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Journal of Acute Disease

journal homepage: www.jadweb.org

Review article http://dx.doi.org/10.1016/j.joad.2016.08.001

Research progress of Tunisian medicinal plants used for acute diabetes

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ARTICLE INFO

Article history:
Received 27 Apr 2016
Received in revised form 7 Jun 2016
Accepted 5 Jul 2016
Available online 11 Aug 2016

Keywords:
Diabetes
Medicinal plants
Tunisia
Anti-diabetic potential

ABSTRACT

The use of the medicinal plants in treating diabetes is frequent in Africa, especially in Tunisia, and it is ritually transmitted from generation to generation within cultures. Many of Tunisian medicinal plants have been experimentally validated. A comprehensive review was conducted to pile up information from scientific journal articles, including indigenous knowledge researches, about Tunisian medicinal plants used for the treatment of diabetes. The aim of this review article is to provide the reader with information concerning the importance of Tunisian medicinal plants in the treatment of diabetes and to draw attention of the health professionals and scientists working in the field of pharmacology and therapeutics to develop new drug formulations to cure different kinds of diabetes.

1. Introduction

Since ancient time, plants have been the main source of medicines and all human societies have practically utilized plants not only as sources of nutrition but also as therapy against diseases and ailments. Plants contain various phytochemicals which can play an important role in reducing occurrences of many diseases by boosting up various organ functions of the human body, by acting as antioxidants and by supplying necessary nutrients[1]. Hence, plants have formed the basis of refined traditional medicine systems which have been in existence for thousands of years and continue to provide mankind with new remedies. Natural products and their derivatives represent more than 50% of all drugs in clinical used in the world. It is also a fact that one quarter of all medicinal prescriptions are formulations based on substances resulting from plants or plant derived synthetic analogs[2]. It is estimated that 70%–80% of people worldwide rely chiefly on traditional, largely herbal medicine to meet their primary healthcare needs[1]. In developed countries, the raw materials for manufacturing essential drugs are extracted from medicinal plants, harnessing its natural properties of healing. In many developing countries, traditional medicine is still the mainstay of healthcare and most of the drugs and cures come from plants[3]. Tunisia has about 2 163 plant species and 149 have been claimed to possess medicinal properties[4]. To this day, traditional medicine has an important place in Tunisia that is at the conglomeration of several civilizations, where the use of traditional medicine is a matter of concern especially in the management of diabetes which is a common disease in this country[5], presenting 9.3%–11.0% (between 2010 and 2030) with similarity to the percentage observed in other countries[6,7]. The World Health Organization has listed 21 000 plants which are used for medicinal purposes around the globe[2,8] and about 800 herbal plants with anti-diabetic potential are known[9].

In recent years, diabetes has become a major health problem worldwide and it is one of the five leading causes of death in the world. Diabetes affects more than 371 million people worldwide and it is expected to reach 552 million by 2030[10]. In fact, it is one of the most common chronic diseases in nearly all countries, and continues to increase in number and significance due to the changing lifestyles that lead to the reduction of physical activity and increase of obesity[6,7]. There are two main types of diabetes which are: type-1 diabetes and type-2 diabetes. Patients with type-1 diabetes present a state of insulin deficiency due to severe defect in islet β-cell function whereas patients with type-2 diabetes show a combination of resistance to action of insulin and insufficiency in insulin secretion. Eventually, as results of these, severe complications were created in both types of diabetes such as nephropathy, retinopathy, neuropathy, dyslipidemia and cardiovascular diseases[11]. In addition, the use of hypoglycemic drugs, like insulin, biguanides, sulfoylureas and α-glucosidase

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Peer review under responsibility of Hainan Medical College. The journal implements double-blind peer review practiced by specially invited international editorial board members.

inhibitors, are accompanied by unpleasant side effects such as severe hypoglycemia, lactic acidosis, peripheral edema and abdominal discomfort[11]. Synthetic hypoglycemic agents produce serious side effects, whereas bioactive compounds derived from natural resources are frequently considered safe and cost effective[12]. Thus, plants may play an important role in drug development programs. Several plants have been traditionally recommended for treatment of diabetes and the role of these plants in the management of diabetes *in vitro* and/or *in vivo* conditions have been determined by many researchers. So, the present review circumscribes Tunisian medicinal plants that have been experimentally tested and shown to be of some value in diabetes.

