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Medicinal Plants and Natural Compounds from the Genus *Morus* (Moraceae) with Hypoglycemic Activity: A Review

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1. Introduction

Diabetes mellitus (DM) is a metabolic disorder resulting from defects in insulin secretion or reduced sensitivity of the tissues to insulin action or both [1]. It is characterized by chronic high blood glucose that causes glycation of body proteins which could lead to severe complications. These complications are classified into acute, sub-acute and chronic.

Acute complications include hypoglycemia, diabetic ketoacidosis, hyperosmolar and hyperglycaemic non-ketotic syndrome while sub acute complications are thirst, polyuria, lack of energy, visual blurriness and weight loss. The chronic complications of diabetes mellitus include hypertension, neuropathy, nephropathy, retinopathy and diabetic foot ulcers which could result in amputation [2].

On the basis of aetiology and clinical presentation, diabetes mellitus can be grouped into type 1 known as insulin- dependent diabetes mellitus (IDDM) and type 2 also known as non insulin-dependent diabetes mellitus (NIDDM). The World Health Organization (WHO) recommends that the terms type 1 and type 2 should be reintroduced, because they classify the patients on the basis of the pathogenesis and not on the basis of treatment. Type 1 diabetes mellitus is caused by immunological destruction of pancreatic β cells leading to insulin deficiency [3], whereas type 2 diabetes results from defects in insulin secretion or rather insulin resistance. It is the most common type of diabetes, afflicting 85-95% of all diabetic individuals. It is a prevalent form of the disease and common in individuals over 40

years of age. The increasing number of ageing population, consumption of calorie-rich diet, obesity and sedentary life style have led to a tremendous increase in the number of diabetes mellitus world wide [2]. About 173 million people suffer with this disease. The number of people with diabetes mellitus will be more than double over the next 25 years to reach a total of 366 million by 2030 [4].

The only therapy of type 1 diabetes is the substitution of insulin. Many and diverse therapeutic strategies for the treatment of type 2 diabetes are known. Conventional treatments include the reduction of the demand for insulin, stimulation of endogenous insulin secretion, enhancement of the action of insulin at the target tissues and the inhibition of degradation of oligo- and disaccharides. One group of drugs introduced in the management of type 2 diabetes is represented by the inhibitors of α -glycosidase [4].

In a general manner DM is a group of metabolic disorders characterized by hyperglycemia. These metabolic disorders include alterations in carbohydrate, fat and protein metabolisms associated with absolute and relative deficiencies in insulin secretion and/or insulin action [5]. Insulin is a hormone needed to convert sugar, starch and other food into energy needed for daily life. The cause of diabetes continues to be a mystery, although both genetic and environmental factors such as obesity and lack of exercise appear to play a part [6]. The control of DM normally involves exercise, diet and drug therapy. In the last years there has been an increasing demand for natural products with antidiabetic activity, mainly due to the side effects associated with the use of insulin and oral hypoglycemic agents [7]. The available therapies for diabetes include insulin and oral antidiabetic agents such as sulfonylureas, biguanides and α -glycosidase inhibitors. Many of these oral antiabetic agents have a number of serious adverse effects [8]. Thus, the management of diabetes without any side effects is still a challenge.

Plants have always been an important source of drugs and many of the currently available drugs have been derived directly or indirectly from them. Ethnobotanical reports indicate about 1200 plants in the world with anti-diabetic potential [9], of which more than three hundred have been reported in the literature referring to a large variety of identified chemical substances. The discovery of the widely used hypoglycemic drug, metformin (*N,N*-dimethylguanylguanidine) came from the traditional approach through the use of *Galega officinalis* [10].

In this regard, several medicinal plants among which are those belonging to the genus *Morus* have been reported to be used in traditional medicine for the treatment of DM. Medicinal plants are one of the few therapeutic resources available to most population. According to this reality it is essential to search new alternatives for the treatment of DM. Several plant species have been studied as potential antidiabetic agents.

Considering the importance of species of the genus *Morus* in treatment of diabetes mellitus, this chapter is a review of medicinal plants and natural products with hypoglycaemic activity from genus *Morus* and the main methods used in the assessment of hypoglycemic potential of these plants.

