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Chapter 11

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

Jackson Roberto Guedes da Silva Almeida, Grasielly Rocha Souza, Edigênia Cavalcante da Cruz Araújo, Fabrício Souza Silva, Julianeli Tolentino de Lima, Luciano Augusto de Araújo Ribeiro, Xirley Pereira Nunes, José Maria Barbosa Filho, Lucindo José Quintans Júnior and Márcio Roberto Viana dos Santos

Additional information is available at the end of the chapter

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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

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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 subspecie, 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 cultived 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.

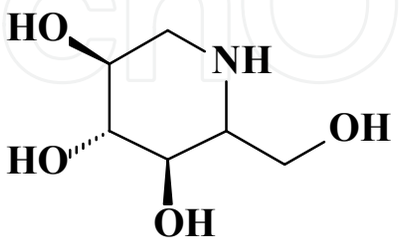


Figure 1. Chemical structure of compound (**1**) isolated from species of *Morus*.

This genus contains a variety of phenolic compounds including isoprenylated flavonoids, stilbenes, 2-arylbenzopyrans, coumarins, chromones, xanthones 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-κB, 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 contain an alkaloid, 1-deoxynojirimycin (**1**) that inhibited glycogenolyses, 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 is 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 carragenan-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
Morus alba	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; *Cis*-mulberrosideA; Oxyresveratrol; Isoquercetin; Kwanon G; Moracin E, F, G and H; Kwanon D, E, F; Deoxynojirimycin-1	Root, stem, leaves, fruit	Astringent, anti-helmintic, HIV, cough, antiinflammatory, exudative, high blood pressure, diaphoretic, purgative, emollient, diarhoea, **diabetes**, atherosclerosis, anti-tumor, hypoglycemia
Morus australis	Australone A; triterpenoid 3β-[(*m*-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-helmintic, purgative, antiplatelet
Morus bombycis	*N*-methyl-1-Deoxynojirimycin; Kwanon G, H; Moracin A-Z; Albanins A-H; γ-aminobutyric acid; *L*-asparagine; *L*-arginine; *L*- lysine; choline; Mulberrofuran I	Root, leaves	Hypotensive, antimicrobial, **diabetes**, HIV, antiphlogistic, diuretic
Morus laevigata	Citrulline; hydroxyproline; free amino acids	Fruit	Plaster for sores, cools the blood
Morus nigra	Deoxynojirimycin	Root, leaves, fruits	**Diabetes**, AIDS, purgative, arterial pressure, vermifuge, cancer
Morus serrata	β-Amyrin acetate; betulinic acid; cerylalcohol; quercetin; morin	Root	-----
Morus rubra	Rubraflavones A, B, C, D	Root	Anti-dysenteric, laxative, purgative, vermifuge, urinary problems, weakness
Morus macroura	Guangsangons A-N; albafuran C; Kwanon J, X, Y; Mulberrofuran G, K, J	Stem	Antiinflammatory, antioxidative
Morus cathayana	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 and 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 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 contains 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 specie 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 albafuran A, albafuran 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 specie [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*.