2. Methodology

The search was done in electronic databases of PubMed, Scopus, ScienceDirect, and Google Scholar for studies using the key terms: diabetes, medicinal plants, Tunisia and anti-diabetic potential. The references list included all articles related to the subject and published from 1999 to 2016. All plant species were taxonomically validated; the latin scientific name and family were confirmed using The Plant List site (http://www.theplantlist.org/).

3. Plants with anti-diabetic potential

3.1. Argania spinosa L. (A. spinosa) (Sapotaceae)

The argan tree (*A. spinosa*) was introduced into Tunisia in the past times and it is presently cultivated in some botanic gardens[13]. It is a slow-growing tree exclusively endemic to the barren lands of Southwest Morocco[14]. All the argan parts have value with, particularly, the almond oil which is largely used in Moroccan traditional medicine: to decrease blood cholesterol and hypertension[15]; to treat skin diseases such as juvenile acne, chicken pox pustules scars, eczema, psoriasis and skin inflammation[16]. In Morocco, the antidiabetic effect of argan seed extract[15] and oil[14] had been studied. In Tunisia, El Adib *et al.*[13] had demonstrated the *in vitro* inhibitory effect of leaf, seed, and pulp extracts of two argan varieties (*mutica* and *apiculata*) against the enzyme α-amylase related to diabetes.

3.2. Artemisia campestris L. (A. campestris) (Compositae)

This species is a perennial scarcely aromatic herb originating in Asia and now distributing to North America and North Africa. *A. campestris* is widespread in the south of Tunisia, commonly known as “T'gouft”. The leaves of this plant are widely used in traditional medicine as decoction or infusion against some respiratory diseases such as influenza, bronchitis, sinusitis and sore throat[17]. The administration of leaf aqueous extract from *A. campestris* to alloxan-induced diabetic rats at a dose of 200 mg/kg resulted in a significant reduction in glycemia[18].

3.3. Artemisia herba-alba Asso. (A. herba-alba) (Compositae)

It is commonly known as “shih” in Tunisia. It is an aromatic and medicinal shrub, 20–40 cm high, growing wild in arid areas of the Mediterranean basin. In Tunisia, this species is found from the mountains around Jebel Oust to the south of the country[19]. In traditional medicine, the plant is used to treat colds, intestinal diseases, diabetes and hypertension[20]. The ethanol extract of *A. herba alba* aerial part was given orally (2 g/kg) and daily for a period of 8 weeks to normal and diabetic (type I and II) albino rats. Results showed that *A. herba alba* treatment reduces the blood glucose level significantly in type II diabetic rat[21].

3.4. Camellia sinensis L. (C. sinensis) (Theaceae)

The green tea, obtained from the tea plant *C. sinensis*, is the most consumed drink in the world after water[22,23]. It is a cultivated evergreen shrub or tree that can grow to a height of 9 m, but is usually clipped to a height of 0.76 m in cultivation[24]. Tea is native to China, later spread to India and Japan, then to Europe and Russia, arriving in the New World in the late 17th century[22]. The medicinal effects of tea have a history dating back almost 5000 years. The chemical components of green tea chiefly include polyphenols (catechins and flavonoides), caffeine and amino acids. Polyphenols, known for their strong antioxidant activities, are primarily responsible for the beneficial healthful properties of tea[22]. Green tea is a ‘non-fermented’ tea and contains more catechins than black tea. Tea beverage is generally an infusion of the dried leaves of *C. sinensis*[23]. Green tea decoction is also a very popular beverage through large areas of North Africa, especially in Tunisia. Green tea decoction is characterized by the cooking of the dried tea leaves in boiling water for a variable period of time, overall not exceeding 60 min. Fifteen-minute cooked green tea decoction appeared the better one in term of preservation of polyphenols as compared to tea infusion[25]. Research showed that acute administration of green tea decoction (0.5 mL/100 g) 30 min before an oral load by gavage or through an intraperitoneal injection of glucose improved glucose tolerance of rats[25].