2. Methods

With the objective of contributing to these studies, a literature search on the ethnomedical information and use of natural products (crude plant extracts, semi-purified fractions and chemically defined molecules) from the genus *Morus* which have already been evaluated particularly for hypoglycemic activity was carried out. The keywords used for the literature search for this review were *Morus*, Moraceae, hypoglycemic activity, antidiabetic activity, medicinal plants and natural products. The search was carried out using Biological Abstracts, Chemical Abstracts, and the data bank of the University of Illinois in Chicago NAPRALERT (Acronym for NATural PRoducts ALERT), updated to December 2011. The references found in the search were then studied in detail. Only those plants whose extracts and/or isolated constituents that showed clear pharmacological effects with hypoglycemic activity in animal models were included in this review.

3. Results and discussion

In this section we present some considerations about the Moraceae family, the main species from the genus *Morus* and chemical constituents isolated from species of this genus with hypoglycemic activity as well as important methods for assessing the hypoglycemic potential of natural products and plant extracts.

Consultation of various literature sources resulted in the elaboration of a list of some active biomolecules of different *Morus* species and natural products evaluated for hypoglycemic activity (Tables 1, 2 and 3). It should be noted that most of the references cited are not first-hand observations, but compilations copied from other sources. For details on the models or mechanism-based bioassays utilized for selecting crude plant extracts, fractions and other preparations for hypoglycemic activity, the original references should be consulted.

3.1. The family Moraceae and the genus *Morus*

Moraceae is a family of flowering plants that comprises about 40 genera and over 1000 species [11]. The genus *Morus*, is widely distributed in Asia, Europe, North America, South America, and Africa, and is cultivated extensively in the eastern, central, and southern Asia for silk production. Mulberry (*Morus* sp.) has been domesticated over thousands of years and has been adapted to a wide area of tropical, subtropical, and temperate zones of the world [12].

Morus is a genus with species of deciduous trees [11]. There are 24 species of *Morus* and one subspecies, with at least 100 known varieties. Mulberry is found from temperate to subtropical regions of the Northern hemisphere to the tropics of the Southern hemisphere and they can grow in a wide range of climatic, topographic and soil conditions [13]. Some species of this genus are widely cultivated in many countries, in particular in China and Japan, where mulberry is used for its foliage to feed the silkworm [14].

Species of this genus has also been used in folk medicine (especially in Chinese traditional medicine) as antiphlogistic, hepatoprotective, hypotensive, antipyretic, analgesic, diuretic, expectorant, antidiabetic [14, 15] as well as to treat anemia and arthritis [12]. The leaves of mulberry species are consumed in Korea and Japan as anti-hyperglycemic nutraceutical food for patients with diabetes mellitus because the leaves are rich in alkaloid components, including 1-deoxynojirymicin (**1**), which is known to be one of the most potent α -glycosidase inhibitors [16] that decreases blood sugar levels.

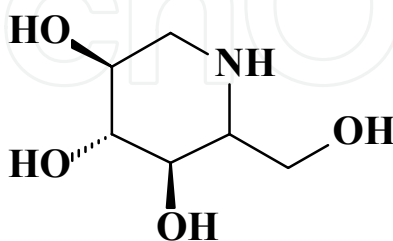


Figure 1. Chemical structure of compound (**1**) isolated from species of *Morus*.

This genus contains a variety of phenolic compounds including isoprenylated flavonoids, stilbenes, 2-arylbenzopyrans, coumarins, chromones, xanthenes and a variety of Diels-Alder adduct compounds [14, 17]. Some of these compounds exhibit interesting biological properties such as antiphlogistic, antiinflammatory, diuretic, hypotensive effects and some are known as phytoalexins [18]. The antioxidant potential of some phenolic compounds of *Morus alba* also been reported in the literature [19].

The production of mulberry fruits in 2005 was 78,000 tonnes in Turkey and its cultivation in Turkey have been known for more than 400 years [20].

3.2. *Morus alba* L.

Morus alba, known as white mulberry, is a species native to China and now widely cultivated in other countries. It has white and purple fruits with a very sweet taste and low acidity. Its fruits are perishable and mostly used for fresh consumption. The fruit of white mulberry (which is also found in the Eastern United States) is white to pinkish, unlike the red or black berries of most other *Morus* species. According to sources, white mulberry is the species that has been used exclusively in Chinese medicine since A.D- 659. The Chinese Pharmacopoeia (1985) lists the leaves, root bark, branches, and fruits as ingredients in medicinal preparations, but other parts, including the sap and wood ash, are also widely used [21].

