Journal of Medicinal Plants Studies
www.PlantsJournal.com

ISSN 2320-3862
JMPS 2016; 4(6): 95-103

Received: 15-09-2016
Accepted: 16-10-2016

Elizabeth Alejandrina Guzmán Hernández
Sección de Estudios de Posgrado e Investigación, Escuela Superior de Medicina, Instituto Politécnico Nacional, México, DF, México

David Segura-Cobos
Laboratorio de Farmacología, Unidad de Investigación Interdisciplinaria en Ciencias de la Salud y la Educación, Facultad de Estudios Superiores Iztacala, Universidad Nacional Autónoma de México, Tlalnepantla, Estado de México

Pedro López-Sánchez
Sección de Estudios de Posgrado e Investigación, Escuela Superior de Medicina, Instituto Politécnico Nacional, México, DF, México

Correspondence
Elizabeth Alejandrina Guzmán Hernández
Sección de Estudios de Posgrado e Investigación, Escuela Superior de Medicina, Instituto Politécnico Nacional, México, DF, México

Plants present in Mexico with studies in metabolic syndrome

Elizabeth Alejandrina Guzmán Hernández, David Segura-Cobos and Pedro López-Sánchez

Abstract
Metabolic syndrome represents one of the major risk factors for developing cardiovascular disease, with high risk affecting most of the worldwide adult population in both sexes. In Mexico, cardiovascular diseases are the first cause of morbidity and mortality. Generally, for the therapeutic management of both diseases is using multiple drugs with different mechanisms of action, which aim to reduce risk factors, associated with metabolic syndrome. These are managed for a long time, which often represents a high economic cost. On the other hand, some patients have no adherence to treatment as this one, is ineffective, the adverse effects are situations that require change or discontinue medication immediately. Mexico has a large diversity of plants widely used in traditional medicine and with a high potential for use in treating metabolic syndrome.

Keywords: Metabolic syndrome, medicinal plants

Introduction
Metabolic syndrome (SM) is a disorder characterized by the presence of multiple risk factors, including central obesity, hyperglycemia, hypertriglyceridemia, low plasma high density lipoprotein (HDL) - cholesterol and hypertension. Concurrence of at least 3 of these factors means that an individual has MS [1]. The relation of MS with the risk of developing several chronic diseases, such as diabetes mellitus and cardiovascular diseases is well established, and it is also associated with a high mortality risk [2].
In developed countries SM appears to affect around 25% of the population. Moreover, its prevalence is increasing rapidly throughout the world, in parallel with the increasing prevalence of diabetes and obesity and becoming a major public health problem [3]. The prevalence of SM in Mexican adults was of 41 % in accordance with ENSANUT 2012. Cardiovascular disease is the primary cause of death for both sexes. This increased tendency could be associated with significant changes in lifestyle behaviour including physical inactivity, high carbohydrate diets, alcohol, and tobacco consumption [4].
Pharmacological treatment of SM in addition to lifestyle including weight loss, a targeted approach for control of individual components of the SM is often necessary. Because there are drugs proven effective in reducing specific components of SM, must be individualized.

a) An anti-obesity: such as lorcaserin is approved for its use in obese adults who have high blood pressure and cholesterol. Lorcaserin acts as a selective 5 - HT 2C receptor agonist on pro-opiomelanocortin neurons, which in turn causes release of α-melanocyte-stimulating hormone (α-MSH). Further α - MSH acts on melanocortin 4 receptor in the paraventricular nucleus in the hypothalamus, leading to a decrease in appetite and body weight.

b) Insulin sensitizers: Thiazolidinedione (TZD) is a synthetic ligand of peroxisome proliferator-activated receptor-γ (PPARγ). TZDs reduce the intracellular levels of toxic lipid metabolites, resulting in less lipotoxicity, protect against the cytostatic effect of free fatty acids and restores glucose-mediated insulin release, increase insulin sensitivity in the liver and muscle tissue, promote adipose tissue differentiation in subcutaneous adipose tissue regions, which increases the synthesis of adiponectin, thereby further reducing insulin resistance, reduce circulating levels of free fatty acids and proinflammatory cytokines as resistin, interleukin 6 (IL-6), tumor necrosis factor a (TNF-α), and intercellular adhesion molecule 1 (ICAM-1) [5].

Metformin is the only biguanide that is available in most regions of the world. Its mechanism for lowering the glucose level is based on reduction of hepatic glucose output and enhancement of insulin sensitivity in skeletal muscle and adipocytes. Metformin monotherapy is expected to decrease glycosylated hemoglobin A1c (HbA1C) by 1.0–2.0 % [6]. The major non-glycemic effect of metformin is either weight stability or modest weight loss. There are some evidences that metformin has antioxidant properties. Reported antioxidant properties of metformin are: decreasing the xanthin oxidase and lipid peroxidase activity, increasing the enzymatic antioxidants activity, chelating metal ions such as copper and iron, scavenging oxygenated free radicals generations, decreasing ROS level by activating different pathways such as AMP-protein kinase (AMPK)-mediated signaling, inhibition of advanced glycation end products (AGEs) formation, decreasing β-cell apoptosis, and also decreasing the production of TNF-α [7]. Improvement of some markers of endothelial function in patients with type 2 diabetes has been reported by metformin usage [8].

c) Lipid lowering: Statin, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor, and fibrate, a peroxisome proliferator activated receptor a (PPARα) agonist, are pharmacologic agents for dyslipidemia, are competitive inhibitors of HMG-CoA reductase, blocking the rate-limiting step in cholesterol biosynthesis; so that reduced circulating total of low-density lipoprotein (LDL) cholesterol levels, via lipoprotein lipase-mediated hydrolysis of very-low-density lipoprotein (VLDL).

d) Hypertension: the renin angiotensin system have an important relationship with insulin resistance and endothelial dysfunction. Angiotensin II inhibits insulin signaling and produces oxidative stress that accelerates hyperglycemia and atherosclerosis. Angiotensin converting enzyme (ACE) inhibitor reduces the plasma levels of angiotensin-II, leading to a decrease in blood pressure by peripheral vasodilatation. The beneficial effect of ACE inhibitors on glucose metabolism is demonstrated by clinical trials such as the HOPE (Heart Outcomes Prevention Evaluation) Study, which showed a reduced rate of new onset diabetes mellitus in patients taking the ACE inhibitor ramipril although this effect has been variable. Angiotensin-II receptor blocker is also known to exert blood pressure lowering, insulin sensitizing, induce PPARγ activity, reduce serum uric acid and proinflammatory cytokines such as IL-6 and TNF-α.

e) Novel antidiabetic agents: Glucagon like peptide-1 (GLP-1) agonists improves hyperglycemia by enhancing glucose-stimulated insulin secretion through activation of cyclic adenosine monophosphate (cAMP) and upregulates protein kinase A (PKA), which leads to rapid increases in intracellular calcium and insulin exocytosis in a glucose-dependent manner, disadvantage GLP-1 agonists have the potential to reduce insulin resistance which helps reverse insulin resistance-associated defects in the failing β-cells [9].

