya koenigii	aqueous	leaves	200, 300, 400	male albino rabbits	alloxan	[88]
	ethanolic	leaves	100, 250	male albino Swiss mice	dexamethasone	[89]
Opuntia ficus-indica	petroleum ether	stems	200	male ICR mice	streptozotocin	[90]
Origanum vulgare	methanolic	leaves	5	male C57BL/6 mice	streptozotocin	[91]
Passiflora nitida	hydro-ethanolic	leaves	50	female Wistar rats	streptozotocin	[92]
Paspalum scrobiculatum	aqueous and ethanolic	grains	250, 500	male Wistar albino rats	alloxan	[93]
Persea americana	hydro-alcoholic	leaves	150, 300	male Wistar rats	streptozotocin	[94]
	aqueous	seed	20, 30, 40 g/L	male Wistar albino rats	alloxan	[95]
Phoenix dactylifera	ethanolic	leaves	50-400	male Wistar rats	alloxan	[96]
Phyllanthus niruri	aqueous	leaves	200, 400	male Wistar rats	streptozotocin-nicotinamide	[97]
Phyllanthus simplex	petroleum ether, ethyl acetate, methanol and water fraction		100–400	rats	alloxan	[98]
Picralima nitida	methanolic	steam bark and leaves	75, 150, 300	Wistar rats	streptozotocin	[99]
Piper longum	aqueous	root	200, 300, 400	male Wistar albino rats	streptozotocin	[100]
Sonchus oleraceus	hydro-alcoholic	whole plant	75, 150, 300	Wistar rats	streptozotocin	[99]
Syzygium jambolana	ethanolic	seed	200	adult rabbits	alloxan	[63]
Tamarindus indica	ethanolic	stem bark	250, 500	Wistar rats	alloxan	[69]
	ethanolic	seed coat	500	Wistar albino rats	alloxan	[101]
Terminalia chebula	chloroform	seed	100, 200, 300	male Sprague–Dawley rats	streptozotin	[102]
Terminalia catappa	petroleum ether, methanol and aqueous	fruit	68, 40, 42	Wistar albino rats and mice	alloxan	[103]

Species	Extract	Part of the Plant	Dosage (mg/kg)	Experimental Model	Induction of Diabetes	Reference
Trigonella foenum-graecum	**ethanolic**	**seed**	**100, 500, 1000, 2000**	**male Wistar albino rats**	**alloxan**	[104]
	hydro-alcoholic	**seed**	**500, 1000, 2000**	**Sprague–Dawley rats**	**alloxan**	[105]
Vaccinium arctostaphylos	**ethanolic**	**fruit**	**200, 400**	**male Wistar rats**	**alloxan**	[106]
Vernonia amygdalina	**aqueous**	**leaves**	**100**	**Wistar albino rats**	**alloxan**	[107]
Witheringia solanacea	**aqueous**	**leaves**	**500, 1000**	**male Sprague–Dawley rats**	**GTT**	[108]
Zaleya decandra	**ethanolic**	**roots**	**200**	**Wistar albino rats**	**alloxan**	[109]
Zizyphus mauritiana	**petroleum ether, chloroform, acetone, ethanol and aqueous**	**fruit**	**200, 400**	**female Wistar rats**	**alloxan**	[110]

* unless otherwise noted, GTT glucose tolerance test; ICR Institute of Cancer Research.

3.1.1. *Acacia arabica* (Fabaceae)

Two doses of chloroform extracts of *Acacia arabica* (250 and 500 mg/kg, p.o. (orally) for two weeks) were evaluated in alloxan-induced diabetic albino rats [53]. The results of this study showed an antidiabetic effect in the two doses tested, decreasing serum glucose level and restoring TC, TG, and high-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels. Additionally, in this study chloroform extracts of *Benincasa hispida* fruit, *Tinispora cordifolia* stem, *Ocimum sanctum* aerial parts, and *Jatropha curcus* leaves were evaluated, showing similar effects.