The different parts of this plant have been used in the traditional Chinese medicine for many purposes. The white mulberry leaves, an important food for silkworm, are used to treat hypertension, arthritis, and the fruit is a diuretic and a tonic agent. The root bark of the plant is considered as an important medicine to treat cough, inflammation, diabetes, cancer, hepatitis and heart diseases. Previous studies showed that *M. alba* mainly contained polyphenolic constituents including prenylated flavonoids, benzofurans and Diels–Alder

type adducts with various biological activities such as cytotoxicity, antioxidant, inhibition of NF- κ B, LOX-1, cancer cell invasion and migration, and hepatoprotection. The glycosidase inhibitory activity of several alkaloids in *M. alba* has also been reported [22]. The root is astringent and bark is anti-helmintic. Root is one of the constituents of the Chinese drug named "Sohaku-hi" which reduces the plasma sugar level in mice. Decorked bark is used against chronic bronchitis and emphysema [23].

The root bark also contains an alkaloid, 1-deoxynojirimycin (**1**) that inhibited glycogenolysis, glycoprotein processing and saccharide hydrolysis enzymes whereas its derivatives have great therapeutic potential for the treatment of viral infections, diabetes, obesity and cancer [21]. *Morus alba* leaves containing many nutritional components are the best feed for silkworms and they have been used in traditional Chinese medicine as an antihyperglycemic to treat and to prevent diabetes mellitus. The components are flavones, steroids, triterpenes, amino acids, vitamins and other trace minerals. Among the 6 N-containing sugars isolated, 2-O- α -D-galactopyranosyl-DNJ (GAL-DNJ) and fagomine have the most potent antihyperglycemic effects [24]. Table 1 lists some active biomolecules of different *Morus* species with their medicinal properties.

3.3. *Morus bombycis*

This plant is found in China, Japan, Korea and Southern Sakhaline. Root bark contains quinones named as Kwanons G and H with hypotensive activity, phytoalexins like Moracin A-Z and Albanins A-H with antimicrobial activity. The leaves also contain N-methyl-1-deoxynojirimycin which is used against diabetes mellitus. This compound also inhibits the infectivity of human immunodeficiency virus [21].

3.4. *Morus indica* L.

Over the years, medicinal plants and their extracts are gaining importance in the treatment of hyperglycemia and diabetes. The extracts of *Morus indica*, commonly known as mulberry, have been reported to possess medicinal properties, including hypoglycemic, hypotensive and diuretic activities. The hypoglycemic effect of mulberry leaves or shoot culture extract has been demonstrated using streptozotocin-induced diabetic animals [25]. The ethanol extract from the leaves of *Morus indica* showed antiinflammatory activity on carrageenan-induced edema in rats and cotton pellet granuloma models [26].

3.5. *Morus insignis*

Ethyl acetate and n-butanol-soluble fractions of the leaves of *Morus insignis* showed a significant hypoglycemic activity on streptozotocin (STZ)-induced hyperglycemic rats. From these hypoglycemic activity-showing fractions, two new compounds, mulberrofuran U and moracin M-3-O- β -D-glucopyranoside were isolated, along with six known compounds (β -sitosterol, β -sitosterol-3-O- β -glucopyranoside, ursolic acid, moracin M, kaempferol-3-O- β -glucopyranoside and quercetin-3-O- β -glucopyranoside) [27]. The fungicidal, bactericidal

and hypoglycemic activities of leaves of *M. insignis* have been attributed to benzofurans Mulberrofuran U and Moracin M-3'-O- β -D-glucopyranoside [28].