3.5. Diplotaxis simplex Spreng. (D. simplex) (Brassicacea)

The wild crucifer *D. simplex*, known as “jarjir” in Tunisia, is native to the Mediterranean region and it is largely distributed in North Africa. *D. simplex* is an annual plant, glabrous and stems are much branched, which can reach 50 cm of height. The leaves form a basal rosette and the bright yellow flowers appear in winter to late spring. It grows in many sandy, loamy and stony soils in coast and south of Tunisia[26]. This plant is appreciated by local population for its strong pungent flavor and it is consumed raw or cooked, in salads and soups. *D. simplex* leaves and flowers contain several important nutrients and valuable bioactive compounds with interesting biological properties[27]. Recently, research showed that ethyl acetate extract of *D. simplex* flowers is effective in inhibiting α-glucosidase activity *in vitro* and significantly reduce *in vivo* the rise in blood glucose levels of maltose-loaded mice as compared to the standard antihyperglycemic agent acarbose. In fact, *D. simplex* flowers could be used to delay the quick digestion of starch which may reduce the peak blood glucose and therefore have potential as an anti-hyperglycemic agent[26].

3.6. Ferula lutea Poir. (F. lutea) (Apiaceae)

The genus *Ferula* contains 170 species, frequently finding in arid regions of temperate Eurasia, in the Canary Islands and in North Africa. Only four *Ferula* species have been identified in Tunisia, namely, *Ferula communis*, *F. lutea, Ferula tunetana* and *Ferula tingitana*[28]. Several species of this genus have been used in folk medicine as treatments for convulsions[29] and diabetes[30]. The gum resins of the roots from several *Ferula* species, especially *Ferula foetida*, are reported to have many activities such as anticholesterolemic, anticoagulant, antifertility, antifungal, antihepatotoxic, anti-inflammatory, antioxidant, antiparasitic, antiulcerogenic, anticarcinogenic, anthelmintic, antispasmodic and anti-diabetic[31]. Some species are used in traditional foods as well as in traditional medicine. Scientific research has also demonstrated the inhibitory activity of *F. lutea* extracts against α-amylase enzyme related to diabetes[28].

3.7. Juniperus phoenicea L. (J. phoenicea) (Cupressaceae)

The species *J. phoenicea*, known as "araar" in Tunisia, is a branched shrub up to 6 m high with a trunk up to 1 m in diameter. It is native to the northern lands bordering the Mediterranean Sea from Portugal to Palestine. It is also native to North Africa found in Algeria, Libya, Morocco, Tunisia as well as the Canary Islands[32,33]. This species is considered as an important medicinal plant largely used in the Tunisian traditional medicine. Its leaves are used in the form of decoction to treat diarrhea, rheumatism and diabetes whereas the dried fruit powder is used to help heal of skin ulcers and abscesses[32]. Research demonstrated for the first time the *in vitro* potent inhibitory effect of various extracts of Tunisian *J. phoenicea* leaves as well as its essential oil against key enzymes (α-amylase and lipase) related to diabetes[34].

3.8. Lavandula stoechas L. (Lamiaceae)

Lavender (*Lavendula stoechas*) is commonly known as "khezama" in Tunisia. It is an herbaceous wild plant belonging to the mountain regions of the countries bordering the western Mediterranean. Lavender is a medicinal plant largely used in traditional medicine. It is used as antiseptic, antimicrobial, sedative, diuretic and analgesic agents[35]. Lavender extracts contain beneficial effects on wound, urinal infections, cardiac diseases and eczema[36]. Nowadays, lavender is extensively cultivated throughout the world for its exploitation in aromatherapy, perfumery, cosmetic and flavor and fragrance industries[36]. Furthermore, lavender essential oil is known for its antimicrobial properties[37]. Antidiabetic activity was evaluated after subacute intraperitoneally injection of essential oil from lavender aerial parts (50 mg/kg body weight) to rats during 15 days. Research showed that lavender essential oil decreased blood glucose in alloxan induced diabetic rats[38].

