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Full Length Research Paper

Presenting anti-diabetic plants in Iranian traditional medicine

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The high prevalence of diabetes mellitus and its complications, increase in usage of complementary therapies (especially herbal therapies), and need of developing countries for indigenous medical methods inspired us to introduce some plants in Iranian traditional medicine that are used in the treatment of diabetes. By studying the topic of "ziabetes" (the synonym of diabetes) mentioned in some Iranian traditional medical texts, we collected the text related to the anti-diabetic edible plants and identified their scientific names. Pub-med and Scopus databases were used to search the hypoglycemic effects of these medicinal herbs on laboratory animal or human. Many medicinal herbs and minerals in single or compound form have been used in Iranian traditional medicine. Plants such as *Punica granatum, Rosa damascene, Plantago psyllium, Glycyrrhiza glabra, Coriandrum sativum, Portulaca oleracea*, and *Rumex patientia* are the most popular among them. The hypoglycemic effects of some of these plants on laboratory animal or human have been presented from different published articles. The effects of some anti-diabetic plants used in Iranian traditional medicine were evaluated and their efficacies were mainly demonstrated on animals. However, we need more clinical trials to prove the safety and efficacy of these herbs on human.

Key words: Traditional medicine, phytotherapy, herbal medicine, diabetes mellitus, Iran.

INTRODUCTION

Diabetes mellitus is a metabolic disease affecting glucose, fat, and protein metabolism. It is a major health problem with increasing prevalence all over the world. It causes complications such as nephropathy, neuropathy, retinopathy and blindness and increases mortality rate (Atalay and Laaksonen, 2002; Memisogullari et al., 2003; Raskin et al., 2000).

The global prevalence of type 2 diabetes was approximately 2.8% in the year 2000 and it is estimated that this will reach 4.4% by 2030. Total patients with type 2 diabetes will reach 366 million in 2030 (Wild et al., 2004a, b)

Diabetes management means changing lifestyle, including proper diet and exercise, apart from considering the hypoglycemic medications to avoid the side effects (Warren, 2004). Although, oral hypoglycemic agents and insulin are cornerstones of treatment of diabetes, side effects of drugs, their low efficacy in controlling the disease, and preventing the complications encourage researchers to explore and assess new methods and more appropriate ways to control the disease and its complications (Burcelin et al., 1999).

Inadequate response to some common treatments for diabetes has caused the use of some complementary/ alternative therapeutic methods by 2 to 3.6 million diabetic patients in USA. Among the multiple methods of complementary medicine, most attention is on herbal remedies and dietary treatments for diabetes (Ogbera et al., 2010). Iranian traditional medicine is one of the holistic medical subjects with several hundred years of history. It is also known as "humoral" or "sinai" medicine (related to Avicenna who was the most famous Iranian physician and philosopher). Nowadays, this subject has been revived by WHO recommendations for development of indigenous knowledge and use of alternative national medicine. Some of the universities in Iran also start

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training physicians in this field.

In Iranian traditional medicine, the diagnosis of diseases is based on measuring and assessing the temperament of total body and its organs. The treatment is performed by changing the imbalance of temperament. “Temperament” is the quality derived from mixing four elements (fire, air, water, and soil), of which all living organisms come from these elements. The qualities of these elements are “warm-dry”, “warm-humid”, “cold-humid” and “cold-dry”, respectively (Naseri et al., 2009).

Although, the use of medicinal plants is not the only therapeutic methods in traditional medicine, they are the cornerstone of medical prescriptions. Many published articles have shown significant effects of some of these plants on laboratory animal or human.

In this paper, we introduced some of the herbal compounds of Iranian traditional medicine for treatment of diabetes mellitus, and some published studies that evaluated the hypoglycemic effects of these herbs.

METHODOLOGY

The Arabic and Persian translation of the word “Diabetes” was searched in the following books: “Qanon”, “Alaghraz Altebbiyah”, “Exir azam”, ”tebbe akbary”, and “Qrabadin azam”. These books are some of the well-known texts in Iranian traditional medicine discussing the treatment of the different diseases in detail. We looked for the treatment of diabetes in the aforementioned book. Different herbal combinations used as oral treatment which most books made reference to were selected. It was followed by using online version of Dehkhoda dictionary (a Persian/Arabic to Persian dictionary), “Alaghraz Altebbiyah” and “Makhzanoladvyah (one of the most important Iranian traditional pharmacopeia)” to find the synonymous names for the ingredients of these herbal combinations.