Name of Morus species	Active constituents	Plant part used	Medicinal properties
<i>Morus alba</i>	Kwanon I; Kwanon I hexamethyl ether; Kwanon I octamethyl ether; 2'-Hydroxy-2,4,4'-trimethoxychalcone; 2'-Hydroxy-3'-prenyl-2,4,4'-trimethoxychalcone III; Mulberrofuran T; Kwanon E; Morusin, Mulberrofuran D, G, K; Kwanon G, H; Mulberroside A; <i>Cis</i> -mulberrosideA; Oxyresveratrol; Isoquercetin; Kwanon G; Moracin E, F, G and H; Kwanon D, E, F; Deoxynojirimycin-1	Root, stem, leaves, fruit	Astringent, anti-helminthic, HIV, cough, antiinflammatory, exudative, high blood pressure, diaphoretic, purgative, emollient, diarrhoea, diabetes , atherosclerosis, anti-tumor, hypoglycemia
<i>Morus australis</i>	Australone A; triterpenoid 3 β -[(<i>m</i> -methoxybenzoyl) oxy]-urs-12-en-28-oic acid; morusin; Kwanon C; betulinic acid; β -amyrin; quercetin; ursolic acid; Mulberrofuran D; sanggenols N and O	Root, leaves, fruits	Astringent, anti-helminthic, purgative, antiplatelet
<i>Morus bombycis</i>	<i>N</i> -methyl-1-Deoxynojirimycin; Kwanon G, H; Moracin A-Z; Albanins A-H; γ -aminobutyric acid; <i>L</i> -asparagine; <i>L</i> -arginine; <i>L</i> -lysine; choline; Mulberrofuran I	Root, leaves	Hypotensive, antimicrobial, diabetes , HIV, antiphlogistic, diuretic
<i>Morus laevigata</i>	Citrulline; hydroxyproline; free amino acids	Fruit	Plaster for sores, cools the blood
<i>Morus nigra</i>	Deoxynojirimycin	Root, leaves, fruits	Diabetes , AIDS, purgative, arterial pressure, vermifuge, cancer
<i>Morus serrata</i>	β -Amyrin acetate; betulinic acid; cerylalcohol; quercetin; morin	Root	-----
<i>Morus rubra</i>	Rubraflavones A, B, C, D	Root	Anti-dysenteric, laxative, purgative, vermifuge, urinary problems, weakness
<i>Morus macroura</i>	Guangsangons A-N; albafrican C; Kwanon J, X, Y; Mulberrofuran G, K, J	Stem	Antiinflammatory, antioxidative
<i>Morus cathayana</i>	Sanggenols F, G, H, I, J, K; cathayanon A, B	Root	Antiinflammatory, hypertension

Adapted from reference [21].

Table 1. Active biomolecules of different *Morus* species

3.6. *Morus nigra* L.

Morus nigra, known as black mulberry, is one of the most important species of the genus *Morus*. It has juicy fruits with extraordinary color and a unique, slightly acidic flavor. The fruits are 2-3 cm long [12].

A medium or small sized tree 6-9 m high, native to West Asia. It is also cultivated in Kashmir, Darjeeling, leaves are ovate-cordate, flower dioecious or monoecious, fruits are syncarp, ovoid, purple to black, juicy, edible. The root bark is purgative and vermifuge. Root has an effect on pancreas and glycogenolysis while its juice reduces the blood sugar level in diabetic patient. The root bark extract contains deoxynojirimycin (DNJ), an alkaloid which is said to be active against AIDS virus. An infusion of leaves causes a drop in blood sugar, sometimes diuresis and a reduction of arterial pressure [21].

DNJ is a potent source α -glycosidase inhibitor and helpful to establish greater glycemic control in type 2 diabetes. Young mulberry leaves taken from top part of branches in summer contain the highest amount of DNJ. In a human study, DNJ enriched powder of mulberry leaves significantly suppressed elevation of post-prandial glucose. Newly developed DNJ enriched powder can be used as a dietary supplement for preventing diabetes mellitus [21].

Morus nigra and other members of its genus can be grown without protection in many countries. The berries, bark and leaves of the black mulberry are all used medicinally, the berries for inflammation and to stop bleeding, the bark for toothache, and the leaves for snake bites and as an antidote to action poisoning. In Europe, black mulberry leaves have been used recently to stimulate insulin production in diabetes. Mulberry contains soluble plant chemicals known as bioflavonoids. These powerful antioxidants may be responsible for their medicinal properties [29].

Morus nigra has been used in folk medicine as an analgesic, diuretic, antitussive, sedative, anxiolytic and hypotensive, in addition to its uses in the treatment of a variety of ailments, including inflammatory disorders [17]. There are few studies involving the chemical composition and evaluation of biological and pharmacological properties of *Morus nigra*. Morusin, the main prenylflavonoid present in the root bark of this species have been investigated in classical models of pain in mice and exhibits a promising antinociceptive or analgesic profile [30]. In recent studies, Naderi et al. [29] demonstrated that extracts of *Morus nigra* fruits have a protective action against peroxidative damage to biomembranes and biomolecules. Antiinflammatory properties of methylene chloride extract from leaves [31] as well as antinociceptive effects [32] were reported. Three new compounds including two flavonoids and a new 2-phenylbenzofuran, named morunigrols A-C, together with three known compounds albufuran A, albufuran B and mulberrofuran L were isolated from the barks of *Morus nigra* [33]. Two new prenylflavonoids, mornigrol E and mornigrol F were isolated from the barks of this species [34], as well as germanicol, betulinic acid and β -sitosterol [31]. Figure 2 shows the chemical structures of some chemical constituents isolated from species of the genus *Morus*.

