



Medicinal Plants as Potential New Target Drugs in Endocrine Disorders- Review Article

*Shirin HASANI-RANJBAR*¹, **Bagher LARIJANI*²

1. *Obesity and Eating Habits Research Center, Endocrinology and Metabolism, Molecular Cellular Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran*
2. *Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran*

*Corresponding Author: Email: larijanib@sina.tums.ac.ir

(Received 12 Sep 2013; accepted 09 Jan 2014)

Abstract

Noncommunicable diseases pose a real threat to and their incidence is forecast to increase in both developed and developing countries; and, diabetes, obesity, and related complications are predicted to pose a great burden on health care systems all across the world. However, current used conventional medications and surgical interventions fall short of effectively controlling the rampant spread of obesity and diabetes. Moreover, as the world population grows older, increases the need for more effectively controlling old-age diseases such as obesity and diabetes. It is clear that many traditional plants are used for treatment of diseases in Iran and throughout the world as adjuncts to conventional therapy. This work aimed to present current science on the efficacy and safety of medicinal plants useful in diabetes mellitus, obesity, hyperlipidemia, hyperprolactinemia and antioxidant effects by reviewing all human and some animal studies. Amongst reviewed studies, some natural products were found effective in the treatment of these metabolic disorders that deserve further works to isolate and characterization of their constituents to reach novel therapeutic agents. The findings of the current study demonstrated that some medicinal plants are effective in the treatment of different metabolic and endocrine disorders. For example *Citrulluscolocynthis*, *Silybummarianum*, *Psyllium*, *Teucriumpolium*, pomegranate, ginseng, *Aloe vera* and fenugreek decreased blood glucose significantly. Moreover, a variety of herbal supplements were found to be effective in the management of obesity such as ephedra, *Cissusquadrangularis*, ginseng, bitter melon (*Momordicacharantia*), and zingiber.

Keywords: Medicinal plants, Diabetes, Obesity, Hyperlipidemia, Antioxidant

Introduction

The prevalence of obesity, diabetes mellitus and metabolic disorders is increasing in the world presenting an association with major health problems such as ischemic heart disease, stroke, and cancer (1-3). According to the report of center for disease and prevention (CDC) nowadays CHD is the main cause of death in the world (3). Change in behaviors, nutrition and sedentary lifestyle are the main causes of these disorders and complications.

Pharmacologic treatment and surgical interventions are not always appropriate. For example despite short-term benefits of drug treatment in obesity, it is often associated with rebound weight gain after the cessation of drug use, side effects from the medication, and the potential for drug abuse (4,5). 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. Certain dietary supplements and several dietary approaches may influence lipid alterations (6,7). Despite awareness of the target LDL-C levels, lipid management is not optimal. As an example, one study in patients with hyperlipidemia, overall, only 38% achieved ATPIII target LDL-C levels (8). On the other hand free radicals are by-product of abnormal body metabolism in several chronic diseases and are important factors for late complications and secondary disease (9, 10). Medicinal herbs have been identified as an appropriate source of antioxidant (11).

When conventional medicine fails to treat chronic diseases and conditions such as obesity, efficaciously, it is not unlikely that many people use unconventional therapies including herbal medicine (12). We believe that researches, evidences and knowledge regarding traditional medications including herbal medicine, mineral material and animal material are limited.

In human the earliest indications of medicinal plants have been found in the Middle East and date back to the Stone Age. Cross-pollination of ideas between European and Asian cultures produced advanced knowledge about medicinal plants to standardize their uses (13). In the recent years, the popularity of alternative medicine has increased again. Surveys conducted in Australia and U.S. indicates that almost 48.5% and 34% of respondents had used at least one form of unconventional therapy, including herbal medicine, respectively. The world health organization (WHO) has also recommended evaluation of effective medicinal plants for some disorders like diabetes due to lack of safe modern drugs (14). In some countries, herbal medication is the most popular complementary and alternative medicine (CAM) modality (15). Most pharmacists are not adequately prepared educationally to meet patients' requests for information on herbal products. Many herbs have been identified as unsafe, but potentially safe herbs are available too and the clinical trial results are suggestive of efficacy of some herbal therapies for some conditions (16).

Considering above points it is clear that many traditional plants are used for treatment of diseases.

So this work aimed to present current science on the efficacy and safety of medicinal plants useful in diabetes mellitus, obesity, hyperlipidemia, hyperprolactinemia and antioxidant effects by reviewing all human studies (17-22).

Herbal medicine used in diabetes

Search strategy: For medicinal plants useful in diabetes mellitus, Embase, Scopus, PubMed, Web of Science, Google Scholar, and IranMedex databases have been searched. The search terms were "diabetes" and "plant", "herb", "traditional", "natural or herbal medicine". The key outcomes were blood glucose and serum lipids (17). We updated the search and included other systematic reviews for this report.

Human studies

Capparis spinosa L. (caper) is one of the investigated plants which are traditionally used by diabetic patients as an anti-hyperglycemic food. The results of a clinical trial in patients with type 2 diabetes showed that two months administration of 400 mg caper fruit extract three times a day significantly decreases fasting blood glucose levels and glycosylated hemoglobin in caper treated patients compared to placebo group at the end of the study. The certain mechanism of caper's hypoglycemic effects is not clear but it may occur due to its antioxidant content such as phenolic compounds, tocopherols, carotenoids and vitamin C (23).