Characteristics of the different plants in these compounds and their scientific names were also determined by “Makhzanoladvyah” and help of experts (Mozaffarian, 2003; Aghili Khorasani Shirazi, 2008). In addition, any articles or researches that revealed the hypoglycemic effects of these plants were collected from Pub-med or Scopus databases of electronic library of Tehran University of Medical Sciences. Probable toxicity of these plants were searched in Patient Desk Reference (PDR) book (Fleming, 2009).

RESULTS

"Diabetes" or "Ziabetes" (Greek word) describing the same symptom of diabetes mellitus has been used in Iranian traditional medicine. The symptoms include thirst, polyuria, and polydipsia. The Iranian Hakims (traditional doctors) knew cold or warm mal-temperament of kidney as causes of this disease (depending on the severity or weakness of symptoms), when the following symptoms appear: severe thirst, warmth on the back and flank persist with colored and burning urine, the diagnosis of the Hakim would be the heat in the kidney (warm mal-temperament of kidney). If there were symptoms, like thirst or thirst for warm or tepid water along with the signs of losing weight, energy and appetite, the diagnosis of the Hakim would be cold in the kidney (cold mal-temperament of kidney).

Therefore, “Diabetes” was categorized into “cold diabetes” and “warm diabetes”, and there were specific treatments for either of them. These treatments included special diets along with herbs and minerals in singular or combination form as an ointment, tablet or hot steam (Aghili Khorasani Shirazi, 2008; Jorjani, 2006; Arzani, 2007; Ibn-Sna and Al-Qanon, 1981; Nazem Jahan, 2008). The treatment of diabetes includes a large number of plants; some of them are a part of the diet and some of them are prescribed as medications. The following recipes are some recipes of herbal combination used as oral medication to treat the warm type diabetes. The Persian names of each herb are in parentheses.

1. Combination 1 is known as “Golnar tablet”, a combination of aghaghia, Damask rose (Gol Mohammady), pomegranate flower (Golnar), Arabic gum (samghe araby), *Astragalus* (katira), and psyllium seed (esfarzeh).
2. Combination 2 is known as “diabetes tablet”, a combination of tabashir, licorice (shirinbayan), purslane seed (khorfeh), coriander (geshniz), sorrel (torshak), Armenian mud (gel armany), white sandal (sandal sefid), pomegranate flower, *Rhus coriaria* (sumac), Arabic gum, purslane water, lettuce (kahu), and sour pomegranate (anar torsh).
3. Combination 3 is a combination of tabashir, sandal, purslane, coriander, sorrel, lettuce seeds, squash (kadu), Arabic gum, Armenian mud, camphora (kaphur).

Some of the constituents, like Armenian mud are minerals, but others are derived from plants like kaphur, samghe araby, Katira, and aghaghia, of which the last three items are gums. Characteristics of these plants and materials and some contemporary literature on the hypoglycemic efficacy of them are described subsequently. Also, approved side effects have been written in each part, but the side effects of some of these plants and minerals have not yet been assessed.

Damask rose (*Rosa damascene*)

It is a plant of Rosaceae family commonly called Persian rose, Damask rose or rose-water flower. It is said to be cold and dry in nature (temper). Damask rose petals and essential oils (golab) are used in the traditional medicine of Iran (Aghili Khorasani Shirazi, 2008). The effects of methanol extract of *R. damascene* have been compared with acarbose (an alpha-glucosidase inhibitor) between the normal and diabetic rats and the result has confirmed potent inhibitory effect of alpha-glucosidase. Also, oral administration of its extract (100 to 1000 mg/kg) has significantly reduced blood sugar in animals (Nazem Jahan, 2008). Another herbal formulation includes licorice, ginger, Damask rose and some other plants that have

been tested in the diabetic rats. Consuming 300 mg/kg per day of this herbal formulation for 4 weeks has significantly reduced blood sugar and cholesterol and also increased antioxidant activity in the diabetic rats (Gholamhoseinian et al., 2009).