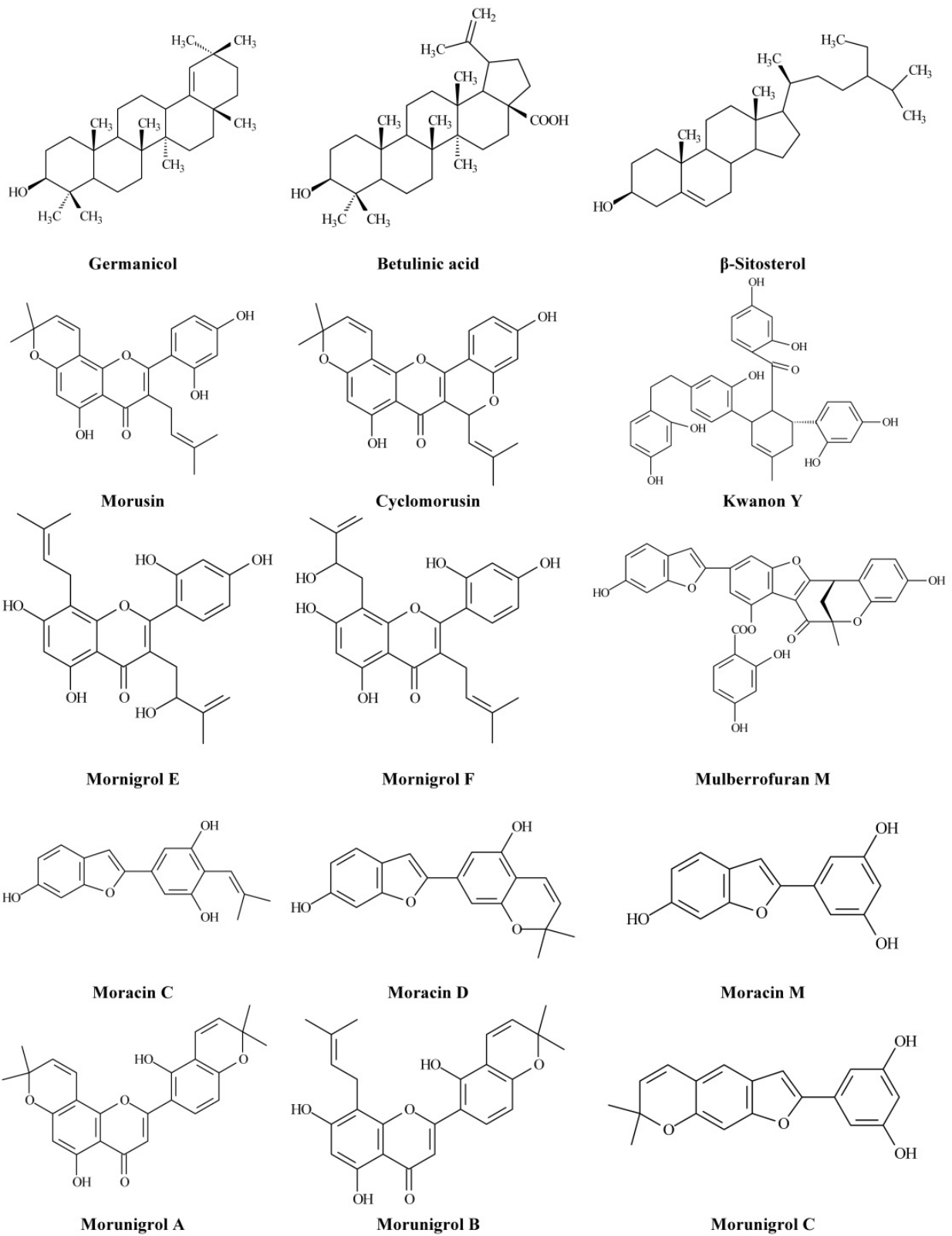


Figure 2. Chemical structures of some natural compounds isolated from species of the genus *Morus*.