In a different study, *Citrullus colocynthis* (L) decreased fasting blood sugar and glycosylated hemoglobin (Hb A1C) significantly. Most effective dose of it was 300 mg/day in three divided doses. The acting mechanism of *C. colocynthis* is not clear. *C. colocynthis* had an insulin tropic effect on isolated pancreatic islets (17). It inhibited the toxic effect of streptozotocin on pancreatic cells in rats. *C. colocynthis* contains a wide number of active constituents that directly or indirectly affect glucose or insulin metabolism via interaction several metabolism pathways. It contains cucurbitacins (including cucurbitacin E-, 1-, L-glucosides), Caffeic acid derivatives (chlorogenic acid) and fatty oil (in the seeds) (17).

Another plant that investigators have studied is *Silybum marianum*. *S. marianum* with the common name of Mediterranean Milk Thistle has hepato-protective and anti-inflammatory effects. Three placebo-controlled clinical trials have reported that *S. marianum* seed extract administration to diabetic cirrhotic patients reduces insulin resistance and the need for exogenous administration of insulin (17). *S. marianum* compounds flavonoides (especially apigenin-, luteolin- and kaempfer-01-7-O-glycosides, apigenin-4, 7'-di-O-glucoside, and kaempferol-7-O-glucoside-3-sulfate), steroids (beta-sitosterol, beta-sitosterol-glucoside), polyynes and organic acid (fumaric acid 3.3%). *S. marianum* decreased the production of superoxide radicals and nitric oxide by the Kupfer cells; it means *S. marianum* is a free radical scavenger and act as an anti-oxidant. Thus the reduction in lipoperoxidative damage resulted in a significant decrease in mean fasting and daily blood glucose levels and total daily glucosuria levels (24, 25).

Psyllium (*Plantago ovata*) is famous medicinal plant which has various therapeutic effects. Several studies showed that Psyllium decreased post prandial glucose, fasting blood sugar and HbA1C. They suggest that Psyllium is a useful adjunct to dietary control in diabetic patients (17, 26). Psyllium consist of 20-30% mucilages (arabinoxylans, galacturonosidorhamnos), Fatty oil, Iridoids (aucubin) and Proteic Substances. Several closely related mechanisms have been proposed for Psyllium. First, because Psyllium forms a viscous gel in aqueous solution, it may slow the access of glucose to the small intestine's absorptive epithelium, thereby blunting postprandial glucose peaks (27, 28). Second, soluble fibers slow carbohydrate uptake by delay gastric emptying (28). A third mechanism that may contribute to the postprandial effect is the sequestration of carbohydrates ingested with the meal, retarding carbohydrate access to digestive enzymes (30).

Trigonella foenum-graecum (Fenugreek) contain of Mucilages (25-45%, mannogalactans), Proteins (25-30%), Proteinase inhibitors, Steroid saponins (1.2-1.5%), Steroid saponin-peptide ester (including foenugraecin), Sterols (65% 24xi-ethyl-cholest-

5-en-3beta-ole), Flavonoides, 0.4% Trigonelline (cofearin, N-methylbetaine of the nicotinic acid), 0.01% Volatile oil. Fenugreek seeds can be used as an adjuvant in the control of type 2 diabetes (31). The seed fiber of *T. foenum-graecum* reduces the rate of glucose absorption and may also delay gastric emptying, thereby preventing the rise in blood sugar levels following a meal (32). Seed's fiber also powerfully stimulates insulin and increase insulin receptor sites to burn cellular glucose at high fiber diet (33).

Urtica dioica (Stinging Nettle) is common in most temperate regions of the world. It have been studied and found to have profound anti-diabetic properties. In a study in 2007 scientists examined the effect of an herbal combination which includes *U. dioica*. Results demonstrate safety, tolerability and efficacy of their combination in decreasing glucose level and Hb A1C. (34).

Another plant which has been studied by many scientists in the field of diabetic research is Ginseng. Their focus has been placed on two widely used type of ginseng: American (*Panax quinquefolius* L.) and Asian ginseng (*Panax ginseng* CA Meyer). Ginseng can leads to an increase in insulin production, reduces death of pancreatic β -cells and insulin resistance and improves post prandial glycemia in diabetic patients (35, 36).

Pomegranate (*Punicagranatum*) consists of Tannins (25 to 28%; Gallatannins), including punicalin (granatine DJ, punicalagin (granatine C), granatine A, granatine B. as pomegranate is a potent source of antioxidants, despite the sugar content, consumption by diabetic patients can help to relieve oxidative stress (37).

Cinnamon contains biologically active ingredients which have insulin-mimetic properties at in vitro and in vivo studies but there are conflicting studies about the effect of cinnamon on glucose control. Baker et al. conducted a meta-analysis of randomized controlled trials of cinnamon to illustrate its impact on plasma glucose. They analyzed 5 randomized controlled trials. They concluded that cinnamon does not appear to be effective on Hb A1C and FBG in diabetic patients, as well as its ability to prevent diabetes in high risk and pre-diabetic patients is unknown (38).

Teucrium polium (Poley) is containing of diterpenes, Volatile oil (0.1 to 1%), Iridoids, Flavonoides. A study which compared *T. polium* with glibenclamid in a period of 6 weeks showed that *T. polium* can reduce Hb A1C like glibenclamid (17).