Pomegranate (*Punica granatum*)

Pomegranate is a fruit of a tree from Punicaceae family that grows in different areas of Iran. Golnar is the flower of pomegranate tree which have no fruit. It is said to be cold and dry in nature (Aghili Khorasani Shirazi, 2008).

In Iranian traditional medicine, using pomegranate juice in the diet of the diabetic patients and also Golnar together with the other herbs have been experimented and recommended. In a study on the hydroalcoholic extract of *P. granatum* flowers, 400 mg/kg of this extract significantly reduced blood glucose level in the diabetic rats (Jafri et al., 2000). In another study, the two important elements of Golnar extract were confirmed: one is the hypoglycemic effects and the other is intestinal α-glucosidase enzyme as an inhibitor (a possible mechanism of hypoglycemic effect of Golnar extract) (Li et al., 2005). In a study of pomegranate peel extract, 200 mg/kg of this extract regulated blood sugar in the alloxan-induced diabetic rats (Parmar and Kar, 2007). Also, oral administration of 300 mg/kg and 600 mg extract of pomegranate seeds significantly reduced blood sugar (47 and 52%, respectively) in the streptozocin-induced diabetic rats (Das et al., 2001). According to researches, pomegranate has no adverse effects on therapeutic dosage (Fleming, 2009).

Sumac (*R. coriaria*)

Sumac (Samaghil in traditional medicine) is a shrub of Anacardiaceae family, and its fruit is mainly used as food flavoring. It is said to be cold and dry in nature (Aghili Khorasani Shirazi, 2008). The hypoglycemic effects of *R. coriaria* fruit extract have been studied on laboratory animals. A study on the ethanol extract of Sumac showed that it decreases postprandial glucose (PBG) in the treatment group (26%) as compared to the control group (Mohammadi et al., 2010). In another study, alpha-amylase inhibition activity of Sumac extract was described as the best treatment and preventer of diabetes (Wu et al., 2005).

Arabic gum (*Acacia arabica*)

Acacia or Wattle is a plant of Mimosaceae family; it grows in Southern region of Iran. Arabic gum is the dried resins components of the herbal anti-diabetic combination of Iranian traditional medicine. It is a non-starch polysaccharide which is not digested in the intestines, but produces short chain fatty acids in large bowel; therefore, it carries extensive biological effects. Also, the extract of *A. arabica* has shown anti-diabetic effects by increasing the insulin release (Philips and Philips, 2011). In a study, Arabic gum powder granules showed significant hypoglycemic effects in healthy rabbits, but revealed no significant reduction in blood sugar in the alloxan-induced diabetic rabbits (Hou et al., 2003). Also, oral administration of 400 mg/kg of aqueous extract of Arabic gum in the diabetic rats significantly reduced blood sugar, cholesterol, and triglycerides (Wadood et al., 1989). Large doses of *A. arabica* taken internally can lead to indigestion and constipation (Fleming, 2009).

***Astragalus* L.**

Katira is the dried resins of the *Astragalus* plant, a plant from Papilionaceae family. It appears like gum and it is said to be moderate or cold and dry in nature (Aghili Khorasani Shirazi, 2008). In a study on the polysaccharide extracted from the aqueous extract of *Astragalus membranaceus*, administration of 400 mg/kg of this polysaccharide to the diabetic rats for 5 weeks, significantly reduced body weight and plasma glucose, followed by increasing insulin sensitivity (Wu et al., 2005). Also, in another study, the effect of *A. membranaceus* polysaccharides in the prevention of type-1 diabetes mellitus was evaluated. In this study, administration of 2 g/kg of *A. membranaceus* polysaccharide for 10 weeks in the non-diabetic obese rats was compared with the normal saline group. Blood glucose, serum c-peptide levels, and histological features of pancreas were assessed after 40 weeks. The result suggests that the incidence of type-1 diabetes in the rats of *A. membranaceus* group is lower than the normal saline group. Also, the following observation has been recorded in the treatment group (*Astragalus* group): lower serum C-peptide levels, normal histological result, and less Th_1/Th_2 imbalance (Chen et al., 2008). A study on 40 male diabetic rats showed that *A. membranaceus* polysaccharides reduce blood glucose levels and improve insulin resistance in the cardiac tissue. This protective mechanism has been suggested to increase expression of glucose transporter 4 in the myocardial tissue of the type 2 diabetic rats (Mao et al., 2005). Over dosage (>6 g/daily) of *Astragalus* species, due to the selenium content, may result in neurological damage leading to paralysis (Fleming, 2009)