Botanical name	Origin (Part used)	Use	Preparation	Via	Organism	References
<i>Morus alba</i>	Japan (B)	Used for diabetes	Decoction	Oral	Human adult	[42]
	Japan (C)	Used as an antidiabetic	Bark	Oral	Human adult	[43]
	Chile (L)	Used to treat diabetes	Infusion	Oral	Human adult	[44]
	Spain (L)	Used as a hypoglycemic	Hot H ₂ O extract	Oral	Human adult	[45]
	Turkey (L)	Used for diabetes	Decoction	Oral	Human adult	[46]
	Yugoslavia (L)	Used for diabetes	Hot H ₂ O extract	Oral	Human adult	[47]
	Peru (L + S)	Used as an antidiabetic	Hot H ₂ O extract	Oral	Human adult	[48]
	France (L)	Used for diabetes	Hot H ₂ O extract	Oral	Human adult	[49]
<i>Morus lhou</i>	Italy (L)	Used as an antidiabetic	Infusion	Oral	Human adult	[50]
<i>Morus nigra</i>	Canary Islands (FL)	Used as a hypoglycemic	Infusion	Oral	Human adult	[51]
	Iran (L)	Used in diabetes	Decoction	Oral	Human adult	[52]
	Yugoslavia (L)	Used for diabetes	Hot H ₂ O extract	Oral	Human adult	[53]
	Puerto Rico (NS)	Used for diabetes	Hot H ₂ O extract	Oral	Human adult	[54]
	Iran (RB)	Used in diabetes	Decoction	Oral	Human adult	[52]
<i>Morus species</i>	USSR (L)	Used for diabetes mellitus	Hot H ₂ O extract	Oral	Human adult	[55]

B= barks; C= cortex; F= fruit; FL= flowers; L= leaf; NS= not specified; RB= root bark; S= stem

Table 2. Ethnomedical information of *Morus*.

The leaves of *M. nigra* are commonly used by women in menopause as a substitute for the conventional hormonal replacement therapy, with a similar effect to that obtained after estrogen use. Moreover, the leaves are also used by younger women as a reliever of the symptoms of the premenstrual tension. The use of *M. nigra* usually involves the preparation of a "tea" (i.e. through decoction or infusion of the leaves) and is reported to ameliorate the

symptoms of menopause, particularly hot flashes, which are related to the sudden vasodilatation that causes the feeling of intense heat and redness of the skin, namely the face [35].

In Brazil, the cultivation of *M. nigra* began with the Japanese migration into the country, adapting well to conditions of climate and soil. In a recent study realized by our research group [36], we evaluated the hypoglycemic potential and acute toxicity of the crude ethanol extract of the leaves, and we observed that the extract may be considered of low toxicity since it did not cause death or alterations on hematological and biochemical parameters in animals.

Botanical name	Origin (Part used)	Activity	Extract	Dose/concent.	Result	References
<i>Morus alba</i>	Iran (B)	Antihyperglycemic	Decoction	500.0 mg/kg	Inactive	[56]
	Japan (B)	α -Glycosidase inhibition	Hot H ₂ O extract	80.0 mg/kg	Active	[57]
	South Korea (B)	Hypoglycemic activity	MeOH extract	2.0 mg/kg	Inactive	[58]
	China (BR)	Antihyperglycemic	Hot H ₂ O extract	1.25 mg/kg	Active	[59]
	China (BR)	Hypoglycemic activity	Hot H ₂ O extract	1.25 mg/kg	Active	[59]
	China (BR)	Antihyperglycemic	H ₂ O extract	2.1 mg/kg	Active	[59]
	Japan (C)	Glucose transport stimulation	MeOH extract	5.0 mcg/ml	Weak activity	[43]
	Iran (F)	Antihyperglycemic	Decoction	500.0 mg/kg	Inactive	[56]
	Chile (L)	Antihyperglycemic	Infusion	0.40 g/animal	Active	[44]
	Chile (L)	Antihyperglycemic	Infusion	0.40 g/animal	Inactive	[44]
	China (L)	Antihyperglycemic	Hot H ₂ O extract	200.0 mg/kg	Active	[60]
	Egypt (L)	Hypoglycemic activity	EtOH (100%) extract	Dose not stated	Active	[61]
	Egypt (L)	Antihyperglycemic	EtOH (100%) extract	Dose not stated	Active	[61]
	Egypt (L)	Antihyperglycemic	Leaf	Dose not stated	Active	[61]
	Egypt (L)	Antihyperglycemic	EtOH (100%) extract	Dose not stated	Inactive	[61]
	Iran (L)	Antihyperglycemic	Decoction	500.0 mg/kg	Inactive	[56]
	Iran (L)	Hypoglycemic activity	Decoction	500.0 mg/kg	Inactive	[56]
Japan (L)	Antihyperglycemic	Hot H ₂ O extract	80.0 mg/kg	Active	[57]	