Alfalfa (*Medicago sativa*) is aboriginal to the Mediterranean region widely cultivated variety worldwide. It contains *L.canavaine*, Betaine (stachydrine, homostachydrine), Trigonelline and Fatty oil. Alfalfa exhibited hypoglycemic effects in streptozotocin induced diabetic mice, which destroys pancreatic cells, while having no significant effect in nondiabetic mice (39).

Garlic which scientifically named *Allium sativum* ingiberofficinale is one of the famous medicinal herbs. It consists of alliin (alkylcysteinesulfoxides) especially allylalliin, propenylalliin and methylalliin, frocosans (polysaccharides) and saponins. In a human study in 2001 significant decrease in glucose levels were seen in the men and women following garlic treatment (40).

Another effective plant in the treatment of diabetic patients is Bilberry (*Vaccinium myrtillus*). Compounds including: 1-7% Catechin tannins (oligomeric proanthocyanidins), Flavonoides, Iridoid monoterpene, Caffeic acid derivatives, Phenolic acids, quinolizidine alkaloids. The scientists concluded that bilberry has a significant effect on diabetic retinopathy. Boniface in 1996 studied twelve diabetic patients who were treated with 600 mg anthocyanosides per day for 2 months. The use of radio-labeled amino acids showed a significant decrease in biosynthesis, especially polymeric collagen. Thus anthocyanosides may help to prevent diabetic patients from injuries caused by malfunction of synthesis activities during normal diabetic treatment (41).

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 Anthracycline 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 (42).

So according to these results there are some human studies showed a significant decrease in blood glucose after treatment with plants including Citrullus Colocynthis, Silybum marianum, Psyllium, Teucrium polium, pomegranate, ginseng, *Al-oe vera* and fenugreek. However for future trials the effect size and clinically significant results and outcomes should be considered.

Herbal medicine used in obesity

Search strategy: For review of the efficacy and safety of herbal medicines used in the treatment of obesity, PubMed, Scopus, Google Scholar, Web of Science, and Iranmedex databases were searched. The search terms were "obesity" AND ("herbal medicine" OR "plant", "plant medicinal" OR "medicine traditional"). All of the human and animal studies on the effects of herbs which considered these key outcomes have been included: 1- change in anthropometric measures 2- amount of food intake and 3- appetite (18). The databases searched up and updated again to August 20, 2010.

Human studies

Weight and fat loss effect: The majority of herbal studies including a weight loss program such as an energy restricted diet with or without physical activity, reported an additional weight loss effect of the herb, however, not significant such as Bofutsusho-san containing Ephedrae and other herbs, a compound of Aralia mandshurica and Engelhardtia chrysolepis, a white bean extract, Carallum fimbriata, Hydroxycitric acid alone or in a compound and Guggulu. The exceptional studies which demonstrated significant superior efficacy to low calorie diet were with: 1- two formulations containing extracts of Cissus quadrangularis, 2- ephedra extract, 3- Calcium hydroxycitrate in Garcinia atroviridis, 4- Xanthigen (brown marine algae fucoxanthin + pomegranate seed oil), and 5- Triphala which is comprised of three plants, namely Terminalia chebula, Terminalia bellerica and Emblica officinalis (43, 44). It is noteworthy that findings of a different study with a natural dietary supplement comprised of capsicum and other isotropic nutrients demonstrated significant decrease

in body fat percentage, fat mass & fat free mass without any effect on body weight (18,45-49).

After a thorough review of herbal clinical trials and the literature ; compounds of ephedra and herbal caffeine source, a natural dietary compound of capsicum and other lipotropic nutrients, *Cissusquadrangularis* alone or combined with *Irvingiagabonensis* and *Evodiarutaecarpa* resulted significant loss of body weight compared to controls (18,45-54). It is noteworthy that studies with green tea (a highly bioavailable green tea extract), Slimax (extract of several plants including *Zingiberofficinale*), *Bofu-tsusho-san* containing *Ephedrae* and other herbs, compound of *Sambucusnigra* and *Asparagus officinalis*, white bean extract and Xanthigen (brown marine algae fucoxanthin + pomegranate seed oil) reported a significant decrease in body weight compared to baseline levels (18,49,55-57).

Also, a recent systematic review has reported a significant reduction in body weight by *Nigella sativa*, *Camellia sinensis*, *Crocus sativus* L, seaweed *laminariadigitata*, Xantigen, virgin olive oil, Catechin enriched green tea, Monoselect *Camellia*, Oolong tea, Yacon syrup, *Irvingia Gabonensi*, Weighlevel, RCM-104 compound of *Camellia*, *Sinensis*, Pistachio, *Psylliumfibre*, black Chinese tea, sea buckthorn and bilberries (58,59).

The body fat mass has decreased with compounds such as *Bofu-tsusho-san* which effectively decreased from baseline the abdominal visceral fat estimated from the bioelectrical impedance method or calcium hydroxycitrate in *Garcinia-atroviridis* showed loss of body fat mass by significant decrease in the skin fold thickness compared to both the controls and baseline levels (18,47). In several studies the body fat mass changes was measured by DXA (Dual energy X-ray absorptiometry) method or by air displacement plethysmography (BodPod1 Body Composition System) and in other the fat mass was estimated by the bioelectrical impedance method. Compared to controls loss of body fat mass with compounds of ephedra and Caffeine, *Cissusqua-drangularis/ Irvingiagabonensis* combination and Xanthigen was significant (48,50-52).