In another study performed in streptozotocin-induced diabetic rats, the extract of *Acacia arabica* (100 and 200 mg/kg, p.o. for 21 days) provoked a significantly decrease in serum glucose, TC, TG, LDL, and malonyldialdehyde (MDA) levels and a significantly increase in HDL and coenzyme Q10 in a dose-dependent manner [54].

3.1.2. *Achyranthes rubrofusca* (Amaranthaceae)

Hypoglycemic activity of the aqueous and ethanolic extracts of *Achyranthes rubrofusca* leaves was studied in alloxan-induced diabetic rats [55]. The two extracts (200 mg/kg, p.o. for 28 days) significantly decreased the blood glucose level and increased pancreatic enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione levels. Better results were obtained with the aqueous extract but were not statistically significant.

3.1.3. *Albizzia lebbeck* (Fabaceae)

Oral administration of a methanol/dichloromethane extract from *Albizzia lebbeck* Benth. stem bark (100, 200, 300, or 400 mg/k, for 30 days) was evaluated in streptozotocin-induced diabetic rats [56]. The treatment significantly decreased fasting blood glucose (FBG) and glycated hemoglobin and enhanced plasma insulin levels. Moreover, it significantly decreased the levels of TC, TG, LDL, and VLDL and significantly increased the level of HDL. The treatment also resulted in a marked increase in reduced glutathione, glutathione peroxidase, CAT, and SOD and a diminished level of lipid peroxidation in liver and kidneys of streptozotocin-induced diabetic rats. Moreover, the histopathological analysis of the pancreas, liver, kidney, and heart showed that the treatment protected these organs in diabetic rats and reduced the lesions in a dose-dependent manner. In another study in streptozotocin-nicotinamide-induced diabetic rats, the methanolic extract of *Albizzia lebbeck* bark significantly decreased the level of serum glucose, creatinine, urea, TC, TG, LDL, and VLDL and increased HDL level [57].

3.1.4. *Aloe vera* (Asphodelaceae)

Aloe vera extract was evaluated in streptozotocin-induced diabetic mice and in mouse embryonic NIH/3T3 cells [58]. Administration of an extract at a dosage of 130 mg/kg per day for four weeks resulted in a significant decrease in blood glucose, TG, LDL, and TC, an effect comparable to that of metformin. Moreover, this study showed that a lyophilized aqueous aloe extract (1 mg/mL) upregulated GLUT-4 mRNA synthesis in NIH/3T3 cells. In a more recent study, *Aloe*

vera extract (300 mg/kg) exerted antidiabetic effects by improving insulin secretion and pancreatic β-cell function by restoring pancreatic islet mass in streptozotocin-induced diabetic rats [59].

3.1.5. *Amaranthus tricolor* (Amaranthaceae)

Methanolic extract of *Amaranthus tricolor* whole plant at different doses (50, 100, 200, or 400 mg/kg) was administered one hour before glucose administration in the oral glucose tolerance test (GTT) [60]. The results of this study showed significant antihyperglycemic activity in glucose-loaded mice at all doses of the extract tested, with the maximum effect observed at the maximum dose tested and with an effect comparable to glibenclamide (10 mg/kg).

3.1.6. *Anacardium occidentale* (Anacardiaceae)

Hypoglycemic role of *Anacardium occidentale* was reported in streptozotocin-induced diabetic rats [61]. The rats were treated with 175 mg/kg of the aqueous extract, twice daily, beginning 2 days before streptozotocin injection. Three days after streptozotocin administration, there was a significantly lower blood glucose level in pretreated rats compared to control diabetic rats. Moreover, the treatment prevented glycosuria, body weight loss, polyphagia, and polydipsia. A more recent study performed with 100 mg/kg of methanol extract for 30 days showed a decrease of blood glucose levels of streptozotocin-induced diabetic rats and comparable effects to the standard drug Pioglitazone [62].

3.1.7. *Azadirachta indica* (Meliaceae)

One study was designed to evaluate the hypoglycemic effects of different plant extracts (*Azadirachta indica* leaves, *Momordica charantia* fruits, and *Syzygium jambolana* seeds) in single and in combined formulation in alloxan-induced diabetic rabbits [63]. Treatment of diabetes with plant extracts started at 8 days after alloxan injection. A dose of 200 mg/kg of an ethanol extract from the leaves of *Azadirachtaindica* caused a hypoglycemic effect 72 h after administration in diabetic rabbits, with a persistence of up to 24 h.