Sodium glucose transporter-2 (SGLT-2) inhibitors: The kidney plays an important role in glucose homeostasis by mediating reabsorption of glucose from the glomerular filtrate, which happens through SGLT-2 and SGLT-1. SGLT-2 inhibitors block 90% of reabsorption of filtered glucose in the proximal tubules, leading to increased urinary glucose excretion, which eventually reduces hyperglycemia. In 2013 and 2014, the US FDA approved three drugs in this class: canagliflozin, empagliflozin, and dapagliflozin as antidiabetic medications, as reduce cardiovascular risk not only via glucose lowering effect but via beneficial effects on body weight, blood pressure and serum uric acid [10].

Phosphodiesterase inhibitor: Cilostazol a selective phosphodiesterase-3 (PDE-3) inhibitor with anti-thrombotic and vasodilating properties. Activates AMPK and causes phosphorylation of endothelial nitric oxide synthase, leading to increased production of nitric oxide, while it inhibits cytokine-induced NFkB activation and suppresses vascular cell adhesion molecule 1 (VCAM-1) gene expression. In a clinical trial, administration of cilotazol reduced triglycerides and increase in lipoprotein lipase activity [11].

These groups of drugs have proven effective for the treatment of SM, so it is often the desired effect with side effects and/ or toxic arise, and would find no scope for a large segment of the population, they have made the patient leaves treatment, and resort to other alternative treatments.

Medicinal plants are used as a source of drugs for the treatment of various human health disorders all over the world from ancient times to the present day. They are important natural wealth. They provide primary healthcare services to people from all walks of life. They serve as important therapeutic agents as well as important raw materials for the manufacture of traditional and modern medicines. A total of 250,000 species of flowering plants are referred to as medicinal plants. The World Health Organization (WHO) enlisted some 21,000 medicinal plant species. The present global herbal market is worth about US$ 62 billion per annum. The annual growth of herbal market is about 15% and the global herbal market by 2050 is expected to be about US$ 5 trillion [12].

Plants are one of the most important sources of medicines. Today the large number of drugs in use is derived from plants, like morphine from *Papaver somniferum*, Ashwagandha from *Withania somnifera*, ephedrine from *Ephedra vulgaris*, atropine from *Atropa belladonna*, reserpine from *Rouwolfia serpentine* [13].

The medicinal plants are rich in secondary metabolites which are potential sources of drugs and essential oils of therapeutic importance.

The tendency to use traditional medicinal becomes clear with MS, given the high costs can represent treatment, and may be in some population it is inaccessible, especially in patients with low socioeconomic status and those living in rural areas, use alternative medicine, which is less costly and more accessible than a biomedical treatment. Also, patients are exposed to standard treatments, which are not only expensive but also display several side effects that eventually discourage patients. Alternative therapies, on the contrary, are believed to have few consequences for the body and their proximity to people beliefs and perception of disease and well-being make them popular [13].

Considering the need for the introduction of new drugs into the market, the plants have an added advantage when compared with synthetic ones, as their molecular diversity and consequent changes in biological function are more complex. With respect to research and development of newer potential herbal drugs, screening and evaluation of their phyto-pharmacological effect are essential [13].

The biodiversity and plant assets are often the basis for the development of synthetic drugs, which show a combination of chemical structures and yet unexplored physicochemical properties. This current review focuses on medicinal plants used in the treatment of MS in Mexico.

The bibliographies of all identified studies and review articles were reviewed to look for additional studies of interest. So, we preferably selected papers reporting recent comprehensive reviews or meta-analyses, or original clinical trials on substance with action on at least two or more components of MS.

Psacalium decompositum (Matarique): hypoglycemic properties of this plant have been extensively studied; extracts and fractions are effective in reducing glucose levels in normoglycemic and mildly diabetic mice [14], as well as in temporally hyperglycemic rabbits, but not in severely diabetic animals. Aqueous fraction contains a carbohydrate-type fructan (inulin), which showed hypoglycemic effect in healthy and alloxan-induced diabetic mice. Phytochemical studies revealed that contain various hypoglycemic sesquiterpenic compounds (furanoeremophilanes), such as cacalol, and the mixture of 3-hydroxycacalolide, and epi-3-hydroxycacalolide. Fructooligosaccharide (FOS) fraction obtained from the root of *P. decompositum* showed anti-inflammatory, anti-obesity fructose-induced in Wistar rats [15].

Swietenia humilis Zucc., commonly named as zopilote, gateado, cobano and caobilla; the seeds of the plant are valued as blood depurative, a popular way to raw and dried (crude drug) and decoction are consumed as antidiabetic agents in Mexican folk medicine [16].

An aqueous extract from the seeds of *Swietenia humilis* (3.6–100 mg/kg bw) lowered blood glucose levels in nicotinamide–streptozotocin induced hyperglycemic mice [17]. Furthermore, when administered to fructose-fed rats with metabolic syndrome, decoction showed antihyperglycemic, hypoglycemic and hypolipidemic effects, as well as an augmentation of hepatic glycogen [17].

Hibiscus sabdariffa L. (Hs) (roselle): Mexico ranks seventh production of this plant. Several studies have showed that extracts (water and ethanolic extracts of dried calyces or leaves) decrease LDL-C, triglycerides, total cholesterol lipid peroxidation *in vivo* and VLDL cholesterol [18-19] along with an increase in serum level of HDL cholesterol levels [19-20]. Several groups of compounds in the extract, such as anthocyanins and protocatechuic acid, have been implicated as responsible for these effects [21-22].

Standardized (33.64 mg of total anthocyanins per each 120 mg) water extract was able to reduce weight gain in obese mice while at the same time it increases the liquid intake in healthy and obese mice [25]. This effect is probably achieved through the modulation of phosphatidylinositol 3-kinase /Akt (PI3K/Akt) and extracellular signal-regulated kinase (ERK) pathway, which play pivotal roles during adipogenesis [23].

In vitro and *in vivo* studies shoed that *Hibiscus* extract (or tea) inhibited the activity of α-amylase, blocking sugars and starch absorption, which may assist in weight loss [24-25].

The aqueous extract was more efficient in inhibiting triglyceride accumulation when devoid of fibre and polysaccharides, but when polyphenols were fractionated and isolated, the benefits of the whole extract was greater than the sum of its parts [26].

The protective effect of a polyphenol extract of *Hibiscus* at a dose of 200 mg/kg, reduced serum triacylglycerol, cholesterol and the ratio of LDL/HDL, as well as reduced the plasma AGE formation and lipid peroxidation [27]. *Hibiscus* extract on intestinal α-glucosidase and pancreatic α-amylase activity in vitro, shown to be a potent pancreatic α-amylase inhibitor [28]. Similar results were found for hibiscus-type (2S, 3R)-hydroxycitric acid lactone [29], which inhibited pancreatic α-amylase and intestinal α-glucosidase enzyme [30-31].

In alloxan-induced diabetic rats was showed that an ethanolic extract of flowers (200 mg/kg) had hypolipidemic as well as antioxidant effect, which suggest that this activity might be linked to polyphenolic compounds dihydrobenzoic and protocatechuic acids [32].

Decoctions of calyces have been used traditionally in West Africa and Mexico as an anti-hypertensive remedy. The administration of 125 to 500 mg/kg of decoctions reduce systolic and diastolic pressures, heart rate [33-35]. Anti-hypertensive activity might be through inhibition of angiotensin-converting enzymes, presumably anthocyanins, as delphinidin-3-O-sambubioside (hibiscin) and cyanidin-3-O-sambubioside (gossypicyanin) [36-38] and vaso-relaxant effects through activation of the endothelium-derived nitric oxide/cGMP-relaxant pathway, or endothelium-independent through inhibition of Ca^{2+} influx [32].

