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Asian Journal of Animal and Veterinary Advances

Academic
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www.academicjournals.com

Asian Journal of Animal and Veterinary Advances 6 (12): 1271-1275, 2011
ISSN 1683-9919 / DOI: 10.3923/ajava.2011.1271.1275

Recent Update on Animal and Human Evidences of Promising Anti-diabetic Medicinal Plants: A Mini-review of Targeting New Drugs

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ABSTRACT

Improving the world health has resulted in increasing some kind of debilitating diseases. Among these debilitating diseases, the type 2 diabetes is one of the major concerns. In the recent years, new treatment options such as herbal products have emerged to improve glycemic control in these patients. However, the efficacy and safety of these new remedies are still a concern. Recent updates prove benefit of some herbal medicines like *Citrullus Colocynthis, Silybum marianum, Plantago ovata, Teucrium polium, Vaccinium myrtillus, Urtica dioica, Medicago sativa, Punica granatum, Panax ginseng, Aloe vera, Allium sativum, Satureja khuzestanica* and *Trigonella foenum-graecum*. Although, animal studies seem complete in demonstrating benefit of these medicines but clinical trials are not complete yet. Standardization of genus and type of the plant, higher sample size trials to specify the dosage and time treatment, or synergistic effects when used in mixtures with other herbs/drugs and profiling adverse effects/toxicities are the issues that should be taken into account in future. The constituents of these medicinal herbs should be targeted for new anti-diabetic drugs.

Key words: Review, new drugs, diabetes, natural products, animal, clinical trial

INTRODUCTION

Increasing the prevalence of diabetes, obesity and metabolic disorders in the world is associated with major health problems such as cardiovascular disease and cancer. Among these debilitating diseases, the type 2 diabetes is one of the major concerns. In the recent years, new treatment options such as herbal products have emerged to improve glycemic control in these patients. However, the efficacy and safety of these new remedies are still a concern. At the time being, some herbal preparations are used by diabetic patients especially those who are candidate for insulin therapy and among unsuccessfully treated patients. On the other hand, medicinal plants contain a wide variety of natural antioxidants (Karim *et al*., 2011; Hasani-Ranjbar *et al*., 2009a) and could reduce free radicals which are by-product of abnormal body metabolism, so are important factors for prevention of late complications of chronic disorders including diabetes (Rahimi *et al*., 2005). To make well-informed choices among the options for achieving glucose control, clinicians and patients need comprehensive information about the safety and efficacy of such therapies. With this in mind, recently we tried to review all available knowledge on the efficacy and safety of medicinal plants useful in diabetes mellitus or related metabolic disorders (Hasani-Ranjbar *et al*., 2008, 2009b, 2010a; Mehri *et al*., 2011). Amongst reviewed studies, some natural products were found effective

in the treatment of these metabolic disorders that deserve further works to isolate and characterize their constituents to reach novel therapeutic agents.

In human, *Citrullus colocynthis* (L.) reduced fasting blood sugar and glycosylated hemoglobin (HbA1C) significantly. The acting mechanism of *Citrullus colocynthis* is not clear but it contains a wide number of active constituents that directly or indirectly affect glucose or insulin metabolism. Cucurbitacins, caffeic acid derivatives and fatty oil seem responsible for beneficial effects of this herb (Hasani-Ranjbar *et al*., 2008).

Another plant that investigators have studied is *Silybum marianum* called Mediterranean Milk Thistle that has shown anti-inflammatory and hepatoprotective effects. Three placebo-controlled clinical trials have reported that administration of *S. marianum* seed extract to diabetic cirrhotic patients reduces insulin resistance and the need for exogenous administration of insulin (Hasani-Ranjbar *et al*., 2008). This herb contains flavonoides, steroids, polyenes and organic acid. *S. marianum* reduces the production of oxidative stress.

Several studies showed that Psyllium (*Plantago ovata*) reduces post-prandial glucose, fasting blood sugar and HbA1C. Psyllium is suggested as a useful adjunct to dietary control of diabetic patients (Hasani-Ranjbar *et al*., 2008). Psyllium consist of mucilages, fatty oil, iridoids and protein Substances. Psyllium forms a viscous gel in aqueous solution that may slow the access of glucose to the small intestine's absorptive epithelium, thereby blunting postprandial glucose peaks. Also, soluble fibers slow carbohydrate uptake by delay of gastric emptying. Psyllium sequesters ingested carbohydrates and thus retards effects of digestive enzymes.