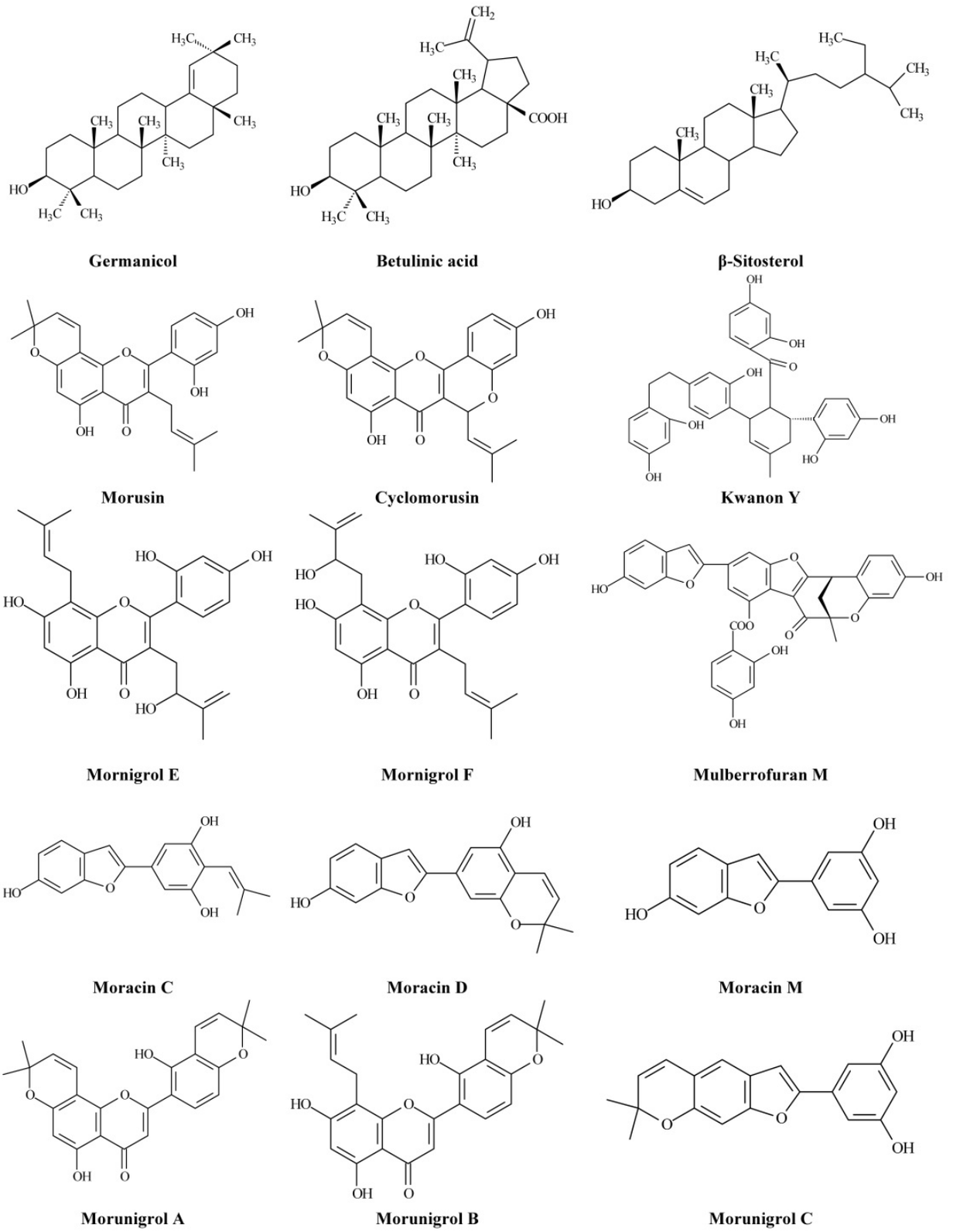


Figure 2. Chemical structures of some natural compounds isolated from species of the genus *Morus*.

Botanical name	Origin (Part used)	Use	Preparation	Via	Organism	References
Morus alba	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_2O extract	Oral	Human adult	[45]
	Turkey (L)	Used for diabetes	Decoction	Oral	Human adult	[46]
	Yugoslavia (L)	Used for diabetes	Hot H_2O extract	Oral	Human adult	[47]
	Peru (L + S)	Used as an antidiabetic	Hot H_2O extract	Oral	Human adult	[48]
	France (L)	Used for diabetes	Hot H_2O extract	Oral	Human adult	[49]
Morus lhou	Italy (L)	Used as an antidiabetic	Infusion	Oral	Human adult	[50]
Morus nigra	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_2O extract	Oral	Human adult	[53]
	Puerto Rico (NS)	Used for diabetes	Hot H_2O extract	Oral	Human adult	[54]
	Iran (RB)	Used in diabetes	Decoction	Oral	Human adult	[52]
Morus species	USSR (L)	Used for diabetes mellitus	Hot H_2O 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**
Morus alba	Iran (B)	Antihyperglycemic	Decoction	500.0 mg/kg	Inactive	[56]
	Japan (B)	α-Glycosidase inhibition	Hot H_2O 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_2O extract	1.25 mg/kg	Active	[59]
	China (BR)	Hypoglycemic activity	Hot H_2O extract	1.25 mg/kg	Active	[59]
	China (BR)	Antihyperglycemic	H_2O 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_2O 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_2O extract	80.0 mg/kg	Active	[57]