-size changes: Waist and hip circumferences decreased efficiently with a compound containing ephedra and Caffeine, Slimax (extract of several plants including *Zingiber officinal*), whereas, in studies with *Bofu-tsusho-san*, *Carallumafimbriata*, *Cissusquadrangularis/ Irvingiagabonensis* combination, Xanthigen patients with non-alcoholic fatty liver disease demonstrated efficient waist circumference decrease (18, 49,50,52,56) .

- Negative results: 50 g daily of chia seed (*Salvia hispanica* L) for 12 weeks in an randomized clinical trial (RCT) for 12 weeks had no influence on body mass or composition, or various disease risk factor measures (60). No significant effect was also observed on weight, appetite/satiety scores or oxidative parameters for fenugreek seed extract (61).

-Safety: In all reviewed studies no mortality was reported and compared to control groups no significant adverse effect was shown except studies with compounds containing ephedra that caused minor adverse effects such as dry mouth, insomnia, nervousness, palpitation and headache and *Bofutsushosan* which caused loose bowel movements (18).

The efficacy of compounds noted in Table-1 is considerable in two aspects first when such effective herbs make compounds with other efficacious ingredients or plants , the effect size becomes larger like *Cissusquadrangularis* combined with *Irvingiagabonensis* caused more weight loss than the extract alone thus further studies are required to elucidate synergistic effects. Second by rigorous evaluation of RCTs on selected efficient compounds apart from the type of the plant, the dosage and time treatment would be a noticeable factor implying efficacies in various clinical trials, the example is for compounds containing ephedr.

Approach to mechanisms of action, such as decreasing food intake by suppressing the appetite and/or increasing satiety, thermogenesis, and improvement of lipid metabolism and inhibition of dietary calories absorption, modifying metabolic and inflammatory cytokines and antioxidative effects would open a vast applicable knowledge for novel useful patented compounds.

Table 1: Anti-obesity effect of herbal medicines in randomized controlled trials

Reference	Herb	Efficacy(Significant Compared To Controls)	Groups	Suggested Mechanisms & Adverse Effects
(46)	Ephedra sinica extract	I:~ -1.7 kg/m ² vs C:~ -0.6 kg/m ² of BMI	I:extract C:placebo	Failed to prove that ephedra has any chronic promoting effect. dry mouth, nausea and vomiting, insomnia and anorexia
(49)	Xanthigen (brown marine algae fucoxanthin + pomegranate seed oil (PSO))	in NAFLD1 group = I: -6.9 ± 1.9 kg vs C: -1.4 ± 0.7 kg of body wt in NLF2 group = I: ~ -6.3 kg vs C: ~ -1.4 kg in NAFLD group = I: ~ -4.4 kg vs C: no change of body fat in NLF group = I: ~ 5.2 kg vs C: no change of body fat in NAFLD group = I: ~ -5 cm vs C: no change of waist circumference	I: Xanthigen in NALFD & NLF patients C:placebo in NALFD & NLF patients	normalization of indices of inflammation such as CRP that positively correlate with central adiposity
(50)	Herbal supplement containing Ma Huang, Guarana	I: -4.0 ± 3.4 kg vs C: -0.8 ± 2.4 kg of body wt I: -2.1 ± 3.0% vs C: -0.2 ± 2.3% percentage of body fat	I:compound C:placebo	reducing food intake as well as by increasing thermogenesis
(51)	Herbal supplement containing caffeine and ephedra	I: -3.5 ± 0.6 kg vs C: -0.8 ± 0.5 kg of body wt I: -7.9 ± 2.9% vs C: -1.9 ± 1.1% percentage of body fat	I:compound C:placebo	Increasing resting metabolic rate No serious adverse effect
(52)	A combination of Cissusquadrangularis only, And Irvingiagabonensis	I: -10.79 kg vs C: -2.05 kg of body wt I: -20.06% vs C: -3.97% percentage of body fat	I:compound C:placebo	Reducing the oxidative stress and the ability to inhibit certain enzymes like alpha amylase, glucosidase and lipase.
(47)	calcium hydroxycitrate as Garciniaatroviridis	I: -2.8 ± 0.1 kg vs C: -1.4 ± 0.1 kg of body wt	I:low calorie diet + Garciniaatroviridis C: low calorie diet + placebo	suppresses the fatty acid synthesis and lipogenesis, and suppress food intake
(53)	a multinutrient supplement containing ephedra and caffeine	I: ~ -7.18 kg vs C: ~ -2.25 kg of body wt I: ~ -5.33 kg vs C: ~ -0.99 kg weight of body fat	I:multinutrient supplement C:control supplement	
(54)	compound containing ephedrine, caffeine	I: -2.10 ± 0.35 kg vs C: -0.46 ± 0.37 kg of body wt	I:compound C:placebo	
(45)	Cissusquadrangularis	I: CORE = ~ -8.1 kg / CQR-300 = ~ -4.8 kg vs C: ~ +1.2 kg of body wt	I:two formulations: CQR-300, CORE C:placebo All groups had dietary restriction	scavenging free radicals to reduce oxidative stress and/ or by clearing the plasma of the potential oxidants products
(44)	ItrifalSaghir	I: ~ 4.37 kg vs C: ~ +0.45 kg of body wt I: ~ -1.47 kg/m ² vs C: ~ +0.18 kg/m ² of BMI	I: ItrifalSaghir C: Placebo	Scavenging free radicals and decreasing oxidative stress and inflammation