3.1.8. *Barleria prionitis* (Acanthaceae)

Antidiabetic activity of alcoholic extracts of leaf and root of *Barleria prionitis* (200 mg/kg, p.o. for 14 days) was tested in alloxan-induced diabetic rats [64]. Animals treated with leaf extract significantly decreased blood glucose and glycosylated hemoglobin levels. Moreover, serum insulin and liver glycogen levels were significantly increased. The root extract showed a moderate but nonsignificant antidiabetic activity.

3.1.9. *Bauhinia thoningii* (Fabaceae)

A study conducted on alloxan-induced diabetic rats showed the antidiabetic effect of aqueous leaf extract from *Bauhinia thoningii* [65]. The extract administered orally at a dose of 500 mg/kg for seven days provoked a significant reduction in blood glucose, LDL, and coronary risk index.

3.1.10. *Caesalpinia ferrea* (Fabaceae)

Aqueous extract of the stem bark of *Caesalpinia ferrea* (300 and 450 mg/kg, daily for four weeks) was administered orally to streptozotocin-induced diabetic rats [66]. The results of this study showed a significant reduction of blood glucose levels and an improvement of the metabolic state of the animals (low levels of TC, TG, and epididymis adipose tissue).

3.1.11. *Camellia sinensis* (Theaceae)

The hypoglycemic activity of the crude tea leaves extract of *Camellia sinensis* was investigated on streptozotocin-induced diabetic mice [67]. The tea (0.5 mL/day) was administered for 15 and 30 days and caused antihyperglycemic and hypolipidemic (TG and TC) activities in diabetic rats. Moreover, protective effects such as recovery of certain altered hematobiochemical parameters—creatinine, urea, uric acid, aspartate aminotransferase (AST), and alanine aminotransferase (ALT)—and reduced body weight were observed.

3.1.12. *Casearia esculenta* (Flacourtiaceae)

The extract of *Casearia esculenta* root in streptozotocin-induced diabetic rats (200 and 300 mg/kg, p.o. for 45 days) significantly restored levels of glucose, urea, uric acid, creatinine, and albumin; the albumin/globulin ratio; and the activities of diagnostic marker enzymes AST, ALT, alkaline phosphatase (ALP), and γ-glutamyltranspeptidase (GGT) [68].

3.1.13. *Cassia fistula* (Fabaceae)

Alcoholic extracts of stem bark of *Cassia fistula* administered to alloxan-induced diabetic rats at 250 or 500 mg/kg for 21 days significantly decreased blood glucose levels [69]. The extract also recovered normal levels of serum cholesterol, TG,

creatinine, albumin, total proteins, and body weight. Moreover, the alcoholic extract showed significant antioxidant activity by reducing 2,2-diphenyl-1-picrylhydrazyl (DPPH), nitric oxide, and hydroxyl radical induced in vitro.

3.1.14. *Cassia grandis* (Fabaceae)

The aqueous and ethanolic extracts of *Cassia grandis* (150 mg/kg, p.o. for 10 days treatment) were evaluated for antidiabetic activity by a GTT in normal rats and alloxan-induced diabetic rats [70]. The two extracts showed antidiabetic potential, decreasing the blood glucose, TC, and TG levels.

3.1.15. *Catharanthus roseus* (Apocynaceae)

Dichloromethane-methanol extracts of *Catharanthus roseus* leaves and twigs in streptozotocin-induced diabetic rats significantly reduced blood glucose levels and hepatic enzyme activities of glycogen synthase, glucose 6-phosphate-dehydrogenase, succinate dehydrogenase, and malate dehydrogenase [71]. In another study performed in streptozotocin-induced diabetic rats, the ethanolic extracts of *Catharanthus roseus* (100 and 200 mg/kg) detrained the glucose transport system in the liver for 4 weeks and significantly amplified the expression of the GLUT gene [72].