Botanical name	Origin (Part used)	Activity	Extract	Dose/concent.	Result	References
	Japan (L)	Antihyperglycemic	Hot H_2O 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_2O (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_2O extract	1.0 mg/kg	Strong activity	[68]
	China (R)	Antihyperglycemic	Hot H_2O extract	200.0 mg/kg	Active	[60]
Morus bombycis	China (NS)	Hypoglycemic activity	EtOH (95%) extract	Dose not stated	Active	[69]
Morus indica	India (L)	Antihyperglycemic	H_2O extract	250.0 mg/animal	Active	[70]
	India (SC)	Antihyperglycemic	H_2O extract	130.0 mg/animal	Active	[70]
Morus insignis	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_2O 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
Morus nigra	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_2O extract	Dose not stated	Active	[49]
	France (L)	Hypoglycemic activity	Hot H_2O 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]
	Iran (RB)	Antihyperglycemic	Decoction	500.0 mg/kg	Inactive	[56]
Morus species	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 intraperitonial 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.

Author details

Jackson Roberto Guedes da Silva Almeida, Grasielly Rocha Souza,
Edigênia Cavalcante da Cruz Araújo, Fabrício Souza Silva,
Julianeli Tolentino de Lima, Luciano Augusto de Araújo Ribeiro and Xirley Pereira Nunes
1Nucleus of Studies and Research of Medicinal Plants, Federal University of San Francisco Valley, Petrolina, Pernambuco, Brazil

José Maria Barbosa Filho
Federal University of Paraíba, João Pessoa, Paraíba, Brazil

Lucindo José Quintans Júnior and Márcio Roberto Viana dos Santos
Department of Physiology, Federal University of Sergipe, São Cristóvão, Sergipe, Brazil

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5. References

[1] Lanza RP, Ecker DM, Kuhtreiber WM, Marsh JP, Ringelling J, Chink WL. Transplantation of islets using microencapsulation: studies in diabetic rodents and dogs. Journal of Molecular Medicine 1999;77(1), 206-210.

[2] Oyedemi SO, Bradley G, Afolayan AJ. Ethnobotanical survey of medicinal plants used for the management of diabetes mellitus in the Nkonkobe municipality of South Africa. Journal of Medicinal Plants Research 2009;3(12), 1040-1044.