Psyllium (*Plantago ovata*)

Flaxseed plantain or psyllium seed is obtained from a plant of the Plantaginaceae family and called “Ghatuna” and “Espaghool” in Iranian traditional medicine. It is said to be cold and humid in nature. Analgesic effects of psyllium on laboratory animals have been reported in various studies. Existence in large amount of bran and

fiber in the seeds delays the intestinal absorption of glucose and controls the blood glucose level. This mechanism of action has been shown with aqueous extract of *P. ovata* in types 1 and 2 diabetic rats (Hannan et al., 2006). A study shows the effects of consuming 5 g of psyllium bran twice a day when compared with common anti-diabetic drugs in a controlled clinical trial. The results indicate a significant reduction in the following variants: fasting blood glucose (FBG), HbA1C, and the ratio of low density lipoprotein/high density lipoprotein (LDL/HDL) in the treatment group (Ziai et al., 2005). Another study, on type 2 diabetic patients shows that consuming 5.1 g/bid of psyllium for eight weeks reduces postprandial plasma glucose (PPG) in the treatment group when compared with the control group (cellulose) (Anderson et al., 1997). Psyllium is contraindicated in pathologic constriction and inflammatory illnesses of the gastrointestinal tract, ileus, and severe variable of diabetes mellitus (Fleming, 2009).

Squash (*Cucurbita pepo*)

Different types of squash are grown in Iran. It is a plant of Cucurbitaceae family. *C. pepo* is said to be cold and humid, and is mentioned in the traditional medicine for the treatment of diabetes (Aghili Khorasani Shirazi, 2008).

A study performed on a polysaccharide banded with the isolated protein from *C. pepo* revealed the following observation: increase in insulin serum levels, reduce the blood glucose, and improvement of glucose tolerance in the diabetic rats (Li et al., 2005). In another study, ethanol extract of *C. pepo* skin caused the adjustment of blood glucose and serum lipid in the alloxan-induced diabetic rats (Dixit et al., 2010). Indigestion and diarrhea have been reported with consumption of *C. pepo* (Fleming, 2009).

Licorice (*Glycyrrhiza glabra*)

Licorice, known as “suce”, is a plant of Papilionaceae family. The roots of this plant are used in Iranian traditional medicine and it is said to be warm and dry (Aghili Khorasani Shirazi, 2008). A study was carried out on protective effect of *G. glabra* on the kidneys of the streptozocin-induced diabetic rats, and the result confirmed that consuming 1 g/kg of this herbal extract reduces the blood glucose and protects the renal function in the treatment group (Kataya et al., 2011). In another study, ethanol and ethyl acetate extract of *G. glabra* decreases the blood glucose and abdominal fat tissue in the KK-Ay diabetic rats (Mae et al., 2003). A combination of the *G. glabra* and several other plants of Chinese traditional medicine significantly reduce the blood glucose in the KK-CA(y) diabetic rats (Kimura et al., 1999). Another study has shown that flavonoid oil from this plant has hypoglycemic effects. Its mechanism of action is attributed to the potential activity of peroxidase proliferator-activated receptor-δ (PPAR-δ) (Nakagawa et al., 2004). In a study, the effect of glycyrrhizin (the main water-soluble component in the licorice root) was compared with glybenclamide on diabetic rats; and the result showed that licorice causes reduction in the serum glucose level and damages on pancreas and kidney caused by diabetes (Sen et al., 2011).

Licorice is contraindicated in chronic hepatitis, cholestatic diseases, and cirrhosis of the liver, severe renal insufficiency, diabetes mellitus, hypertonic neuromuscular disorders, arrhythmias, hypertension, hypertonia, and hypokalemia. Tobacco use has been associated with licorice toxicity (Fleming, 2009).