3.9. Nigella sativa L. (N. sativa) (Ranunculaceae)

N. sativa, an annual herbaceous plant which is native to Southern Europe, North Africa and Southwest Asia[39]. *N. sativa* seeds, commonly known as "sinouj" in Tunisia, have been used as a spice and food preservative. It has been also employed as a curative remedy for asthma, diarrhea, obesity, fever and dyslipidaemia[40]. *N. sativa* seed revealed a broad spectrum of pharmacological activities including antihistaminic, antidiabetic, anti-hypertensive, anti-inflammatory, and antimicrobial activities[41]. In addition, Tunisian research showed that oral administration of *N. sativa* seeds in diet of alloxan diabetic male rats at the dose of 2% for 30 days caused the decrease of blood glucose level[42].

3.10. Olea europea L. (O. europea) (Oleaceae)

Olive tree (*O. europea*) represents one of the most important crops in the Mediterranean countries and plays an important role in the diets, economies and cultures of the region[43]. Indeed, olive and olive oil consumption has been shown to be associated with a variety of health benefits, including a lower incidence of heart disease and some types of cancer[44]. Olive tree has been widely revealed for the richness of its oil, fruit, leaf, stem and mill waste in antioxidant molecules such as oleuropein, hydroxytyrosol, oleuropein aglycone and tyrosol[45]. In fact, a research showed that the intraperitoneal injection of hydroxytyrosol olive mill waste extract (20 mg/kg body weight) for two months decreased the serum glucose in alloxan induced diabetic rats[46]. Another study found that the oral administration, for 4 weeks, of oleuropein and hydroxytyrosol rich olive leaf extracts, leading to 8 and 16 mg/kg body weight of each compound, significantly decreased the serum glucose in alloxan induced diabetic rats[45]. Other research showed the *in vitro* potent inhibitory effect of two triterpenes (oleanolic acid and oleanolic acid demethyl) isolated for the first time from *O. europea* stem against key enzymes (α-amylase and lipase) related to diabetes[44].

3.11. Origanum glandulosum Desf. (O. glandulosum) (Lamiaceae)

Oregano (*O. glandulosum*) is an endemic spontaneous plant, growing in North Africa, namely, Algeria and Tunisia[47]. In Tunisia, *O. glandulosum* is an aromatic shrub called ''zaâter moulouk" which is mostly used in folk medicine to treat whooping cough, cough, fever and bronchitis[48]. Oregano essential oil has been widely studied for its antioxidant[47], antifungal[47,48], antibacterial[49] and insecticidal activities[50]. Moreover, the essential oil of *O. glandulosum* may have potential for use in the treatment of diabetes due to its strong capacity *in vitro* to inhibit the degradation of starch by pancreatic and salivary α-amylase[51].

3.12. Pelargonium graveolens L'Her. (P. graveolens) (Geraniaceae)

Rose-scented geranium (*P. graveolens*) is commonly known as "Aterchia" in Tunisia. It is an important, high-value perennial, aromatic shrub that can reach a height of up to 1.3 m and a spread of 1 m[52]. This species grows in cool-temperate region in the world[53] and it is widely known for its sweet-rosy essential oil odor. *P. graveolens* essential oil has been anciently used as antiasthmatic, antiallergic, antioxidant, antidiarrhoeic, antihepatotoxic, diuretic, tonic, hemostatic, stomachic and diabetic[54]. In accordance to its claimed anti-diabetic effect in traditional medicine, Boukhris *et al.*[7] had proven that the oral

administration of the essential oil of *P. graveolens* at two doses of 75 mg/kg and 150 mg/kg, for 30 days, brought about significant hypoglycemic effects in alloxan-induced diabetic rats mainly at 150 mg/kg.