Clinical studies randomised, double-blind, placebo-controlled clinical trial showed that tea (1.25 g of *Hibiscus sabdariffa* per 240 mL boiled water; 3 servings a day for 6 weeks) reduced blood pressure in pre- and mildly-hypertensive adults [39]. Similar effects on decreasing systolic and diastolic blood pressures were observed in mildly hypertensive type II diabetic individuals when taking green or hibiscus (sour) tea for 4 weeks (three times a day, 2 h after each meal) [40].

Ibervillea sonorae Greene (syn. *Maximowiczia sonorae* S.Wats) (IS), popularly known as “wareque”, is one of the most widely used plant remedies for the treatment of diabetes. In previous acute studies, a single intraperitoneal administration of aqueous decoction and the raw extract (juice) showed dose-dependent hypoglycemic activity in healthy and alloxan diabetic mice and rats. Moreover, when it was intraperitoneally injected at doses as high as 850 mg/kg body weight, or orally administered at doses as high as 2000 mg/kg, no signs of toxicity were observed in healthy mice [41].

Antidiabetic properties by means of hydrosoluble compounds stimulating the glucose uptake in human preadipocytes by a PI3K-independent pathway and without proadipogenic effects [42].

Murine model of obesity and hyperglycaemia, induced by a high-calorie diet, for 8 weeks simultaneous treatment aqueous extracts, at doses of 100, 200, and 400 mg/kg, decreased triglycerides and glycaemia levels, prevented an increase in body weight in a dose-dependent manner, and decreased hepatic lipid oxidation at a dose of 200 mg/kg, however, high doses may induce toxicity [43].

Medicago sativa (Alfalfa): in various studies on animal models (e.g. rats, prairie dogs, and monkeys), as well as on human volunteers, plant seeds, root and flowering tops have displayed anti-hypercholesterolemia properties [44]. Contains glycosylated triterpenoid saponins, mainly derivatives of medicagenic acid, zanhic acid, lucernic acid, hederagenin, bayogenin and soyasapogenols, these compounds are thought to play a role in plasma cholesterol lowering activities. A saponin-enriched leaf extract has been found to modulate the expression of genes involved in hepatic cholesterol in the rat, providing some hint about the mechanism of action of saponins, and suggesting their potential usefulness in the treatment of hyperlipidemia [45].

The administration of methanolic extract (500 mg/kg), petroleum ether (32.5 mg) and butanol fractions (60 mg), aqueous extract (1 mg/mL) for 4 weeks exhibit activity antihyperlipidemic and antihyperglycemic. Characterization and identification of isolated compounds from the active fractions afforded 9 compounds: β-sitosterol and stigmasterol from the petroleum ether fraction; 10-hydroxy-coumestrol,

apigenin, genistein, p-hydroxy-benzoic-acid, 7, 4'-dihydroxyflavone, quercetin-3-glucoside and sissotrin from the ethyl acetate fraction [46-47].

Taraxacum officinale (Dandelion) it has been considered as an herbal medicine due to its antidiabetic, anti-obesity, and diuretic properties [48].

Hypolipidemic effects of leaf (1 % w/w) in rabbits fed with a high-cholesterol diet, (-36 % on triglycerides, -11 % on LDL values, and 29 % higher of HDL concentration) [49] additionally [50-51] showed that leaf extract (2 and 5 g/kg) on high-fat-diet-induced C57BL/6J mice improved fasting glucose, insulin resistance and reduced the body weigth.

1. Aqueous extract (20 mg/kg), to alloxan or streptozotocin-induced rats, decrease serum glucose, additionally in vitro aqueous extracts, can inhibit α-glucosidase with IC_{50s} of 2.3, 3.5, and 1.83 mg plant extract/mL [52-54].

Allium sativum (garlic), in particular alliin, is well known for its anti-diabetic, hypotensive and lipid-lowering properties suggesting a role in the management of SM [55].

Garlic extracts have mainly a significant blood pressure lowering effect [56]. The dry aged garlic extract has an inhibitory activity on ACE and acts as calcium channel blocker, which reduces the sensitivity to catecholamines; it also increases the levels of bradykinin and nitric oxide and consequently improves arterial compliance [57]. A recent meta-analysis of randomized clinical trials controlled with placebo has shown an average reduction in systolic blood pressure in the group of patients treated with garlic; moreover, in the subgroup of patients with hypertension it has been found a mean reduction in systolic blood pressure and diastolic pressure [58].

Garlic reduces the lipogenic and cholesterogenic activities of enzymes such as malic enzyme, fatty acid synthase, glucose-6 phosphate dehydrogenase, and 3-hydroxy-3-methyl-glutaryl CoA (HMGCoA) reductase in liver cells. Enhanced the excretion of acidic and neutral steroids and exert hypocholesterolemia effects in cholesterol-fed rats [59].

In a recent study of 43 subjects [60], the intake of aged garlic extract for 12 weeks has proved to be effective in increasing the levels of adiponectin, inversely associated to both body weight and cardiovascular disease risk [61].

Anti-obesity garlic is a result of its ability to activate AMP-activated protein kinase (AMPK). AMPK activation led to increase thermogenesis and decreased expression of multiple genes involved in adipogenesis, 1,2-vinyldithiin, reduced lipid accumulation by decreasing the expression of CCAAT-enhancer-binding proteins a (C/EBPα), PPARg2, and lipoprotein lipase (LPL) [62].

Allium cepa Linn (Onion) is rich in sulfur-containing compounds and is used as foodstuff, condiment, flavoring and folk medicine. Sulfur-containing compounds in onion may be volatiles and non-volatiles. When cutting onions, volatile compounds such as dialk (en)yl disulfides and dialk(en)yl trisulfides provide the characteristic flavor and odor through the action of alliinase (E.C. 4.4.1.4, S-alk(en)yl-L-cysteine sulfoxide lyase). Non-volatile cysteine sulfoxides (such as S-methyl-L-cysteine sulfoxide, S-propyl-L-cysteine sulfoxide and S-allyl-L-cysteine sulfoxide) are known as the precursors of the volatile compounds. Onion contains a considerable amount of compounds highly beneficial for human health [63].

Onion has been reported to exert moderately hypolipidemic effects on experimental animals such as healthy pigs fed a high-fat diet and consequently reduction of cardiovascular disease risk and obesity [64-65].

Among bioactive compounds involved in this effect, are quercetin that reduce serum cholesterol levels [66] and S-methyl cysteine sulfoxide with hypoglycemic effect [67-69]. It was inferred that the beneficial in hyperglycemia in part due inhibiting alpha-glucosidase activity and reduce lipid peroxidation [70].

The administration of peel hydroalcoholic extract for 3 weeks reduced the blood pressure via inhibition of calcium influx but without involving nitric oxide [71].

Persea americana (Avocado): anti-obesity effects have been reported for both the leaf and fruit. Aqueous, methanolic, hydro-alcoholic fruit and leaves extracts (10 and 100 mg/kg body weight) for 8 and 14 weeks in hypercholesterolemia albino rats and rats fed at high-fat diet (23 % fat), caused reduction in the body weight gain and body mass index compared to the control [72-73]. This effect was attributed o the up-regulation of PPAR-γ. Chemical constituent's alkanols (aliphatic acetogenins), terpenoid glycosides, various furan ring-containing derivatives, flavonoids, and a coumarin [74].