[3] Notkins AL. Immunologic and genetic factors in type 1 diabetes. Journal of Biological Chemistry 2002;277(46), 43545-43548.
[4] Funke I, Melzig MF. Traditionally used plants in diabetes therapy - phytotherapeutics as inhibitors of α-amylase activity. Brazilian Journal of Pharmacognosy 2006;16(1), 1-5.
[5] Rao BK, Kesavulu MM, Apparao Ch. Antihyperglycemic activity of *Momordica cymbalaria* in alloxan diabetic rats. Journal of Ethnopharmacology 2001;78(1), 67-71.
[6] Barbosa-Filho JM, Vasconcelos THC, Alencar AA, Batista LM, Oliveira RAG, Guedes DN, Falcão HS, Moura MD, Diniz MFFM, Modesto-Filho J. Plants and their active constituents from South, Central, and North America with hypoglycemic activity. Brazilian Journal of Pharmacognosy 2005;15(4), 392-413.
[7] Cunha WR, Arantes GM, Ferreira DS, Lucarini R, Silva MLA, Furtado NAJC, Silva-Filho AA, Crotti AEM, Araújo ARB. Hypoglicemic effect of *Leandra lacunosa* in normal and alloxan-induced diabetic rats. Fitoterapia 2008;79(5), 356-360.
[8] Zhang BB, Moller DE. New approaches in the treatment of type 2 diabetes. Current Opinion in Chemical Biology 2000;4(4), 461-467.
[9] Alarcon-Aguilar FJ, Roman-Ramos R, Flores-Saenz JL, Aguirre-Garcia F. Investigation on the hypoglycaemic effects of extracts of four Mexican medicinal plants in normal and alloxan-diabetic mice. Phytotherapy Research 2002;16(4), 383-386.
[10] Grover JK, Yadav S, Vats V. Medicinal plants of India with anti-diabetic potential. Journal of Ethnopharmacology 2002;81(1), 81-100.
[11] Pawlowska AM, Oleszek W, Braca A. Quali-quantitative analyses of flavonoids of *Morus nigra* L. and *Morus alba* L. (Moraceae) fruits. Journal of Agricultural and Food Chemistry 2008;56, 3377-3380.
[12] Ozgen M, Serçe S, Kaya C. Phytochemical and antioxidant properties of anthocyanin-rich *Morus nigra* and *Morus rubra* fruits. Scientia Horticulturae 2009;119(3), 275-279.
[13] Ercisli S, Orhan E. Chemical composition of white (*Morus alba*), red (*Morus rubra*) and black (*Morus nigra*) mulberry fruits. Food Chemistry 2007;103(4), 1380-1384.
[14] Nomura T. Phenolic compounds of the mulberry tree and related plants. Progress in the Chemistry of Organic Natural Products 1988;53, 87-201.
[15] Chen FJ, Nakashima N, Kimura I, Kimura M. Hypoglicemic activity and mechanisms of extracts from mulberry leaves (folium mori) and cortex mori radicis in streptozotocin-induced diabetic mice. Yakugaku Zasshi 1995;115, 476-482.
[16] Kim JW, Kim SU, Lee HS, Kim I, Ahn MY, Ryu KS. Determination of 1-deoxynojirimycin in *Morus alba* L. leaves by derivatization with 9-fluorenylmethyl chloroformate followed by reversed-phase high-performance liquid chromatography. Journal of Chromatography A 2003;1002(1-2), 93-99.
[17] Nomura T, Hano Y. Isoprenoid-substituted phenolic compounds of moraceous plants. Natural Products Reports 1994; 11(2); 205-218.
[18] Syah YM, Achmad SA, Ghisalberti EL, Hakim EH, Iman MZN, Makmur L, Mujahiddin D. Andalasin A, a new stilbene dimmer from *Morus macroura*. Fitoterapia 2000;71(6), 630-635.
[19] Fukai T, Satoh K, Nomura T, Sakagami H. Antinephritis and radical scavenging activities of prenylflavonoids. Fitoterapia 2003;74(7-8), 720-724.
[20] Ercisli S, Orhan E. Some physico-chemical characteristics of black mulberry (*Morus nigra* L.) genotypes from Northeast Anatolia region of Turkey. Scientia Horticulturae 2008;116(1), 41-46.