Purslane (*Portulaca oleracea*)

Purslane is a plant of Portulaceae family that grows in Southern region of Iran as an edible vegetable. Its seeds or leaves are usable. It is said to be cold and humid (Aghili Khorasani Shirazi, 2008).

A study revealed that the powder of purslane (*P. oleracea*) causes significant reduction of blood glucose in diabetic rats and has no hypoglycemic effect on the normal non-diabetic rats (Cui et al., 2005). In another study, the effect of *P. oleracea* in two different concentrations (200 and 400 mg/kg) on the alloxan-induced diabetic rats was assessed, and the result revealed the reduction of blood glucose (36.58 and 46.17%, respectively), total cholesterol and triglycerides, followed by increase in insulin secretion from pancreatic beta cells in the diabetic rats (Gao et al., 2010). A research done on *P. oleracea* reported that an isolated polysaccharide from this herb significantly reduced FBG, total cholesterol, and triglycerides; yet it increased HDL levels in the diabetic rats (Li et al., 2009).

Coriander (*Coriandrum sativum*)

Coriander is a well-known vegetable in Iran and its seed and leaves are mostly used. It is a plant of Umbelliferae family, and it is said to be cold and dry (Aghili Khorasani Shirazi, 2008).

A study has shown the reduction in blood glucose by adding 62.5 g/kg of *C. sativum* to the diet of streptozocin-induced diabetic rats. This study shows that the aqueous extract of this plant has insulin-like activity and causes insulin release (Gray and Flatt, 1999). In another study about assessing the insulin-releasing activity of coriander, the different concentrations of ethanol extract of *C. sativum* (200 and 250 mg/kg) reduced the blood glucose levels as well as increased pancreatic β-cell acti-vity in the rats (Eidi et al., 2009). The effect of aqueous extract of *C. sativum* combined with some other plants

has been investigated separately. In this study, it has been observed that the aqueous extract of coriander causes significant reduction in the diffusion of glucose in the gastrointestinal system. According to these results, decreasing intestinal absorption of glucose following the consumption of Coriander has been considered as one of the hypoglycemic mechanisms of this plant (Gallagher et al., 2003).

In another study, hypoglycemic effects of the extract of *C. sativum*, walnut and pomegranate leaves were investigated in the alloxan-induced diabetic rats. This combination reduces blood glucose and increases pancreatic β cells in those animals (Jelodar et al., 2007). Coriander has a weak potential for sensitization but has no side effects in therapeutic dosage (Fleming, 2009).

Sorrel (*Rumex* L.)

Sorrel or dock is a plant of Polygonaceae family and is said to be cold and dry. The seeds and leaves of this herb are used in Iranian traditional medicine (Aghili Khorasani Shirazi, 2008).

In a study, the hypoglycemic and lipid effects of *Rumex patientia* were assessed in the streptozocin-induced diabetic rats. The result indicated significant decrease of serum glucose and LDL levels as well as increase of HDL level in those animals (Sedaghat et al., 2010).

Lettuce (*Lactuca sativa*)

Lettuce or milkweed is a plant of Compositae family and is said to be cold and humid. The seeds and leaves of this herb are used (Aghili Khorasani Shirazi, 2008).

A study on the hypoglycemic effects of *L. sativa* and some other plants showed that this herb does not reduce blood sugar in the normal rabbits (Roman-Ramos et al., 1995). But another study, on some materials (sesquiterpene lactone and lignin) isolated from different species of lettuce (*Lactuca indica*) causes significant reduction of blood glucose (Hou et al., 2003).

White sandalwood (*Santalum album*)

Sandal or white sandal wood is a plant of the Liliaceae family and is native of Eastern India and does not grow in Iran. It has three types: white, yellow, and red. White sandal is said to be cold and dry (Aghili Khorasani Shirazi, 2008). No published study was found to show the assessment of the hypoglycemic effects of White sandal.

Aghaghia

Aghaghia is the extract of some kind of a thorny tree called “Moghilan” in Iranian traditional medicine. The extract of its fruit is called *Acacia* and the gum derived from this herb is also called Arabic gum. It is said to be cold and dry (Aghili Khorasani Shirazi, 2008). We did not find any published evidence of the anti-diabetic effects of *Acacia*.