The administration of aqueous and methanolic leaves extracts for 8 and weeks in albino rats with hypercholesterolemia improved the concentration of blood glucose and lipid profile [75-76].

Hypotensive activity: the intravenous administration of doses of leaf aqueous and methanol extract of *P. americana* to normotensive anesthetized rats produced dose-related hypotensive effects, vasorelaxant activity in the rings of rat aorta with intact endothelium was significantly reduced by L-NAME and methylene blue, the vasorelaxant effect may also be produced by the inhibition of Ca^{2+} mobilization through voltage-dependent channels and, to a lesser extent, through receptor-operated channels [77].

Citrus fruits such as oranges (*Citrus sinensis*), mandarin (*Citrus reticulata*), grapefruit (*Citrus paradisi*) and lemon (*Citrus limon*), are especially rich in flavonoids, mainly naringenin, which according to fruits this flavonoid content varies.

Administration of lemon peel for 12 weeks, rats with high fat intake, decreases body weight gain through, induce expression of enzymes involved in β-oxidation, as acyl-CoA oxidase and fatty acid synthase in the liver and adipose tissue. Administration of naringenin (0.003%, 0.006%, and 0.012%) for 6 weeks reduced adiposity, plasma triglycerides and cholesterol because it induces increased expression in liver enzymes of carnitine palmitoyltransferase 1 protein (CPT -1), and decoupling 2, 3 hydroxy-3- methylglutaryl-CoA (HMG-CoA). *Citrus paradisi* has been used as an aid in weight reduction, inhibiting adipogenesis in subcutaneous rat adipocytes. The consumption of fresh fruit before eating any food has an effect on body weight loss, in addition to improving insulin resistance in humans [78-80]. Other effects exhibited naringenin is prevention of lipid peroxidation and oxidative stress because it enhances the antioxidant activity of superoxide dismutase, catalase and glutathione peroxidase, which improves endothelial function through increasing the production of nitric oxide and inhibits proliferation of smooth muscle cells by TNF-α.

The administration of lyophilized *C. sinensis* juice at a dose of 5 g/kg in aqueous vehicle in a volume of 0.5 mL/100 g body weight for 15 days on male Wistar rats, decreased plasma levels of cholesterol, LDL and triglycerides. Microsized insoluble fibers of fruits lowered the concentrations of serum triglycerides and serum total cholesterol by means of enhancing the excretion of cholesterol and bile acids in feces [81].

The effects of citrange (*C. sinensis* × *Poncirus trifoliata*) fruit extracts in high-fat (HF) diet-induced obesity showed citrange peel extract or citrange flesh for 8 weeks. The body weight, blood glucose, serum total cholesterol and LDL cholesterol decreased levels through inhibition of PPARγ and liver X receptor (LXR) α and β, involved in lipid and glucose metabolism [82].

The drinking of commercial decreased diastolic and systolic blood pressure in healthy volunteers using 500 mL/day of orange juice twice a day during four-weeks. However, the administration of natural *Citrus sinensis* juice during four weeks did not have significant effects on either diastolic or systolic blood pressure [83].

Punica granatum (Pomegranate): Juice, seed oil, and flower extracts are rich in many compounds such as proanthocyanidin and ellagitannins [84]. The pomegranate seeds contain high concentration of conjugated fatty acids such as linoleic, linolenic, punicic, stearic and palmitic acid. Minor amounts of conjugated linolenic acid isomers including eleostearic and catalpic acid, are found [85].

Administration punic acid (800 mg / day), seed oil (400 mg) twice daily, for 4 weeks to patients with hyperlipidemia, they reduced the plasma concentration of triglycerides and HDL, cholesterol, LDL-C and glucose unmodified [86].

The anti-obesity effect mechanism reported for flower is at least in part, by activating hepatic expression of genes responsible for fatty acid oxidation. Other anti-obesity mechanisms reported for is inhibition of the pancreatic lipase activity, suppressing energy intake by appetite suppressant [87].

2. The anti-diabetic effect was reported that hydro-ethanolic extract of flowers at 200, 300 and 500 mg/kg/day for 18 days and 6 weeks in obese Zucker and streptozotocin-induced diabetic rats, reduced the serum glucose, cholesterol, triglycerides, LDL, urea, uric acid, creatinine, alanine amino transferase and aspartate amino transferase enzymes levels, while it increased serum HDL level in comparison to control diabetic rats [88].

The antihypertensive effect of juice (100 mg/kg) for 4 weeks decreases systolic blood pressure through to inhibit the activity of angiotensin converting enzyme [89].

Psidium guajava Linn. (guava): is native to tropical and subtropical countries. Its fruit is commonly used as food and processed as juice and aqueous leaf extract caused hypotension in the experimental animal model used via cholinergic mechanisms [90]. Moreover, acute intravenous administrations of the leaf extract (50–800 mg/kg i.v.) produced dose-dependent, reductions in systemic arterial blood pressures and heart rates of hypertensive, Dahl salt-sensitive rats [90]. The proposed mechanism for this effect is through activation of an alpha-adrenoceptor and to a lesser extent by acting via calcium ion channel [90].

Guava contains high levels of dietary fibre and could have health potential in the management of blood glucose level; administration of ethanol extract, (250 mg) decoction of leaves, aqueous leaf extract (0.01–0.625 mg/ml) or capsules (500 mg) on alloxan-induced diabetic rat or diabetic patients, reduced blood glucose level, but is devoid of hypoglycemia effect in normal and normal glucose loaded rats [91]. Tannins, flavonoids, pentacyclic triterpenoids, guiajaverin and quercetin present in the plant are speculated to account for the observed hypoglycemia and hypotensive effects leaf extract [91].

Guava is an excellent anti-LDL glycative agent [92-93] the aqueous (0.01–0.625 mg/ml) and methanol (10 mg/kg) exhibit excellent antiglycation effect, being a rather powerful and effective inhibitor of LDL glycation in both glucose and glyoxal induced models. The antiglycation activities directly related with polyphenolic content (extractable polyphenols 2.62–7.79%). In patients shown that consumption of 400 g / day guava it reduces levels of blood cholesterol and oxidative stress [94].

Malus domestica (Apples) are the fourth most widely produced fruit and approximately 20% of the freshly harvested apples are used for juice production. Apple pomace, the press residue from juice production, represents a mixture of flesh, stem, seeds and peel and is used, for example, as animal feed [95] for the production of pectin, ethanol, natural gas, or citric acid [96] But apple pomace also represents a rich and especially cheap source of polyphenolic compounds, one of the polyphenol compounds in apples is phlorizin, which is relatively stable during drying and long-term storage [97]. The main biological effect of phlorizin is the competitive inhibition of intestinal glucose uptake and renal glucose re-absorption via the sodium d-glucose co-transporters 1 and 2 (SGLT1 and SGLT2) located in the proximal renal tubule [98]. Similar to other inhibitors of SGLT, phlorizin inhibits the re-uptake of glucose in the kidneys and thus lowers the plasma glucose concentration and increases the renal excretion of glucose. Transporter-mediated uptake of glucose accounts for most intestinal glucose uptake under physiological conditions, and phlorizin effectively abolishes intestinal glucose uptake. In addition to its direct anti-hyperglycaemia effect, phlorizin mediates several other pharmacological activities. For example, phlorizin promoted lipolysis and inhibited inflammation in macrophage–adipocyte co-cultures [99-100]. Furthermore, apple polyphenols and phlorizin have been suggested as new trapping agents of reactive dicarbonyl species, which might delay the formation of advanced glycation end-products (AGEs) [100].