[21] Kumar VR, Chauhan S. Mulberry: Life enhancer. Journal of Medicinal Plants Research 2008;2(10), 271-278.
[22] Dat NT, Binh PTX, Quynh LTP, Minh CV, Huong HT, Lee JJ. Cytotoxic prenylated flavonoids from *Morus alba*. Fitoterapia 2010;81(8), 1224-1227.
[23] Bhattarai NK. Folk anthelmintic drugs of central Nepal. International Journal of Pharmacognosy 1992;30(2), 145-150.
[24] Andallu B, Suryakantham V, Srikanthi BL, Reddy GK. Effect of mulberry (*Morus indica* L) therapy on plasma and erythrocyte membrane lipids in patients with type 2 diabetes. Clinica Chimica Acta 2001;314(1-2), 47-53.
[25] Andallu B, Varadacharyulu N.Ch. Antioxidant role of mulberry (*Morus indica* L. cv. *Anantha*) leaves in streptozotocin-diabetic rats. Clinica Chimica Acta 2003;338(1-2) 3-10.
[26] Balasubramanian A, Ramalingam K, Krishnan S, Ajm C. Antiinflammatory activity of *Morus indica* Linn. Iran Journal of Pharmacology 2005;4, 13-15.
[27] Basnet P, Kadota S, Terashima S, ShimizuM, Namba T. Two new 2-arylbenzofuran derivatives from hypoglycemic activity-bearing fractions of *Morus insignis*. Chemical and Pharmaceutical Bulletin 1993;41(7), 1238-1243.
[28] Azevedo MS, Alves APL, Alves GBC, Cardoso JN, Lopes RSC, Lopes CC. Uma nova síntese de α-bromoacetofenonas e sua aplicação na obtenção de 2-benzoil-benzofuranas. Química Nova 2006;29(6), 1259-1265.
[29] Naderi GA, Asgary1 S, Sarraf-Zadegan N, Oroojy H, Afshin-Nia F. Antioxidant activity of three extracts of *Morus nigra*. Phytotherapy Research 2004;18(5), 365-369.
[30] Souza MM, Bittar M, Cechinel-Filho V, Yunes RA, Messana I, Delle-Monache F, Ferrari F. Antinociceptive properties of morusin, a prenylflavonoid isolated from *Morus nigra* root bark. Zeitschrift für Naturforschung 2000;55c, 256-260.
[31] Padilha MM, Vilela FC, Rocha CQ, Dias MJ, Soncini R, Santos MH, Alves-da-Silva G, Giusti-Paiva A. Antiinflammatory properties of *Morus nigra* leaves. Phytotherapy Research 2010;24(10), 1496-1500.
[32] Padilha MM, Vilela FC, Silva MJD, Santos MH, Alves-da-Silva G, Giusti-Paiva A. Antinociceptive effect of *Morus nigra* leaves in mice. Journal of Medicinal Food 2009;12(6), 1381-1385.
[33] Wang L, Cui XQ, Gong T, Yan RY, Tan YX, Chen RY. Three new compounds from the barks of *Morus nigra*. Journal of Asian Natural Products Research 2008;10(9-10), 897-892.
[34] Wang L, Gong T, Chen RY. Two new prenylflavonoids from *Morus nigra* L. Chinese Chemical Letters 2009;20(12), 1469-1471.
[35] Queiroz GT, Santos TR, Macedo R, Peters VM, Leite MN, Sá RCS, Guerra MO. Efficacy of *Morus nigra* L. on reproduction in female Wistar rats. Food and Chemical Toxicology 2012;50(3-4), 816-822.
[36] Almeida JRGS, Guimarães AL, Oliveira AP, Araújo ECC, Silva FS, Neves LF, Oliveira RA, Sá PGS, Quintans-Júnior LJ. Evaluation of hypoglycemic potential and pre-clinical toxicology of *Morus nigra* L. (Moraceae). Latin American Journal of Pharmacy 2011;30(1), 96-100.
[37] Souza VH, Barbosa APO, Cardoso GC, Marreto RN, Barreto-Filho JAS, Antoniolli AR, Santos MRV. Avaliação do potencial antidiabético de cinco plantas medicinais em ratos. Latin American Journal of Pharmacy 2009;28(4), 609-612.