Botanical name	Origin (Part used)	Activity	Extract	Dose/concent.	Result	References
	Japan (L)	Antihyperglycemic	Hot H ₂ O extract	200.0 mg/kg	Active	[60]
	Roumania (L)	Antihyperglycemic	Infusion	150.0 ml/person	Active	[62]
	South Korea (L)	Antihyperglycemic	Not specified	Dose not stated	Active	[63]
	Zimbabwe (L)	Hypoglycemic activity	EtOH (80%) extract	200.0 mg/kg	Active	[64]
	Zimbabwe (L)	Antihyperglycemic	EtOH (80%) extract	200.0 mg/kg	Active	[64]
	Zimbabwe (L)	Insulin level increase	EtOH (80%) extract	200.0 mg/kg	Inactive	[64]
	Japan (L)	Antihyperglycemic	EtOH (5%) extract	200.0 mg/kg	Active	[65]
	Japan (P)	Antihyperglycemic	Lyophilized extract	200.0 mg/kg	Active	[65]
	Iran (R)	Antihyperglycemic	Decoction	500.0 mg/kg	Inactive	[56]
	China (RB)	Hypoglycemic activity	EtOH:H ₂ O (1:1) extract	20.0 mg/kg	Active	[66]
	Egypt (RB)	Antihyperglycemic	EtOH (70%) extract	600.0 mg/kg	Active	[67]
	South Korea (RB)	Antihyperglycemic	H ₂ O extract	1.0 mg/kg	Strong activity	[68]
	China (R)	Antihyperglycemic	Hot H ₂ O extract	200.0 mg/kg	Active	[60]
<i>Morus bombycis</i>	China (NS)	Hypoglycemic activity	EtOH (95%) extract	Dose not stated	Active	[69]
<i>Morus indica</i>	India (L)	Antihyperglycemic	H ₂ O extract	250.0 mg/animal	Active	[70]
	India (SC)	Antihyperglycemic	H ₂ O extract	130.0 mg/animal	Active	[70]
<i>Morus insignis</i>	Argentina (L)	Antihyperglycemic	EtOH (70%) extract	100.0 mg/kg	Active	[27]
	Argentina (L)	Hypoglycemic activity	EtOAc extract	50.0 mg/kg	Active	[27]
	Argentina (L)	Hypoglycemic activity	BuOH extract	50.0 mg/kg	Active	[27]
	Argentina (L)	Hypoglycemic activity	H ₂ O extract	50.0 mg/kg	Active	[27]
	Argentina (L)	Antihyperglycemic	EtOAc extract	100.0 mg/kg	Active	[27]
	Argentina (L)	Antihyperglycemic	BuOH extract	100.0 mg/kg	Active	[27]

Botanical name	Origin (Part used)	Activity	Extract	Dose/concent.	Result	References	
<i>Morus nigra</i>	Iran (B)	Antihyperglycemic	Decoction	500.0 mg/kg	Active	[56]	
	Iran (B)	Antihyperglycemic	Decoction	500.0 mg/kg	Inactive	[56]	
	France (L)	Hypoglycemic activity	Hot H ₂ O extract	Dose not stated	Active	[49]	
	France (L)	Hypoglycemic activity	Hot H ₂ O extract	Dose not stated	Active	[71]	
	Iran (L)	Hypoglycemic activity	EtOH (95%) extract	0.25 mg/kg	Inactive	[72]	
	Iran (L)	Hypoglycemic activity	EtOH (95%) extract	1.0 mg/kg	Inactive	[72]	
	Iran (L)	Antihyperglycemic	EtOH (95%) extract	0.25 mg/kg	Active	[72]	
	Iran (L)	Antihyperglycemic	EtOH (95%) extract	0.5 mg/kg	Active	[72]	
	Iran (L)	Antihyperglycemic	Decoction	500.0 mg/kg	Active	[56]	
	Iran (L)	Hypoglycemic activity	Decoction	500.0 mg/kg	Inactive	[56]	
	Iran (L)	Antihyperglycemic	Decoction	500.0 mg/kg	Inactive	[56]	
	<i>Morus species</i>	India (L)	Antihyperglycemic	EtOH (95%) extract	0.5 ml/animal	Inactive	[73]
		India (L)	Hypoglycemic activity	EtOH (95%) extract	0.5 ml/animal	Equivocal	[73]
		India (L)	Antihyperglycemic	EtOH (95%) extract	0.5 ml/animal	Equivocal	[73]
USSR (L)		Antihyperglycemic	Tincture	Dose not stated	Active	[55]	
Japan (L)		Antihyperglycemic	Infusion	150.0 mg/kg	Active	[74]	

B= barks; BR= branches; C= cortex; F= fruit; FL= flowers; L= leaf; NS= not specified; P= protoplasts; R= root; RB= rootbark; S= stem; SC= shoot culture

Table 3. Biological activities for extracts of *Morus*.