Procyanidin-rich apple polyphenol extract to attenuate disruptions in lipid membranes and lipid metabolism resulting from exposure to dietary cholesterol oxidation products [101]. Feeding the extract to rats for 3 wk resulted in reduction markers of lipid metabolism including reduced lipoperoxides (measured by TBARS) in serum and liver, lowered SOD activity in RBC, lower hepatic Δ6 desaturase activity, altered fecal excretion patterns, and reduced levels of oxidized cholesterol products in serum and liver. Plasma levels of HDL cholesterol increased and liver TG content decreased, although plasma TG levels were somewhat higher, so that the high procyanidin content and metabolites in the apple extract might directly interfere with cholesterol absorption in addition to modulating lipids and lipid-related processes.

In vitro work in cultured human intestinal cells suggested that apples may directly alter lipid absorption and metabolism. Caco-2/TC7 cells were exposed to apple extract, including a polyphenolic concentration equivalent to the consumption of 3apples/d. It was found that the accumulation of esterified cholesterol decreased and the secretion of apo-B (B-48 and B-100) containing lipoproteins was reduced. Similar results were found in cells exposed to an enriched extract of procyanidins (flavanols, catechin, and epicatechin). If these findings are applicable to the in vivo situation, altered intestinal lipid secretion might account for the lipid-lowering effect of AP observed in some studies and suggest one possible mechanism for reduced risk of cardiovascular disease [101].

Antihypertensive effect. On clinical trials, reported that consumption of 425.8 mg epicatechin for 2 weeks decreased blood pressure in hypertension subjects [102].

Lagenaria siceraria is known as Gourd, pumpkin pilgrim,

spoon, waist gourd, calabash, guicola raft, acinturiao bule, itsui, pumaxkat, xical, xicale, buli. xomom, kweentu. Various parts of bottle gourd were utilized as medicines by many peoples around the world.

Administration of fresh bottle gourd juice to healthy volunteers received reduced plasma glucose and cholesterol. Other studies showed that the pulp and seed extract stimulate insulin secretion of pancreatic beta cells, followed by the decrease of blood glucose [103-104].

Anti- hyperlipidemia activity: The cardiotonic and cardioprotective effects were assayed by the methanolic extracts in hyperlipidaemic induced rats. The lipid level in rats were reduced gradually after 30 days of evaluation and observed *L. siceraria* fruits have a capacity to increase the excretion of bile salts [105].

Antihypertensive activity: *L. siceraria* fruit powder administered in the dexamethasone-induced rats on long term, decrease in the hypertensive activity in *lagenaria* siceraria rats [106], and other study showed administration of fruit (500 mg/kg) antihypertensive and cardioprotective activity inhibition of nitric oxide synthesis induced hypertension in rats [107].

Conclusion

The severity of metabolic syndrome per se as well as its complications and the global rise of people affected encourage research and search for new drugs that help control. Mexican ethnobotany offers scientific study of plants used empirically to validate experimentally the effects.

References

1. Ma X, Zhu S. Metabolic syndrome in the prevention of cardiovascular diseases and diabetes--still a matter of debate?. Eur J Clin Nutr. 2013; 67(5):518-21.
2. Salas R, Bibiloni Mdel M, Ramos E, Villarreal JZ, Pons A, Tur JA *et al*. Metabolic syndrome prevalence among Northern Mexican adult population. PLoS One. 2014; 20:9(8):e105581.
3. Spalding A, Kernan J, Lockette W. The metabolic syndrome: a modern plague spread by modern technology. J Clin Hypertens (Greenwich). 2009; 11(12):755-760.
4. Isordia-Salas I, Santiago-Germán D, Rodrìguez-Navarro H, Almaráz-Delgado M, Leaños-Miranda *et al*. Prevalence of metabolic syndrome components in an urban Mexican sample: comparison between two classifications. Exp Diabetes Res. 2012, 202540.
5. Raalte DHV, Diamant M. Glucolipotoxicity and beta cells in type 2 diabetes mellitus: target for durable therapy? Diabet Res Clin Pract. 2011; 93:S37-S46.
6. Mazzola N. Review of current and emerging therapies in type 2 diabetes mellitus. Am J Manag Care. 2012; 18(1 Suppl):S17-26.
7. Rochette L, Zeller M, Cottin Y, Vergely C. Diabetes, oxidative stress and therapeutic strategies. Biochim Biophys Acta. 2014; 1840(9):2709-29.
8. De Jager J, Kooy A, Schalkwijk C, van der Kolk J, Lehert P, Bets D, *et al*. Long-term effects of metformin on endothelial function in type 2 diabetes: a randomized controlled trial. J Intern Med. 2014; 275(1):59-70.
9. Tabatabaei-Malazy O, Larijani B, Abdollahi M. Targeting metabolic disorders by natural products. J Diabetes Metab Disord. 2015; 8:14:57.
10. Shyangdan DS, Uthman OA, Waugh Nb. SGLT-2 receptor inhibitors for treating patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. BMJ Open. 2016; 24:6(2):e009417.
11. Kumar A, Kumar A, Jaggi AS, Singh N. Efficacy of Cilostazol a selective phosphodiesterase-3 inhibitor in rat model of Streptozotocin diabetes induced vascular dementia. Pharmacol Biochem Behav. 2015; 135:20-30.
12. Greenwell M, Rahman PK. Medicinal Plants: Their Use in Anticancer Treatment. Int J Pharm Sci Res. 2015; 1:6(10):4103-4112.
13. Atanasov AG, Waltenberger B, Pferschy-Wenzig EM, Linder T, Wawrosch C, Uhrin P *et al*. Discovery and resupply of pharmacologically active plant-derived natural products: A review. Biotechnol Adv. 2015; 33(8):1582-614.
14. Jimenez-Estrada M, Merino-Aguilar H, Lopez-Fernandez A, Rojano-Vilchis NA, Roman-Ramos R, Alarcon-Aguilar FJ. Chemical characterization and evaluation of the hypoglycemic effect of fructooligosaccharides from Psacalium decompositum. J Complement Integr Med. 2011; 8:1413-1423.
15. Merino-Aguilar H, Arrieta-Baez D, Jiménez-Estrada M, Magos-Guerrero G, Hernández-Bautista RJ, Susunaga-Notario Adel C, *et al*. Effect of fructooligosaccharides fraction from Psacalium decompositum on inflammation and dyslipidemia in rats with fructose-induced obesity. Nutrients. 2014; 29, 6(2):591-604
16. Romero-Cerecero H, Reyes-Morales L, Aguilar-Santamaría M, Huerta-Reyes J, Tortoriello-García. Use of medicinal plants among patients with diabetes mellitus type 2 in Morelos, Mexico. BLACPMA. 2009; 8(5):380-388.
17. Ovalle-Magallanes B, Medina-Campos ON, Pedraza-Chaverri J, Mata R. Hypoglycemic and antihyperglycemic effects of phytopreparations and limonoids from Swietenia humilis. Phytochemistry. 2015; 110:111-9.
18. Ekor M, Adesanoye OA, Udo IE, Adegoke OA, Raji J, Farombi EO. Hibiscus sabdariffa ethanolic extract protects against dyslipidemia and oxidative stress induced by chronic cholesterol administration in rabbits. Afr J Med Med Sci. 2010; 39Suppl:161-70.
19. Ochani PC, D'Mello P. Antioxidant and antihyperlipidemic activity of Hibiscus sabdariffa Linn. Leaves and calyces extracts in rats. Indian J Exp Biol. 2009; 47(4):276-82.
20. Yang MY, Peng CH, Chan KC, Yang YS, Huang CN, Wang CJ. The hypolipidemic effect of Hibiscus sabdariffa polyphenols via inhibiting lipogenesis and promoting hepatic lipid clearance. J Agric Food Chem. 2010; 27, 58(2):850-9.
21. Chang YC, Huang KX, Huang AC, Ho YC, Wang CJ. Hibiscus anthocyanins-rich extract inhibited LDL oxidation and oxLDL-mediated macrophages apoptosis. Food Chem Toxicol. 2006; 44(7):1015-23.
22. Lee CH, Kuo CY, Wang CJ, Wang CP, Lee YR, Hung CN *et al*. A polyphenol extract of Hibiscus sabdariffa L. ameliorates acetaminophen-induced hepatic steatosis by attenuating the mitochondrial dysfunction in vivo and in vitro. Biosci Biotechnol Biochem. 2012; 76(4):646-51.
23. Alarcon-Aguilar FJ, Zamilpa A, Perez-Garcia MD, Almanza-Perez JC, Romero-Nuñez E, Campos-Sepulveda EA *et al*. Effect of Hibiscus sabdariffa on obesity in MSG mice. J Ethnopharmacol. 2007; 8, 114(1):66-71.
24. Kim JK, So H, Youn MJ, Kim HJ, Kim Y, Park C *et al*. Hibiscus sabdariffa L. water extract inhibits the adipocyte differentiation through the PI3-K and MAPK pathway. J Ethnopharmacol. 2007; 1; 114(2):260-7.