[38] Sabu MC, Smitha K, Kuttan R. Anti-diabetic activity of green tea polyphenols and their role in reducing oxidative stress in experimental diabetes. Journal of Ethnopharmacology 2002;83(1-2) 109-116.
[39] Oberley LW. Free radicals and diabetes. Free Radical Biology and Medicine 1988;5(2), 113-124.
[40] Kim JS, Ju JB , Choi CW, Kim SC. Hypoglycemic and antihyperlipidemic effect of four Korean medicinal plants in alloxan induced diabetic rats. American Journal of Biochemistry and Biotechnology 2006;2(4), 154-160.
[41] Sunila C, Ignacimuthua S, Agastian P. Antidiabetic effect of *Symplocos cochinchinensis* (Lour.) S. Moore. in type 2 diabetic rats. Journal of Ethnopharmacology 2011;134(2), 298-304.
[42] Murakami C, Myoga K, Kasai R, Ohtani K, Kurokawa T, Ishibashi S, Dayrit F, Padolina W G, Yamasaki K. Screening of plant constituents for effect on glucose transport activity in ehrlich ascites tumour cells. Chemical and Pharmaceutical Bulletin 1993;41(12): 2129-2131.
[43] Yamasaki K. Effect on some saponins on glucose transport system. Advances in Cirrhosis, Hyperammonemia, And Hepatic Encephalopathy 1996;404, 195-206.
[44] Lemus I, Garcia R, Delvillar E, Knop G. Hypoglycaemic activity of four plants used in Chilean Popular Medicine. Phytotherapy Research 1999;13(2), 91-94.
[45] Rios J L, Recio M C, Villar A. Antimicrobial activity of selected plants employed in the Spanish mediterranean area. Journal of Ethnopharmacology 1987;21(2), 139-152.
[46] Yazicioglu A, Tuzlac E. Folk Medicinal Plants of Trabzon (Turkey). Fitoterapia 1996;67(4), 307-318.
[47] Tucakov J. Ethnophytotherapy of diabetes: critical view on the use of medicinal plant extracts in our national medicine in the treatment of diabetes mellitus. Srpski Arhiv Celokupino Lekvarstvo 1978;106(2), 159-173.
[48] Ramirez VR, Mostacero LJ, Garcia AE, Mejia CF, Pelaez PF, Medina CD, Miranda CH. Vegetales empleados en medicina tradicional norperuana. Banco Agrario Del Peru & Nacl Univ Trujillo 1988; 54.
[49] Leclerc H. The blood sugar lowering action of the leaves of *Morus alba*. Presse Medicine 1934;42, 1522.
[50] De Feo V, Aquino R, Menghini A, Ramundo E, Senatoare F. Traditional phytotherapy in the Peninsula Sorrentina. Journal of Ethnopharmacology 1992;36(2), 113-125.
[51] Darias V, Abdala S, Martin D, Ramos F. Hypoglycaemic plants from the Canary Islands. Phytotherapy Research Suppl 1996;10, S3-S5.
[52] Zagari A. Medicinal plants. Tehran University Publications 1992;4(1810/4), 969.
[53] Tucakov J. Ethnophytotherapy of diabetes. Critical view on the use of medicinal plant extracts in our national medicine in the treatment of diabetes mellitus. Srpski Arhiv zav Celokupno Lekarstvo 1978;106(2),159-173.
[54] Rivera G. Preliminary chemical and pharmacological studies on "Cundeamor," *Momordica charantia* L. (Part I). American Journal of Pharmacy 1941;113 (7), 281-297.
[55] Kit SM, Boichuk RV, Khananayev LI, Ozarkiv TT. Experimental study of the hypoglycemic effect of some plants found near Carpathia. Farm Zh (Kiev) 1972;27(4), 61.
[56] Hosseinzadeh H, Sadeghi A. Antihyperglycemic effects of *Morus nigra* and *Morus alba* in mice. Pharmaceutical and Pharmacological Letters 1999;9(2), 63-65.