3.1.16. *Cecropia pachystachya* (Urticaceae)

The hypoglycemic effect of the methanolic extract from the leaves of *Cecropia pachystachya* was tested in normal, glucose loading, and alloxan-induced diabetic rats [73]. The methanolic extract provoked a significant hypoglycemic effect, which resulted in a 68% reduction of blood glucose after 12 h of induction. Moreover, the extract presented relevant antioxidant activity with IC_{50} = 3.1 µg/mL (DPPH assay) and EC_{50} = 10.8 µg/mL (reduction power).

3.1.17. *Ceriops decandra* (Rhizophoraceae)

The antidiabetic effects of daily oral administration of an ethanolic extract from *Ceriops decandra* leaves (30, 60, and 120 mg/kg) for 30 days were evaluated in normal and alloxan-induced diabetic rats [74]. Oral administration of 120 mg/kg of the extract modulated all the determined parameters (blood glucose, hemoglobin, liver glycogen, and some carbohydrate metabolic enzymes) to levels seen in control rats. Furthermore, these dose effects were comparable to those of glibenclamide.

3.1.18. *Chiliadenus iphionoides* (Asteraceae)

The ethanolic extracts of *Chiliadenus iphionoides* aerial parts increased insulin secretion from β cells and glucose uptake by adipocytes and skeletal myotubes, in vitro [75]. Moreover, a 30-day oral starch tolerance test was performed on a sand rat, showing hypoglycemic activity.

3.1.19. *Cinnamomum cassia* and *Cinnamomum japonica* (Lauraceae)

Cinnamon bark extracts were administered at doses of 200 and 300 mg/kg for 14 days in high-fat, diet-fed, and low-dose streptozotocin-induced diabetic mice [76]. The results of this study showed that *Cinnamomum cassia* and *Cinnamomum japonica* bark extracts significantly decreased blood glucose concentration. Also, cinnamon extracts significantly increased the consumption of extracellular glucose in insulin-resistant HepG2 cells and normal HepG2 cells compared with controls, suggesting an insulin sensitivity improvement.

3.1.20. *Citrullus colocynthis* (Cucurbitaceae)

The effect of root extracts of *Citrullus colocynthis* was investigated on the biochemical parameters of normal and alloxan-induced diabetic rats [77]. Aqueous extracts of the roots showed a significant reduction in blood sugar levels when compared with chloroform and ethanol extracts. Moreover, the aqueous extract improved body weight and serum creatinine, urea, protein, and lipids and restored levels of total bilirubin, conjugated bilirubin, AST, ALT, and ALP. In another study in alloxan-induced diabetic rats, *Citrullus colocynthis* aqueous seed extract stabilized animal body weight and ameliorated hyperglycemia in a dose- and time-dependent manner, which was attributable to the regenerative effect on β cells and intra-islet vasculature [78].

3.1.21. *Coscinium fenestratum* (Menispermaceae)

Alcoholic extract of the stems of *Coscinium fenestratum* in streptozotocin-nicotinamide-induced diabetic rats regulates glucose homeostasis and decreased gluconeogenesis [79]. The drug also has a protective action on cellular antioxidant defense.

3.1.22. *Eucalyptus citriodora* (Myrtaceae)

Aqueous extract of *Eucalyptus citriodora* leaf in alloxan-induced diabetic rats (250 and 500 mg/kg, p.o. for 21 days) significantly reduced blood glucose levels [80].

3.1.23. *Gymnema sylvestre* (Apocynaceae)

An ethanolic extract of *Gymnema sylvestre* leaf (100 mg/kg, p.o. for 4 weeks) was examined in vitro and in vivo to investigate the role of antioxidants in streptozotocin-induced diabetic rats [81]. The ethanol extract showed antihyperglycemic activity and improved the antioxidant status in diabetic rats. Moreover, the extract showed in vitro antioxidant activity in thiobarbituric acid (TBA), SOD, and 2,2-azino-bis-3-ethylbenzthiazoline-6-sulphonic acid assays.