3.13. Punica granatum L. (Lythraceae)

Punica granatum is a shrub native to occidental Asia and Mediterranean Europe, also grown in warm climate areas of the America and other parts of the world[55], which is popularly referred to as pomegranate[56]. The ripe pomegranate fruit, popularly known as "rumman" in Tunisia, is the most important plant part and is also an important source of food. All pomegranate parts are used medicinally. Hence, pomegranate bark and root contain several alkaloids including isopelletierine that fights against tapeworms. Pomegranate bark, leaf, immature fruit and fruit rind extracts are used to combat diarrhea, dysentery and hemorrhages, whilst powdered flower buds acts as a remedy for nose bleeding[57]. Since antiquity, these different pomegranate parts have been used in the various traditional and the folk systems of medicine to treat diabetes. Scientific studies have also shown that the extract of pomegranate flower[58,59], seed[60], seed oil[61] and seed hull[62] possess antidiabetic effects in various preclinical animal models of study. Additionally, the seed juice is shown to ameliorate the diabetes-induced hyperlipidemia and to prevent the various secondary complications of diabetes[63]. In Tunisia, Bekir *et al.*[64] has recently determined the inhibition effect of pomegranate flower extract on α-amylase and α-glucosidase enzymes related to diabetes.

3.14. Rosmarinus officinalis L. (R. officinalis) (Lamiaceae)

Rosemary (*R. officinalis*) is popularly known as "klil" in Tunisia. It is an aromatic, evergreen, shrubby herb endogenous to Europe, Asia and Africa, mainly in areas surrounding the Mediterranean Sea[65]. In Tunisia, rosemary is used for flavoring food and in traditional medicine to treat auricular diseases, liver diseases, asthma, dermatoses, bronchitis, cough, asthenia, gastralgia, otitis and cold. At present, the demand of *R. officinalis* is increasing for its use, not only in traditional medicine, but also in pharmaceutical industries, cosmetic fields and agribusiness, and for the quality of its essential oil which could be useful in aromatherapy, food preservation and fragrance industries[66]. Today, the interest towards rosemary cultivation is strongly arising due to the well recognized biological actions of its essential oil and its bioactive phenolic compounds especially rosmarinic acid. In this sense, many major biological properties, mainly antioxidant[67], anti-cancer[68], anti-inflammatory[69] and antimicrobial[70], have been attributed to rosemary extracts and their isolated phenolic components. In addition, it has been recently reported that rosemary extract is an *in vitro* potent source of natural inhibitors of α-amylase and pancreatic lipase related to diabetes[71].

3.15. Scabiosa arenaria Forssk. (S. arenaria) (Dipsacaceae)

In Tunisia, the *Scabiosa* genus contains eleven identified species which are: *S. arenaria* Forssk., *Scabiosa arvensis* L., *Scabiosa atropurpurea* L. (*S. atropurpurea*), *Scabiosa crenata* Cyr., *Scabiosa daucoides* Desf., *Scabiosa farinosa* Coss., *Scabiosa robertii* Bonn., *Scabiosa rutifolia* Vahl., *Scabiosa simplex* Desf., *Scabiosa stellata* L. and *Scabiosa succisa* L.[72]. Several species of this genus have been investigated for their ancient medicinal use. *Scabiosa stellata* is beneficial in the treatment of many human diseases; thus, this scabious is expectorant, purifying, diaphoretic, stomachic, appetizer and digestive. It is indicated in cases of bronchitis, bronchial pneumonia, influenza and asthma. The tisane obtained from the aerial part of *S. atropurpurea* is used as a diuretic[73]. An infusion of the flowers of *S. atropurpurea* L. is orally used by the peoples of the Iberian Peninsula in Spain as a hypoglycemic[74]. Scientific research had proven the antidiabetic effect of the aerial part extract of *S. atropurpurea* L. in alloxan-induced diabetic rats[75]. One antidiabetic therapeutic approach is to reduce gastrointestinal glucose production and absorption through the inhibition of carbohydrate-digesting enzymes such as α-amylase and α-glucosidase[76]. Hence, crude extracts of flowers, fruits, (stems and leaves) and roots of the endemic North African plant *S. arenaria* were screened for their ability of α-glucosidase inhibition. Results showed the *in vitro* potent inhibitory effect of these different part extracts of *S. arenaria* against α-glucosidase related to diabetes[76].