[57] Yamada H, Oya I, Nagai T, Matsumoto T, Kiyohara H, Omura S. Screening of alpha-glucosidase II inhibitor from Chinese Herbs and its application on the quality control of mulberry Bark. Shoyakugaku Zasshi 1993;47(1), 47-55.
[58] Kim OK, Lee EB. The screening of plants for hypoglycemic action in normal and alloxan-induced hyperglycemic rats. Korean Journal of Pharmacognosy 1992;23(2), 117-119.
[59] Ye F, Shen Z, Xie M. Alpha-glucosidase inhibition from a Chinese Medical Herb (*Ramulus mori*) in normal and diabetic rats and mice. Phytomedicine 2002;9(2), 161-166.
[60] Chen F, Nakashima N, Kimura I, Kimura M, Asano N, Koya S. Potentiating effects on pilocarpine-induced salvia secretion, by extracts and N-containing sugars derived from mulberry leaves, in streptozotocin-diabetic mice. Biological and Pharmaceutical Bulletin 1995;18(12), 1676-1680.
[61] Sharaf A, Mansour M Y. Pharmacological studies on the leaves of *Morus alba*, with special reference to its hypoglycemic activity. Planta Medica 1964;12(1), 71-76.
[62] Ionescu-Tirgoviste C, Popa E, Mirodon Z, Simionescu M, Mincu I. Effect of a mixture of plants on the metabolic equilibrium in patients with Diabetes Mellitus of the 2nd type. Revista de Medicina Interna 1989;41(2), 185-192.
[63] Kim SY, Ryu KS, Lee WC, Ku HO, Lee HS, Lee KR. Hypoglycemic effect of mulberry leaves with anaerobic treatment in alloxan-induced diabetic mice. Korean Journal of Pharmacognosy 1999;30(2), 123-129.
[64] Bwitti P, Musabayane CT. The effects of plant extracts on plasma glucose levels in rats. Acta Medical Biology 1997;45(4), 167-169.
[65] Kubo M, Ido Y, Matsuda H, Mikami H. Anti-diabetic effect of protoplast preparation from fresh leaves of mulberry (*Morus alba*). Natural Medicines 2001;55(4), 181-186.
[66] Hikino H, Mizuno T, Oshima Y, Konno C. Isolation and hypoglycemic activity of Moran A, a glycoprotein of *Morus alba* root barks. Planta Medica 1985;51(2), 159-160.
[67] Singab ANB, El-Beshbishy HA, Yonekawa M, Nomura T, Fukai T. Hypoglycemic effect of Egyptian *Morus alba* root bark extract: Effect on diabetes and lipid peroxidation of streptozotocin-induced diabetic rats. Journal of Ethnopharmacology 2005;100(3), 333-338.
[68] Kim CJ, Cho SK, Shin MS, Cho H, Ro DS, Park JS, Yook CS. Hypoglycemic activity of medicinal plants. Archives of Pharmacological Research 1990;13(4), 371-373.
[69] Min P. The drugs employed in Chinese Medicine as antidiabetic. Noriyuki sugihara. III. Experimental investigation on the influence of the drugs employed in Chinese Medicine as antidiabetic on the blood sugar of rabbits. Nippon Yakurigaku Zasshi 1930;11(2), 181-187.
[70] Kelkar SM, Bapat VA, Ganapathi TR, Kaklij GS, Rao PS, Heble MR. Determination of hypoglycemic activity in *Morus indica* L. (Mulberry) shoot cultures. Current Science 1996;71(1), 71-72.
[71] Bart C. Hypoglycemic action of mulberry leaves. Comptes Rendus des Seances de La Societe de Biologie Et de Ses Filiales 1932;109, 897.
[72] Oryan S, Eidi M, Yazdi E, Eidi A, Solati J. Hypoglycaemic effect of alcoholic extract of *Morus nigra* L. leaves in normal and diabetic rats. Journal of Medicinal Plants 2006;2(6), 27-32.
[73] Sharaf AA, Hussein AM, Mansour MY. The antidiabetic effect of some plants. Planta Medica 1963;11, 159.
[74] Lizuka Y, Sakurai E, Tanaka Y. Antidiabetic effect of Folium Mori in GK rats. Yakugaku Zasshi 2001;121(5), 365-369.