BMI: body Mass Index, C: control, I: intervention, NAFLD: non-alcoholic fatty liver disease, NLF: normal liver fat, Wt:weight, The results showed that supplements containing ephedra and caffeine, *Cissusquadrangularis* (CQ) or combined with *Irvingiagabonensis* (IG), compound of *Sambucusnigra* (S) and *Asparagus officinalis* (A), calcium hydroxycitrate in *Garciniaatrovirdis*, Slimax as extract of several plants including *Zingiberofficinale*, Bofutsushosan decreased body weight significantly. Significant decrease in body fat was shown with supplements containing ephedra and caffeine, capsicum and some lipotropic nutrients, Bofutsushosan. Both waist and hip circumferences decreased with supplement containing ephedra and caffeine and Slimax (extract of several plants including *Zingiberofficinale*. Bofutsushosan resulted loose bowel movements and minor adverse effects such as dry mouth, insomnia, nervousness, palpitation and headache observed with supplements containing ephedra and caffeine.

Herbal medicine used inhyperlipidemia

Search strategy: In reviewing hyperlipidemia and medicinal plants, PubMed, Scopus, Google Scholar, Web of Science, and IranMedex databases were searched up to 11th May 2010. The search terms were "hyperlipidemia" and ("herbal medicine" or "medicine traditional", "extract plant") without narrowing or limiting search elements. All of the human studies on the effects of herbs with the key outcome of change in lipid profiles were included (19,62).

Human studies

Fifty four relevant clinical trials were reviewed. Amongst reviewed studies, 23 natural products were found effective in the treatment of hyperlipidemia including Daming capsule (DMC), chunghyul-dan, *Glycyrrhizaglabra*, garlic powder (*Allisor*), *Anethumgraveolens* (dill), black tea, green tea, soy drink enriched with plant sterols, *licorice*, *Saturejakbuzestanica*, *Monascuspurpureus*, Went rice, Fenugreek, *Commiphoramukul* (guggul), *Achilleavilhelmsii* C. Koch, Ningzhi capsule (NZC), cherry, *compositiesalviae* dropping pill (CSDP), *shan-zhaxiaozhi* capsule, *Ba-wei-wan* (*hachimijiogan*), rhubarb stalk, *Silybummarianum*, *Rheum Ribes* and *Jingmingdan granule*(primrose oil) which significantly

decreased total cholesterol and LDL cholesterol. Conflicting data exist for red yeast rice, garlic and guggul. Except in studies with DMC, guggul, and *Terminaliabelerica*, *Terminaliachebula*, *Emblicaof-ficinalis*, ginger, and garlic powder (*Allium sativum*) no significant adverse effect or mortality were observed (19).

Herbal medicine used inhyperprolactinemia

Search strategy: To review the effect of herbal medicines on drug-induced hyperprolactinemia, PubMed, Scopus, Web of science, Cochrane library database were searched. All relevant studies that investigated the effect of herbal medicines on drug-induced hyperprolactinemia were included. The search terms were: prolactin, hyperprolactinemia, prolactinoma, galactorrhea and herb, herbal medicine, plant, traditional medicine and antipsychotics, neuroleptic, schizophrenia (20). Some natural products including Shakuyaku-kanzo-to (TJ-68), Peony-Glycyrrhiza Decoction (PGD), Zhuangyang capsule, Tongdatang serial recipe (TDT) had adequate support to be beneficial in drug-induced hyperprolactinemia.

Herbal medicine with antioxidant effect

Search strategy: To review the medicinal plants as anti-oxidative stress agents, Embase, Scopus, PubMed, Web of Science, Google Scholar, IranMedex, and SID databases were searched. The search terms were antioxidant or "lipid peroxidation" and "plant, medicinal plant, herb, traditional, natural or herbal medicine" limited to Iran. Antioxidative effect and lipid peroxidation inhibition were the key outcomes (21). In different clinical circumstances *Ferula szovitsiana*, Saffron, *Rosa damascene* petal, *Phlomisanisodonta*, *Nigella sativa*, Rosemary, *ZatariamultifloraBoiss*, *Amirkabiriao-dorastissimamozaffarian*, *Ficuscarica* Linn., *Ziziphoraclinopoides*, *Carica papaya*, *Chichoriumintybus*, Turmer, Eugenol, Curcumin, and *Pistaciavera* L reduced lipid peroxidation. Human studies showed that *Cinnamomumzeylanicum* and *Echiumamoenum* Fisch & C.A. Mey reduce lipid peroxidation and improve total antioxidant power in healthy subjects. These kinds of compounds are potential target drugs of future.

Teucrium (Commonly called Germanders) has antioxidant effects too. Teucrium species possess free radical and hydroxyl radical scavenging activity as well as antioxidant activity in vitro (22).