25. Preuss HG, Echard B, Bagchi D, Stohs S. Inhibition by natural dietary substances of gastrointestinal absorption of starch and sucrose in rats and pigs: 1. Acute studies. Int J Med Sci. 2007; 6; 4(4):196-202.
26. Carvajal-Zarrabal O, Hayward-Jones PM, Orta-Flores Z, Nolasco-Hipólito C, Barradas-Dermitz DM, Aguilar-Uscanga MG *et al*. Effect of Hibiscus sabdariffa L. dried calyx ethanol extract on fat absorption-excretion, and body weight implication in rats. J Biomed Biotechnol. 2009, 394592.
27. Herranz-López M, Fernández-Arroyo S, Pérez-Sanchez A, Barrajón-Catalán E, Beltrán-Debón R, Menéndez JA *et al*. Synergism of plant-derived polyphenols in adipogenesis: perspectives and implications. Phytomedicine. 2012; 15; 19(3-4):253-61.
28. Peng CH, Chyau CC, Chan KC, Chan TH, Wang CJ, Huang CN. Hibiscus sabdariffa polyphenolic extract inhibits hyperglycemia, hyperlipidemia, and glycation-oxidative stress while improving insulin resistance. J Agric Food Chem. 2011; 28, 59(18):9901-9.
29. Adisakwattana S, Ruengsamran T, Kampa P, Sompong W. *In vitro* inhibitory effects of plant-based foods and their combinations on intestinal α-glucosidase and pancreatic α-amylase. BMC Complement Altern Med. 2012; 31(12):110.
30. Yamada T, Hida H, Yamada Y. Chemistry, physiological properties, and microbial production of hydroxycitric acid. Appl Microbiol Biotechnol. 2007; 75(5):977-82.
31. Hansawasdi C, Kawabata J, Kasai T. Alpha-amylase inhibitors from roselle (Hibiscus sabdariffa Linn.) tea. Biosci Biotechnol Biochem. 2000; 64(5):1041-3.
32. Hansawasdi C, Kawabata J, Kasai T. Hibiscus acid as an inhibitor of starch digestion in the Caco-2 cell model system. Biosci Biotechnol Biochem. 2001; 65(9):2087-9.
33. Farombi EO, Ige OO. Hypolipidemic and antioxidant effects of ethanolic extract from dried calyx of Hibiscus sabdariffa in alloxan-induced diabetic rats. Fundam Clin Pharmacol. 2007; 21(6):601-9.
34. Ajay M, Chai HJ, Mustafa AM, Gilani AH, Mustafa MR. Mechanisms of the anti-hypertensive effect of Hibiscus sabdariffa L. calyces. J Ethnopharmacol. 2007; 12, 109(3):388-93.
35. Inuwa I, Ali BH, Al-Lawati I, Beegam S, Ziada A, Blunden G. Long-term ingestion of Hibiscus sabdariffa calyx extract enhances myocardial capillarization in the spontaneously hypertensive rat. Exp Biol Med 2012; 237(5):563-9.
36. Aliyu B, Oyeniyi YJ, Mojiminiyi FB, Isezuo SA, Alada AR. The Aqueous Calyx Extract of Hibiscus sabdariffa Lowers Blood Pressure and Heart Rate via Sympathetic Nervous System Dependent Mechanisms. Niger J Physiol Sci. 2014; 29(2):131-6.
37. Herrera-Arellano A, Miranda-Sánchez J, Avila-Castro P, Herrera-Alvarez S, Jiménez-Ferrer JE, Zamilpa A *et al*. Clinical effects produced by a standardized herbal medicinal product of Hibiscus sabdariffa on patients with hypertension. A randomized, double-blind, lisinopril-controlled clinical trial. Planta Med. 2007; 73(1):6-12.
38. Ojeda D, Jiménez-Ferrer E, Zamilpa A, Herrera-Arellano A, Tortoriello J, Alvarez L. Inhibition of angiotensin convertin enzyme (ACE) activity by the anthocyanins delphinidin- and cyanidin-3-O-sambubiosides from Hibiscus sabdariffa. J Ethnopharmacol. 2010; 8, 127(1):7-10.
39. Inuwa I, Ali BH, Al-Lawati I, Beegam S, Ziada A, Blunden G. Long-term ingestion of Hibiscus sabdariffa calyx extract enhances myocardial capillarization in the spontaneously hypertensive rat. Exp Biol Med (Maywood). 2012; 237(5):563-9.
40. McKay DL, Chen CY, Saltzman E, Blumberg JB. Hibiscus sabdariffa L. tea (tisane) lowers blood pressure in prehypertensive and mildly hypertensive adults. J Nutr. 2010; 140(2):298-303.
41. Mozaffari-Khosravi H, Ahadi Z, Barzegar K. The effect of green tea and sour tea on blood pressure of patients with type 2 diabetes: a randomized clinical trial. J Diet Suppl. 2013; 10(2):105-15.
42. Alarcon-Aguilar FJ, Campos-Sepulveda S, Xolalpa-Molina E, Hernandez-Galicia R. Roman-Ramos. Hypoglycaemic activity of *Ibervillea sonorae* roots in healthy and diabetic mice and rats. Pharmaceutical Biology. 2002; 40:570-575.
43. Zapata-Bustos R, Alonso-Castro AJ, Gómez-Sánchez M, Salazar-Olivo LA. Ibervillea sonorae (Cucurbitaceae) induces the glucose uptake in human adipocytes by activating a PI3K-independent pathway. J Ethnopharmacol. 2014; 28, 152(3):546-52.
44. Rivera-Ramírez F, Escalona-Cardoso GN, Garduño-Siciliano L, Galaviz-Hernández C, Paniagua-Castro N. Antiobesity and hypoglycaemic effects of aqueous extract of Ibervillea sonorae in mice fed a high-fat diet with fructose. J Biomed Biotechnol. 2011, 968984.
45. Bora KS, Sharma A. Phytochemical and pharmacological potential of Medicago sativa: a review. Pharm Biol. 2011; 49(2):211-20.
46. Shi Y, Guo R, Wang X, Yuan D, Zhang S, Wang J *et al*. The regulation of alfalfa saponin extract on key genes involved in hepatic cholesterol metabolism in hyperlipidemic rats. PLoS One. 2014; 5, 9(2):e88282.
47. Mohamed B, Abderrahim Z, Hassane M, Abdelhafid T, Abdelkhaleq L. Medicinal plants with potential antidiabetic activity A review of ten years of herbal medicine research (1990–2000). Int J Diab Metab. 2006; 14:1-25.
48. Seida A, El-Hefnawy H, Abou-Hussein D, Mokhtar FA, Abdel-Naim A. Evaluation of Medicago sativa L. sprouts as antihyperlipidemic and antihyperglycemic agent. Pak J Pharm Sci. 2015; 28(6):2061-74.
49. Schütz K, Muks E, Carle R, Schieber A. Separation and quantification of inulin in selected artichoke (Cynara scolymus L.) cultivars and dandelion (Taraxacum officinale WEB. ex WIGG.) roots by high-performance anion exchange chromatography with pulsed amperometric detection. Biomed Chromatogr. 2006; 20(12):1295-303.
50. Zhang J, Kang MJ, Kim MJ, Kim ME, Song JH, Lee YM *et al*. Pancreatic lipase inhibitory activity of taraxacum officinale *in vitro* and *in vivo*. Nutr Res Pract. 2008; 2(4):200-3.
51. Davaatseren M, Hur HJ, Yang HJ, Hwang JT, Park JH, Kim HJ *et al*. Taraxacum official (dandelion) leaf extract alleviates high-fat diet-induced nonalcoholic fatty liver. Food Chem Toxicol. 2013; 58:30-6.
52. Petlevski R, Hadzija M, Slijepcevic M, Juretic D. Effect of antidiabetis herbal preparation on serum glucose and fructosamine in NOD mice. J Ethnopharmacol. 2001; 75(2-3):181-4.
53. Choi UK, Lee OH, Yim JH, Cho CW, Rhee YK, Lim SI *et al*. Hypolipidemic and antioxidant effects of dandelion (Taraxacum officinale) root and leaf on cholesterol-fed