Trigonella foenum-graecum (*Fenugreek*) contain of Mucilages, proteins, proteinase inhibitors, steroid saponins and saponin-peptide esters, sterols, flavonoides, trigonelline and volatile oil. Fenugreek seeds can be used as an adjutant in the control of type 2 diabetes (Kassaian *et al*., 2009). The seed fiber of *T. foenum-graecum* reduces the rate of glucose absorption and may delay gastric emptying, thereby preventing the rise in blood sugar levels following a meal (Gupta *et al*., 2001). Seed's fiber also powerfully stimulates insulin receptor sites to burn cellular glucose at high fiber diet (Broca *et al*., 2000).

Urtica dioica (Stinging Nettle) is common in most temperate regions of the world. It has been studied and found to have profound anti-diabetic properties (Mehri *et al*., 2011). A study in 2007, scientists examined the effect of an herbal combination which includes Urtica dioica. Results demonstrate safety, tolerability and efficacy of their combination in decreasing glucose level and HbA1C (Said *et al*., 2008).

Another plant which has been studied by many scientists in the field of diabetic research is Ginseng. American (*Panax quinquefolius* L.) and Asian ginseng (*Panax ginseng* CA Meyer) are two major types of ginseng. Ginseng increases insulin production, reduces death of pancreatic β-cells and insulin resistance and improves postprandial glycemia in diabetic patients (Luo and Luo, 2009; Vuksan *et al*., 2008).

Pomegranate (*Punica granatum*) that consists of Tannins is a potent source of antioxidants that can help diabetic patients to overcome oxidative stress (Rosenblat *et al*., 2006).

Teucrium polium (Poley) contains diterpenes, volatile oils, iridoids and flavonoides. *T. polium* in comparison with glibenclamid in a period of 6 weeks reduced HbA1C like that of glibenclamide (Hasani-Ranjbar *et al*., 2008, 2010b).

Alfalfa (*Medicago sativa*) that is original to the Mediterranean region is widely cultivated worldwide. It contains canavaine, betaine, trigonelline and fatty oil. Alfalfa exhibited hypoglycemic effects in streptozotocin-induced diabetic mice with no significant effect in nondiabetic mice (Gray and Flatt, 1997).

Garlic which scientifically named Allium sativum ingiber officinale is one of the famous medicinal herbs. It consists of alliins, polysaccharides, and saponins. In a human study in 2001, significant decrease in glucose levels were seen in the men and women following garlic treatment (Zhang *et al*., 2001).

Another effective plant in the treatment of diabetic patients is Bilberry (*Vaccinium myrtillus*). It contains catechin tannins, flavonoides, iridoide monoterpenes, caffeic acid derivatives, phenolic acids and quinolizidine alkaloids. The scientists believe that bilberry has a significant effect on diabetic retinopathy (Boniface *et al*., 1985).

Aloe vera is the most well-known species of Aloe. Dried sap of *Aloe vera* is a popular traditional treatment for diabetes. It contains of anthracene derivatives and flavonoides. Aloe gel, obtained from the leaves, contains glucomannan, a hydrosoluble fiber which may induce its hypoglycemic effect. Reports in animal models showed conflicting results. Two non randomized clinical trials reported effectiveness of *Aloe vera* in fasting blood sugar in a period of 6 weeks (Yeh *et al*., 2003).

Another promising herb, Satureja khuzestanica is an endemic plant of Iran that is widely distributed in the Southern part of the country. It has antioxidant properties and thus it seems to be useful in diseases related to oxidative stress such as diabetes and hyperlipidemia. The efficacy of *S. khuzestanica* supplement in metabolic parameters of hyperlipidemic patients with type 2 diabetes mellitus were proved (Vosough-Ghanbari *et al*., 2010). In animal studies, *S. khuzestanica* improved liver metabolism of glucose in favor of hypoglycemia (Saadat *et al*., 2004). This herb is safe and can have a promising place in therapy of metabolic disorders (Abdollahi *et al*., 2003; Momtaz and Abdollahi, 2010).

Taking collectively, *Citrullus colocynthis, Silybum marianum, Psyllium, Teucrium polium, pomegranate, Ginseng, Aloe vera* and *Fenugreek* can be recommended for supplementing diabetic patients so far.

With no doubt, better clinical trials with higher sample size are still needed to reach convincing conclusions. Standardization of genus and type of the plant, the dosage and time treatment, or synergistic effects when used in mixtures with other herbs and watching adverse effects should not be forgotten.

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