7 animal studies showed anti-oxidant properties of Teucrium that are summarized in reference (22). In one study the inhibitory effect of the extract in NADPH-induced lipid peroxidation was greater than that of reference substance, luteonin, and similar with that of thymol. According to histopathological and biochemical evidences, long-term administration or high dose of Teucrium may induce progressive impairment of neuromuscular coordination and reversible or irreversible hepatic damage.

Conclusion

Some medicinal plants are effective in the treatment of different metabolic and endocrine disorders. For example *Citrullus colocynthis*, *Silybum marianum*, *Psyllium*, *Teucrium polium*, pomegranate, ginseng, *Aloe vera* and fenugreek decreased blood glucose significantly. Moreover, a variety of herbal supplements were found to be effective in the management of obesity such as ephedra, *Cissus quadrangularis*, ginseng, bitter melon (*Momordica charantia*), and zingiber.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgements

The authors declare that there is no conflict of interest.

References

1. World Health Organization. Obesity: Preventing and managing the global epidemic. Report of a WHO Consultation on Obesity Geneva; 1997.
2. Sicree R, Shaw J, Zimmet P (2006). Diabetes and impaired glucose tolerance. Delice Gan. Diabetes Atlas. 3rd edition. *International Diabetes Federation*, 51.
3. Centers for Disease Control and Prevention (CDC) (1998). *Coronary heart disease mortality trends among whites and blacks-Appalachia and United States, 1980-1993*.
4. Hardeman W, Griffin S, Johnston M, Kinmonth AL, Wareham NJ (2000). Interventions to prevent weight gain: a systematic review of psychological models and behavior change methods. *Int J Obes Relat Metab Disord*, 24(2):131-43.
5. Abdollahi M, Afshar-Imani B (2003). A review on obesity and weight loss measures. *Middle East Pharmacy*, 11(5): 6-10.
6. Vogel JH, Bolling SF, Costello RB, et al. (2005). Integrating complementary medicine into cardiovascular medicine. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents (Writing Committee to Develop an Expert Consensus Document on Complementary and Integrative Medicine). *J Am Coll Cardiol*, 46: 184.
7. Varady KA, Jones PJ (2005). Combination diet and exercise interventions for the treatment of dyslipidemia: an effective preliminary strategy to lower cholesterol levels? *J Nutr*, 135:1829.
8. Pearson TA, Laurora I, Chu H, Kafonek S (2000). The lipid treatment assessment project (L-TAP): a multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med*, 160:459.
8. Valco M, Izakovic M, Mazur M, Rhodes CJ, Telser J (2004). Role of oxygen radicals in DNA damage and cancer incidence. *Mol Cell Biochem*, 266(1-2): 37-56.
9. Bartsch H, Nair J (2004). Oxidative stress and lipid peroxidation-derived DNA- lesions in inflammation driven carcinogenesis. *Cancer Detect Prev*, 28(6):385-91.
10. Bouayed J, Piri K, Rammal H, et al. (2007). Comparative evaluation of the antioxidant potential of some Iranian medicinal plants. *Food Chemistry*, 104(1): 364-368.
11. Liu JP, Zhang M, Wang W, Grimsgaard S (2004). Chinese herbal medicines for type 2 diabetes