rabbits. Int J Mol Sci. 2010; 6, 11(1):67-78.
54. Onal S, Timur S, Okutucu B, Zihnioğlu F. Inhibition of alpha-glucosidase by aqueous extracts of some potent antidiabetic medicinal herbs. Prep Biochem Biotechnol 2005; 35(1):29-36.
55. Hosseini A, Hosseinzadeh H. A review on the effects of Allium sativum (Garlic) in metabolic syndrome. J Endocrinol Invest. 2015; 38(11):1147-57.
56. Ried K, Fakler P. Potential of garlic (Allium sativum) in lowering high blood pressure: mechanisms of action and clinical relevance. Integr Blood Press Control. 2014; 9, 7:71-82.
57. Butt MS, Sultan MT, Butt MS, Iqbal J. Garlic: nature's protection against physiological threats. Crit Rev Food Sci Nutr. 2009; 49(6):538-51.
58. Ried K, Frank OR, Stocks NP. Aged garlic extract lowers blood pressure in patients with treated but uncontrolled hypertension: a randomised controlled trial. Maturitas. 2010; 67(2):144-50.
59. Ha AW, Ying T, Kim WK. The effects of black garlic (Allium satvium) extracts on lipid metabolism in rats fed a high fat diet. Nutr Res Pract. 2015; 9(1):30-6.
60. Gómez-Arbeláez D, Lahera V, Oubiña P, Valero-Muñoz M, de Las Heras N, Rodríguez Y *et al*. Aged garlic extract improves adiponectin levels in subjects with metabolic syndrome: a double-blind, placebo-controlled, randomized, crossover study. Mediators Inflamm. 2013, 2013:285795.
61. Sobenin IA, Andrianova IV, Demidova ON, Gorchakova T, Orekhov AN. Lipid-lowering effects of time-released garlic powder tablets in double-blinded placebo-controlled randomized study. J Atheroscler Thromb. 2008; 15(6):334-8.
62. Keophiphath M, Priem F, Jacquemond-Collet I, Cle´ment K, Lacasa D. 1, 2-Vinyldithiin from garlic inhibits differentiation and inflammation of human preadipocytes. J Nutr. 2009; 139:2055-2060.
63. Akash MS, Rehman K, Chen S. Spice plant Allium cepa: dietary supplement for treatment of type 2 diabetes mellitus. Nutrition. 2014; 30(10):1128-37.
64. Ostrowska E, Gabler NK, Sterling SJ, Tatham BG, Jones RB, Eagling DR *et al*. Consumption of brown onions (Allium cepa var. cavalier and var. destiny) moderately modulates blood lipids, haematological and haemostatic variables in healthy pigs. Br J Nutr. 2004; 91(2):211-8.
65. Gabler NK, Osrowska E, Imsic M, Eagling DR, Jois M, Tatham BG *et al*. Dietary onion intake as part of a typical high fat diet improves indices of cardiovascular health using the mixed sex pig model. Plant Foods Hum Nutr. 2006; 61(4):179-85.
66. Glasser G, Graefe EU, Struck F, Veit M, Gebhardt R. Comparison of antioxidative capacities and inhibitory effects on cholesterol biosynthesis of quercetin and potential metabolites. Phytomedicine. 2002; 9:33-40.
67. Srinivasan K. Plant foods in the management of diabetes mellitus: Spices as beneficial antidiabetic food adjuncts. Int. J Food Sci. Nutr. 2005; 56:399-414.
68. Kumari K, Augusti KT. Lipid lowering effect of S-methyl cysteine sulfoxide from Allium cepa Linn in high cholesterol diet fed rats. J Ethnopharmacol. 2007; 109:367-371.
69. Lee SU, Lee JH, Choi SH, Lee JS, Ohnisi-Kameyama M, Kozukue N *et al*. Flavonoid content in fresh, home-processed, and light-exposed onions and in dehydrated commercial onion products. J. Agric. Food Chem. 2008; 56:8541-8548.
70. El-Demerdash FM, Yousef MI, Abou El-Naga NI. Biochemical study on the hypoglycemic effects of onion and garlic in alloxan-induced diabetic rats. Food Chem. Toxicol. 2005; 43:57-63.
71. Naseri MK, Arabian M, Badavi M, Ahangarpour A. Vasorelaxant and hypotensive effects of Allium cepa peel hydroalcoholic extract in rat. Pak J Biol Sci. 2008; 15, 11(12):1569-75.
72. Brai BI, Odetola AA, Agomo PU. Hypoglycemic and hypocholesterolemic potential of Persea americana leaf extracts. J Med Food. 2007; 10(2):356-60.
73. Padmanabhan M, Arumugam G. Effect of Persea americana (avocado) fruit extract on the level of expression of adiponectin and PPAR-γ in rats subjected to experimental hyperlipidemia and obesity. J Complement Integr Med. 2014; 11(2):107-19.
74. Yasir M, Das S, Kharya MD. The phytochemical and pharmacological profile of Persea americana Mill. Pharmacogn Rev. 2010; 4(7):77-84.
75. Brai BI, Odetola AA, Agomo PU. Hypoglycemic and hypocholesterolemic potential of Persea americana leaf extracts. J Med Food. 2007; 10(2):356-60.
76. Ezejiofor AN, Okorie A, Orisakwe OE. Hypoglycaemic and tissue-protective effects of the aqueous extract of persea americana seeds on alloxan-induced albino rats. Malays J Med Sci. 2013; 20(5):31-9.
77. Owolabi MA, Jaja SI, Coker HA. Vasorelaxant action of aqueous extract of the leaves of Persea americana on isolated thoracic rat aorta. Fitoterapia. 2005; 76(6):567-73.
78. Fujioka K, Greenway F, Sheard J, Ying Y. The effects of grapefruit on weight and insulin resistance: relationship to the metabolic syndrome. J Med Food. 2006; 9:49-54
79. Owira PM, Ojewole JA. Grapefruit juice improves glycemic control but exacerbates metformin-induced lactic acidosis in non-diabetic rats. Methods Find Exp Clin Pharmacol. 2009; 31(9):563-70.
80. Haze S, Sakai K, Gozu Y, Moriyama M. Grapefruit oil attenuates adipogenesis in cultured subcutaneous adipocytes. Planta Med. 2010; 76(10):950-5.
81. Wu SC, Wu SH, Chau CF. Improvement of the hypocholesterolemic activities of two common fruit fibers by micronization processing. J Agric Food Chem. 2009; 24, 57(12):5610-4.
82. Lu Y, Xi W, Ding X, Fan S, Zhang Y, Jiang D *et al*. Citrange fruit extracts alleviate obesity-associated metabolic disorder in high-fat diet-induced obese C57BL/6 mouse. Int J Mol Sci. 2013; 5, 14(12):23736-50.
83. Asgary S, Keshvari M. Effects of Citrus sinensis juice on blood pressure. ARYA Atheroscler. 2013; 9(1):98-101.
84. Viuda-Martos M, Fernandez-Lopez J, Perez-Alvarez JA. Pomegranate and its many functional components as related to human health: a review. Compr Rev Food Sci F. 2010; 9:635-54.
85. Vroegrijk IO, van Diepen JA, van den Berg S, Westbroek I, Keizer H *et al*. Pomegranate seed oil, a rich source of punicic acid, prevents diet-induced obesity and insulin resistance in mice. Food Chem Toxicol. 2011; 49:1426-30.
86. Mirmiran P, Fazeli MR, Asghari G, Shafiee A, Azizi F. Effect of pomegranate seed oil on hyperlipidaemic subjects:a double-blind placebo-controlled clinical trial. Brit J Nutr. 2010; 104:402-6.
87. Lei F, Zhang XN, Wang W, Xing DM, Xie WD, Su H.