3.1.24. *Heinsia crinata* (Rubiaceae)

Ethanolic extract of *Heinsia crinata* leaf in alloxan-induced diabetic rats (450–1350 mg/kg, p.o. for two weeks) significantly reduced the FBG levels [82].

3.1.25. *Helicteres isora* (Sterculiaceae)

Butanol and aqueous ethanol extracts of *Helicteres isora* root (250 mg/kg, p.o. for 10 days) were investigated in alloxan-induced diabetic rats [83]. The two treatments reduced blood glucose, TC, TG, and urea levels. Further histological examination showed the restoration of pancreatic islets, kidney glomeruli, and liver to their normal sizes.

3.1.26. *Momordica charantia* (Cucurbitaceae)

One study evaluated the antihyperglycemic and antioxidative potential of aqueous extracts of *Momordic charantia* pulp and *Trigonella foenum-graecum* seed in alloxan-induced diabetic rats [84]. The *Momordica charantia* extract treatment for 30 days significantly decreased the blood glucose levels and showed antioxidant potential to protect vital organs such as heart and kidney against damage caused by diabetes-induced oxidative stress. Furthermore, a similar activity was found with the *Trigonella foenum-graecum* extract treatment. In another study already reported [63], an antidiabetic effect from *Momordica charantia* leaves (200 mg/kg) was observed in rabbits 72 h after they were fed a methanolic extract. In a recent study performed in streptozotocin-induced diabetic rat, the treatment of 400 mg/kg of ethanol extract significantly decreased body weight, serum glucose, insulin TNF-α, and interleukin 6 (IL-6) [85].

3.1.27. *Moringa oleifera* (Moringaceae)

One study investigated the antidiabetic and antioxidant effects of methanol extracts of *Moringa oleifera* pods (150 and 300 mg/kg, p.o. for 21 days) in streptozotocin-induced diabetic rats [86]. Both doses induced a significant reduction in serum glucose and nitric oxide levels, with a concomitant increase in serum insulin and protein levels. Furthermore, the methanol extracts increased antioxidant levels in pancreatic tissue and concomitantly decreased TBA levels. Additionally, a histological pancreas examination showed that *Moringa oleifera* treatment significantly reversed the histoarchitectural damage to islet cells provoked by induced diabetes. In a recent study performed in alloxan-induced diabetic rats, the consumption of the *Moringa oleifera* leaves showed a hypoglycemic effect and prevented body weight loss [87].

3.1.28. *Murraya koenigii* (Rutaceae)

Aqueous extract of *Murraya koenigii* leaf in alloxan-induced diabetic rats (200, 300, and 400 mg/kg) significantly reduced blood glucose level and was found to have a beneficial effect on carbohydrate metabolism [88]. Moreover, the ethanolic extract of this plant, in mice, ameliorates dexamethasone-induced hyperglycemia and insulin resistance in part by increasing glucose disposal into skeletal muscle [89].

3.1.29. *Opuntia ficus-indica* (Cactaceae)

Various extracts from edible *Opuntia ficus-indica* (petroleum ether, ethyl acetate, butanolic, aqueous, and water parts) and a standard drug as a positive control (dimethyl biguanide, 100 mg/kg) were tested in streptozotocin-induced diabetic mice [90]. The results of this study showed that all extracts tested significantly decreased blood glucose levels and maintained body weight, except the aqueous extract. Mainly, the petroleum ether extract showed a remarkable decrease in blood glucose levels.

3.1.30. *Origanum vulgare* (Lamiaceae)

The phytochemical analysis of methanolic extract from *Origanum vulgare* showed an enriched composition in biophenols, and it has demonstrated in vitro antioxidant activity in DPPH assays [91]. An in vivo study performed in streptozotocin-induced diabetic mice with methanolic and aqueous extract showed that aqueous extract had no impact on diabetes induction, while methanolic extract reduced diabetes incidence and preserved normal insulin secretion. Moreover,

methanolic extract upregulated antioxidant enzymes (SOD, CAT, glutathione reductase, and peroxidase), attenuated pro-inflammatory activity, and showed cytoprotective activity.

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