- mellitus. *Cochrane Database of Systematic Reviews*, (3):CD003642.
12. Ziai SA (2003). Traditional herbal medicine. *J Med Plants*, 2(1):51-43.
 13. Kim JD, Kang SM, Park MY, Jung TY, Choi HY, Ku SK (2007). Ameliorative anti-diabetic activity of dangnyosoko, a Chinese herbal medicine, in diabetic rats. *Biosci Biotechnol Biochem*, 71(6):1527-34.
 14. Sadighi J, Maftoon F, Moshrefi M (2004). Complementary and alternative medicine (CAM): Knowledge, attitude and practice in Tehran, Iran. *Payesh*, 4(3): 289-279.
 15. Klepser TB, Klepser ME (1999). Unsafe and potentially safe herbal therapies. *Am J Health Syst Pharm*, 56(2): 125-138.
 16. Hasani-Ranjbar S, Larijani B, Abdollahi M (2008). A systematic review of Iranian medicinal plants useful in diabetes mellitus. *Arch Med Sci*, 43: 285–292.
 17. Hasani-Ranjbar S, Nayebi N, Larijani B, Abdollahi M (2009). A systematic review of the efficacy and safety of herbal medicines used in the treatment of obesity. *World J Gastroenterol*, 15(25).
 18. Hasani-Ranjbar S, Nayebi N, Moradi L, Mehri A, Larijani B, Abdollahi M (2010). The Efficacy and Safety of Herbal Medicines Used in the Treatment of Hyperlipidemia; A Systematic Review. *Curr Pharm*, 16(26):2935-47.
 19. Hasani-Ranjbar S, Vahidi H, Taslimi S, Karimi N, Larijani B, Abdollahi M (2010). A systematic review on the efficacy of herbal medicines in the management of human drug-induced hyperprolactinemia: potential sources for the development of novel drugs. *Int J Pharmacol*, 6(5): 691-695.
 20. Hasani-Ranjbar S, Larijani B, Abdollahi M (2009). A systematic review of the potential herbal sources of future drugs effective in oxidant-related diseases. *Inflammation and Allergy - Drug Targets*, 8 (1): 2-10.
 21. Hasani-Ranjbar S, Nayebi N, Larijani B, Abdollahi M (2010). A systematic review of the efficacy and safety of Teucrium species: from anti-oxidant to anti-diabetic effects. *Int J Pharmacol*, 6 (4): 315-325.
 22. Huseini HF, Hasani-Ranjbar S, Nayebi N, Heshmat R, Sigaroodi FK, Ahvazi M, et al. (2013). Capparis spinosa L. (Caper) fruit extract in treatment of type 2 diabetic patients: a randomized double-blind placebo-controlled clinical trial. *Complement Ther Med*, 21(5):447-52.
 23. Velussi M, Cernigoi AM, Viezzoli L, et al. (1997). Silymarin reduces hyperinsulinemia, malondialdehyde levels, and daily insulin need in cirrhotic diabetic patients. *Journal of Hepatology*, 26(4):871-879.
 24. Dehmlow C, Erhard J, De Groot H (1996). Inhibition of Kupffer cell function as an explanation for the hepatoprotective properties of silybinin. *Hepatology*, 23(4) :749-754.
 25. Pastors JG, Blaisdell PW, Balm TK, Asplin CM, Pohl SL (1991). Psyllium fiber reduces rise in postprandial glucose and insulin concentrations in patients with non-insulin-dependent diabetes. *Am J Clin Nutr*, 53:1431-1435.
 26. Edwards CA, Johnson IT, Read NW (1998). Do viscous polysaccharides slow absorption by inhibiting diffusion or convection? *Europ J Clin Nutr*, 42:307-312.
 27. Jenkins DJ, Jenkins AL (1985). Dietary fiber and glycemic response. *Proc Soc Exp Biol Med*, 180: 422–431.
 28. Holt S, Heading RC, Carter DC, Prescott LF, Tothill P (1979). Effect of gel fiber on gastric emptying and absorption of glucose and paracetamol. *Lancet*, 1(8117):636-9.
 29. Dunaif G, Schneeman BO (1981). The effect of dietary fiber on human pancreatic enzyme activity in vitro. *Am J Clin Nutr*, 34(6):1034-5.
 30. Kassaian N, Azadbakht L, Forghani B, Armini M (2009). Effect of fenugreek seeds on blood glucose and lipid profiles in type 2 diabetic patient. *International Journal for Vitamin and Nutrition Research*, 79 (1):34-39.
 31. Gupta A, Gupta R, Lal B (2001). Effect of Trigonella foenum-graecum (fenugreek) seeds on glycemic control and insulin resistance in type 2 diabetes mellitus: a double blind placebo controlled study. *Journal of Association of Physicians of India*, 49:1057-61.
 32. Broca C, Manteghetti M, Gross R, et al. (2000). Hydroxyisoleucine: effects of synthetic and natural analogues on insulin secretion. *Europ J Pharmacol*, 390(3):339-345.
 33. Said, O, Fulder, S, Khalil, KH, Azaizeh, H, Kassis E, Saad B (2008). Maintaining A Physiological Blood Glucose Level with 'Glucoselevel' A Combination of Four Anti-Diabetes Plants Used in the Traditional Arab Herbal Medicine.