3.7. Methods for evaluation of hypoglycemic activity of medicinal plants

3.7.1. Oral glucose tolerance test

The oral glucose tolerance test is a fast and inexpensive technique and allows you to check the effects of drugs on glucose metabolism. In normoglycemic rats, the increase of post-prandial glucose level, after glucose load, and the consequent standardization to baseline levels after about 2 h, characterizes a normal metabolism of glucose. The oral glucose tolerance test is an acute methodology for evaluating the resistance of the body to absorb glucose and reduce blood glucose levels. Therefore, it's a method to perform a screening of

drugs with potential hypoglycemic action, but with a profile in the absorption of glucose (type 2 DM) and not in the production of insulin (type 1 DM) [37].

In this experiment, normal Wistar rats are fasted overnight. They are divided into three groups containing six animals each.

Control rats (Group I) are given 1 ml distilled water orally. Extracts of plants in different concentrations (mg/kg body weight) are administered orally using a syringe to second and third groups. Glucose (2 g/kg b.wt.) is given orally using a syringe to all groups immediately after the extracts administration. Blood samples are collected from the tail vein just prior to and 30, 60, 120 and 240 min after the glucose loading and serum glucose levels are measured [38].

3.7.2. *Alloxan-induced diabetic rats*

Alloxan induces “chemical diabetes” in a wide variety of animal species by damaging the insulin secreting pancreatic β -cell, resulting in a decrease in endogenous insulin release [39]. Numerous studies demonstrated that a variety of plant extracts effectively lowered the glucose level in alloxan-induced diabetic animals. Alloxan produces oxygen radicals in the body, which cause pancreatic injury which is responsible for increased blood sugar seen in the animals. However, it is found that action is not specific to pancreas as other organs such as liver, kidney and haemopoietic system are also affected by alloxan administration as seen from the elevation of marker enzymes and reduction of hematological parameters [40].

In this experiment, diabetes is induced in male rats by single intraperitoneal injection of 120 mg/kg b.wt. of alloxan monohydrate. Serum glucose level is checked after 72 h. Animals with serum glucose levels >250 mg/dl are considered diabetic and are used for the study. The rats are divided into four groups of six rats each. Both group I control normal rats (no alloxan treatment) and group II diabetic animals are given 1 ml of distilled water. Group III and IV are given the extracts orally in different doses on 3rd day after alloxan treatment. Overnight fasted blood samples are collected from the tail vein on 3rd day of alloxan treatment prior to and at 2, 4, 6 and 8 h intervals after the administration of the extract orally. Serum is separated and glucose levels are estimated as before [38].

3.7.3. *Streptozotocin-induced diabetic rats*

Streptozotocin (STZ) at low dose for Wistar rats induces light damage to islet cells, leading to glucose intolerance. Previous studies have showed that STZ-induced diabetic rats had low production of insulin and high levels of blood circulating glucose, which were similar to those found in diabetic humans. The precise mechanisms responsible for this defect remain unknown.

Male rats weighing 150-200 g are used in the study and type 2 diabetes is induced. The rats are fed with high fat diet (diet containing 74% carbohydrate, 22% protein and 4% fat, formulated as 60% total energy is derived from fat) for 15 days except normal control rats and then injected with streptozotocin (40 mg/kg). Five days after injection, the rats are fasted

and the plasma glucose levels are estimated; rats having plasma glucose levels ≥ 300 mg/dl are taken for further studies with administration of plant extracts. The rats are fed with high fat diet throughout the experimental period [41].

4. Conclusion

Diabetes mellitus is a public health problem worldwide. Ethnomedical informations and the scientific knowledge of the hypoglycemic activity of species of *Morus* demonstrate the potential of these species in the treatment of diabetes. *In vivo* testing has become an important tool in the search for new antidiabetic agents. The present work showed that therapy with species from the genus *Morus* traditionally used in many countries could be a possibility to treat diabetes. On the other hand, medicinal plants contain an enormous potential for the development of new antidiabetic drugs. In conclusion, the present study provides data which suggest that therapy with mulberry is capable of enhancing glycemic control in patients with diabetes.

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