Tabashir

Tabashir is a crystal shaped and milky color material derived from a kind of bamboo named *Bambosa arundinaceae* that grows mainly in India. It is said to be cold and dry (Aghili Khorasani Shirazi S.M.H 2008). We did not find any published evidence to show the hypoglycemic effects of Tabashir.

Camphor (*Cinnamomum camphora*)

Camphor is the gum of an evergreen tree with aromatic leaves called *C. camphora* from Lauraceae family that is native of China and Japan, and has also been cultivated in Iran. It is said to be cold and dry (Aghili Khorasani Shirazi, 2008; Mozaffarian, 2003). We did not find any published evidence to show the hypoglycemic effects of this plant.

DISCUSSION

The prevalence of complementary/alternative medicine (CAM) use among the general populations of countries varies from 9 to 75% (Emst, 2000; Zollman and Vickers, 1999). Also, 65 to 80% of the world population uses traditional medicine as their primary form of health care (World Health Organization Fact sheet, 2003; Forster et al., 2006).

According to published articles, 42 to 66% of the Tehran (the capital of Iran) population use at least one of the CAM’s methods in their life (Sedighi et al., 2004; Tehrani Banihashemi et al., 2008). The studies report that almost 38 and 54% of the population use herbal medicines, respectively and herbal medicine is the most commonly used nonconventional method and the most known natural therapy (Sedighi et al., 2004; Tehrani Banihashemi et al., 2008). The knowledge about plants and their efficacy in different disorders comes partly from folk or traditional medicine in each country.

In this paper, we presented the different treatments of diabetes from the viewpoint of Iranian traditional medicine, and then reviewed the anti-diabetic herbal therapeutic compounds through the different conducted studies that tested the hypoglycemic effects of the herbal ingredients mainly on the animal models.

Countless efforts of scientists to realize the real mechanism and pathogenesis of diabetes, risk factors, and effective methods to treat this disease are not yet covered by anybody. This paper did not propose a new method to diagnose diabetes. The main goal of this

article was to introduce an ancient medical science experience accumulated for decades and centuries. With this, we are able to apply this knowledge in addition to the conventional methods. This achievement, especially in developing countries like Iran, means optimum use of available resources.

The plants mentioned in this article, are only a small part of plants commonly used in traditional medicine to treat diabetes. The long list of plants and minerals used to treat different types of this disease should be introduced in another article.

The compounds mentioned in this article are mainly provided from plants and materials with a cold nature, and (as mentioned in the introduction) are used to treat the type of diabetes classified as warm diabetes. Of course, there are some warm or moderate temperament constituents in these preparations, which are necessary to modify the effects of combinations and prevent the side effects of the formulations.

In Iranian traditional medicine, the first step to treat any kind of disease is lifestyle modification, then the treatment is performed in more advanced stages of the disease. The recommended treatment consists of proper diet, drugs (from single plant or minerals), followed by the combination of different herbs.

This paper has shown many natural materials used in these herbal preparations that have different hypoglycemic effects on the animal; however, these are insufficient to decide the efficacy of these preparations in human. Lack of human studies to evaluate the efficacy of these plants and compounds are completely obvious. Thus, human studies on these plants and compounds are suggested.

Of course, the demonstration of hypoglycemic effects of plants on animals is the first step and there is no proof of usefulness for the treatment of human patients. If the efficacy of these compounds and similar compounds will be proved in clinical studies, providing such medications will be more cost-effective than conventional drugs, because their raw materials are more accessible and available.

Another point that should be considered is the safety issue. These plants can also cause different complications. Although, the safety of traditional therapies have been tested through their consumption for several hundreds of years in consecutive generations, and the results of published studies have confirmed the safety of their consumptions. No health hazards or side effects are known in conjunction with the proper administration of designated therapeutic dosage of pomegranate flower, sorrel, sumac, purslane, and lettuce. More studies with scientific methodology are recommended to prove the safety of other herbs and these therapeutic regimens (Fleming, 2009).

We presented some Iranian traditional medical methods to be considered along with the conventional methods to achieve better therapeutic results, lower costs, and easier access to treatment of diabetes.

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