- Evidence-based Complementary and Alternative Medicine*, 5(4):421–428.
34. Luo JZ, Luo L (2009). Ginseng on Hyperglycemia: Effects and Mechanisms. *Evidence-based Complementary and Alternative Medicine*, 6(4):423–427.
 35. Vuksan V, Sung MK, Sievenpiper JL (2008). Korean red ginseng (*Panax ginseng*) improves glucose and insulin regulation in well-controlled, type 2 diabetes: Results of a randomized, double-blind, placebo-controlled study of efficacy and safety. *Nutrition, Metabolism & Cardiovascular Diseases*, 18(1): 46–56
 36. Rosenblat M, Hayek T, Aviram M (2006). Antioxidative effects of pomegranate juice (PJ) consumption by diabetic patients on serum and on macrophages. *Atherosclerosis*, 187: 363–71.
 37. Baker WL, Gutierrez-Williams G, White CM, Kluger J, Coleman CI (2008). Effect of cinnamon on glucose control and lipid parameters. *Diabetes Care*, 31:41–43.
 38. Gray AM, Flatt PR (1997). Pancreatic and extra-pancreatic effects of the traditional anti-diabetic plant medicago sativa (lucerne). *Br J Nutr*, 78(2):325–334.
 39. Zhang XH, Lowe D, Giles P (2001). Gender may affect the action of garlic oil on plasma cholesterol and glucose levels of normal subjects. *Journal of Nutrition*, 131(5):1471–1478.
 40. Boniface R, Miskulin M, Robert AM (1985). Pharmacological properties of myrtillus anthocyanosides: Correlation with results of treatment of diabetic microangiopathy. *Flavonoids and Bioflavonoids*, 293–301.
 41. Yeh GY, Eisenberg DM, Kaptchuk TJ, Phillips RS (2003). Systematic review of herbs and dietary supplements for glycemic control in diabetes. *Diabetes Care*, 26(4):1277–94.
 42. Kamali SH, Khalaj AR, Hasani-Ranjbar S, Esfehiani MM, Kamalinejad M, Larijani B (2013). A systematic review of the antioxidant, anti-diabetic, and anti-obesity effects and safety of triphala herbal formulation. *Journal of Medicinal Plants Research*, 7(14):831–44.
 43. Kamali SH, Khalaj AR, Hasani-Ranjbar S, Esfehiani MM, Kamalinejad M, Soheil O, et al. (2012). Efficacy of 'ItrifalSaghir', a combination of three medicinal plants in the treatment of obesity; A randomized controlled trial. *DARU*, 20(1):33.
 44. Oben JE, Enyegue DM, Fomekong GI, Soukontoua YB, AgborGA (2007). The effect of *Cissusquadrangularis* (CQR-300) and a *Cissus* formulation (CORE) on obesity and obesity-induced oxidative stress. *Lipids Health Dis*, 6:4.
 45. Kim HJ, Park JM, Kim JA, Ko BP (2008). Effect of herbal *Ephedra sinica* and *Evodiarutaecarpa* on body composition and resting metabolic rate: a randomized, double-blind clinical trial in Korean premenopausal women. *J Acupunct Meridian Stud*, 1(2):128–38.
 46. Roongpisuthipong C, Kantawan R, Roongpisuthipong W (2007). Reduction of adipose tissue and body weight: effect of water soluble calcium hydroxycitrate in *Garciniaatroviridis* on the short term treatment of obese women in Thailand. *Asia Pac J Clin Nutr*, 16:25–29.
 47. Hoeger WW, Harris C, Long EM, Hopkins DR (1998). Four week supplementation with a natural dietary compound produces favorable changes in body composition. *Adv Ther*, 15:305–314
 48. Abidov M, Ramazanov Z, Seifulla R, Grachev S (2010). The effects of Xanthigen in the weight management of obese premenopausal women with non-alcoholic fatty liver disease and normal liver fat. *Diabetes Obes Metab*, 12(1):72–81.
 49. BoozerCN, Nasser JA, Heymsfield SB, Wang V, Chen G, Solomon JL (2001). An herbal supplement containing Ma Huang- Guarana for weight loss: a randomized, double-blind trial. *Int J Obes Relat Metab Disord*, 25(3): 316–324.
 50. Greenway FL, De Jonge L, Blanchard D, Frisard M, Smith SR (2004). Effect of a dietary herbal supplement containing caffeine and ephedra on weight, metabolic rate, and body composition. *Obes Res*, 12:1152–1157.
 51. Oben JE, Ngondi JL, Momo CN, Agbor GA, Sobgui CS (2008). The use of a *Cissusquadrangularis*/*Irvingiagabonensis* combination in the management of weight loss: a double-blind placebo-controlled study. *Lipids Health Dis*, 7:12.
 52. Hackman RM, Havel PJ, Schwartz HJ, et al. (2006). Multinutrient supplement containing ephedra and caffeine causes weight loss and improves metabolic risk factors in obese women: a randomized controlled trial. *Int J Obes (Lond)*, 30:1545–1556.
 53. Coffey CS, Steiner D, Baker BA, Allison DB (2004). A randomized double-blind placebo-

- controlled clinical trial of a product containing ephedrine, caffeine, and other ingredients from herbal sources for treatment of overweight and obesity in the absence of lifestyle treatment. *Int J Obes Relat Metab Disor*, 28: 1411-19.
54. Di Pierro F, Menghi AB, Barreca A, Lucarelli M, Calandrelli A (2009). GreenselectPhytosome as an adjunct to a low-calorie diet for treatment of obesity: a clinical trial. *Altern Med Rev*, 14(2):154-60.
 55. Ignjatovic V, Ogru E, Heffernan M, Libinaki R, Lim Y, Ng F (2000). Studies on the use of 'slimax', a chinese herbal mixture, in the treatment of human obesity. *Pharm Biol*, 38: 30-35.
 56. Chrubasik C, Maier T, Dawid C (2008). An observational study and quantification of the actives in a supplement with *Sambucus nigra* and *Asparagus officinalis* used for weight reduction. *Phytother Res*, 22 (7): 913-8.
 57. Hasani-Ranjbar S, Jouyandeh Z, Abdollahi M (2013). A systematic review of anti-obesity medicinal plants - an update. *J Diabetes Metab Disord*, 12(1):28.
 58. Hasani-Ranjbar S, Zahedi HS, Abdollahi M, Larijani B (2013). Trends in Publication of Evidence-based Traditional Iranian Medicine in Endocrinology and Metabolic Disorders. *J Diabetes Metab Disord*, 12(1):49.
 59. Nieman DC, Cayea EJ, Austin MD, Henson DA, McAnulty SR, Jin F (2009). Chia seed does not promote weight loss or alter disease risk factors in overweight adults. *Nutr Res*, 29(6):414-8.
 60. Chevassus H, Gaillard JB, Farret A, Costa F, Gabillaud I, Mas E, Dupuy AM, Michel F, Cantié C, Renard E, Galtier F, Petit P (2010). A fenugreek seed extract selectively reduces spontaneous fat intake in overweight subjects. *Eur J Clin Pharmacol*, 66(5):449-55.
 61. Mansouri M, Nayeibi N, Keshtkar A, Hasani-Ranjbar S, Taheri E, Larijani B (2012). The effect of 12 weeks *Anethum graveolens* (dill) on metabolic markers in patients with metabolic syndrome; a randomized double blind controlled trial. *DARU*, 20(1):47.

Archive of SID