3.16. Trigonella foenum-graecum L. (Leguminoseae)

Fenugreek (*Trigonella foenum-graecum*) is popularly known for its seeds named "hilbeh" in Tunisia. It is one of the world oldest and most commonly used medicinal plants that have earned a special place in the traditional Indian, Egyptian and Greek medicines for its diverse therapeutic applications[77]. This plant is native to an area extending from Iran to northern India and widely cultivated in China, India, Egypt, Ethiopia, Morocco, Ukraine, Greece and Turkey[78]. In Tunisia, fenugreek is especially cultivated in the regions of the North and it is commonly used as a condiment in food preparations for its nutritive and restorative properties and has also been used in folk medicine for centuries for a wide range of diseases including diabetes[79]. In accordance, several researches have proven the potent capacity of fenugreek seed extract and its isolated bioactive compounds to treat diabetes. In fact, the administration of fenugreek galactomannan to diabetic rats reduced glucose concentration in plasma as compared to diabetic untreated[80]. Similarly, the administration of fenugreek saponin to diabetic rats increased the hepatic glycogen content and suppressed the increase of blood glucose level[80]. Hamden *et al.*[81] also administrated the formulation omega-3 fatty acid rich fenugreek essential oil (5% in food) for 8 weeks and they noted a considerable inhibition of key enzymes-related to diabetes such as α-amylase and maltase activities in pancreas and plasma with a significant decrease of the glucose in the plasma and liver of diabetic rats. Moreover, they mentioned that the administration of only fenugreek essential oil to surviving diabetic rats improved starch and glucose oral tolerance additively.

3.17. Vitis vinifera L. (Vitaceae)

Raisins (*Vitis vinifera*), named "zbib" in Tunisia, are one of the most important and popular dried fruits in the world because their high nutritional value[82]. The principal country producers of raisins are United States, Turkey and Iran presenting

together 80% of global production[83]. The richness of raisins in antioxidants has composed a perfect shield for cardiovascular disease, cancer rehabilitation, and constipation[84]. Research had also proven the potential hypoglycemic activity of raisin extract in alloxan-induced diabetic rats[85].

3.18. Zingiber officinale Roscoe (Zingiberaceae)

Ginger (*Zingiber officinale*), known as "skinjbir" in Tunisia, is an example of medicinal plants which is gaining popularity among modern physicians and its underground rhizomes are the medicinally useful part for its hypoglycemic, antioxidant and androgenic activities which were reported in the animal model[86]. Concerning hypoglycemic effect, dietary supplementation of rats with ginger roots (3%) for 1 month after alloxan treatment resulted in significant decline of serum glucose levels[87].

3.19. Zygophyllum album L.f. (Z. album) (Zygophyllacae)

Z. album, commonly known as Bougriba, is one of the most commonly prescribed drugs in Tunisian pharmacopoeia. It is used as an antihyperglycemic, antioxydant and antilipedimic[88]. *Z. album* has been mentioned in Tunisian system of folk medicine to be of value in the treatment of diabetes mellitus. Accordingly to folk medicine, research has also proven that the administration of the ethanol extract from *Z. album* (100 and 300 mg/kg body weight) for 14 days resulted in significant reduction in plasma glucose in streptozocin diabetic mice[88]. In recent scientific study, the administration of *Z. album* leaf essential oil (200 mg/kg) for 30 days to diabetic rats, after alloxan treatment, showed a good effect in the management of diabetes by the inhibition of key-digestive enzymes like α-amylase[89].

4. Conclusion

The present review summarizes numerous reports on the anti-diabetic potential of Tunisian medicinal plants. Indeed, medicinal plants have a long history of use as a traditional medicine and have been employed medicinally in diabetes diseases. However, to the best of our knowledge, there has been no comprehensive review incorporating Tunisian medicinal plants with the effectiveness in diabetes. So, this valuable information reported on anti-diabetic potential of Tunisian medicinal plants may be useful to the health professionals, scientists and scholars working in the field of pharmacology and therapeutics to develop new drug formulations to cure different kinds of diabetes.

Conflict of interest statement

The authors declare no conflict of interest.

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