Evidence of anti-obesity effects of the pomegranate leaf extract in high-fat diet induced obese mice. Int J Obes 2007; 3:1023-9.
88. Eidi M. Antidiabetic effect of Punica granatum L. hydro-ethanolic extract in streptozotocin-induced diabetic rats. Adv Biores. 2014; 5:81-7.
89. Mohan M, Waghulde H, Kasture S. Effect of pomegranate juice on Angiotensin II-induced hypertension in diabetic Wistar rats. Phytother Res. 2010; 24 (Suppl 2):S196-203.
90. Mukhtar HM, Ansari SH, Bhat ZA, Naved T, Singh P. Antidiabetic activity of an ethanol extract obtained from the stem bark of Psidium guajava (Myrtaceae). Pharmazie. 2006; 61(8):725-7.
91. Deguchi Y, Miyazaki K. Anti-hyperglycemic and anti-hyperlipidemic effects of guava leaf extract. Nutr Metab (Lond). 2010; 2(7):9.
92. Ojewole JA. Hypoglycemic and hypotensive effects of Psidium guajava Linn. (Myrtaceae) leaf aqueous extract. Methods Find Exp Clin Pharmacol. 2005; 27(10):689-95.
93. Mukhtar HM, Ansari SH, Ali M, Naved T, Bhat ZA. Effect of water extract of Psidium guajava leaves on alloxan-induced diabetic rats. Pharmazie. 2004; 59(9):734-5.
94. Hsieh CL, Yang MH, Chyau CC, Chiu CH, Wang HE, Lin YC *et al*. Kinetic analysis on the sensitivity of glucose- or glyoxal-induced LDL glycation to the inhibitory effect of Psidium guajava extract in a physiomimic system. Biosystems. 2007; 88(1-2):92-100.
95. Vendruscolo F, Albuquerque PM, Streit F, Esposito E, Ninow JL. Apple pomace: a versatile substrate for biotechnological applications. Crit Rev Biotechnol. 2008; 28(1):1-12.
96. Gullón B, Garrote G, Alonso JL, Parajó JC. Production of L-lactic acid and oligomeric compounds from apple pomace by simultaneous saccharification and fermentation: a response surface methodology assessment. J Agric Food Chem. 2007; 11, 55(14):5580-7.
97. Lavelli V, Vantaggi C, Corey M, Kerr W. Formulation of a dry green tea-apple product: study on antioxidant and color stability. J Food Sci. 2010; 75(2):C184-90.
98. Boyer J, Brown D, Liu RH. Uptake of quercetin and quercetin 3-glucoside from whole onion and apple peel extracts by Caco-2 cell monolayers. J Agric Food Chem. 2004; 17, 52(23):7172-9.
99. Huang WC, Chang WT, Wu SJ, Xu PY, Ting NC, Liou CJ. Phloretin and phlorizin promote lipolysis and inhibit inflammation in mouse 3T3-L1 cells and in macrophage-adipocyte co-cultures. Mol Nutr Food Res, 2013; 57(10):1803-13.
100. Shao X, Bai N, He K, Ho CT, Yang CS, Sang S. Apple polyphenols, phloretin and phloridzin: new trapping agents of reactive dicarbonyl species. Chem Res Toxicol 2008; 21(10):2042-50.
101. Ogino Y, Osada K, Nakamura S, Ohta Y, Kanda T, Sugano M. Absorption of dietary cholesterol oxidation products and their downstream metabolic effects are reduced by dietary apple polyphenols. Lipids. 2007; 42(2):151-61.
102. Balasuriya N, Rupasinghe HP. Antihypertensive properties of flavonoid-rich apple peels extract. Food Chem. 2012; 15, 135(4):2320-5.
103. Bhattacharya S, Das B. Anti-diabetic activity of Lagenaria siceraria pulp and seed extract in normal and alloxan-induced diabetic rats. Int J Pharm Sci Res. 2012; 3:3362-3369.
104. Charu K, Sonali S, Supriya A, Prasad GBKS. Alleviation of diabetes induced dyslipidemia by Lagenaria siceraria fruit extract in human type 2 diabetes. J Herb Med. 2013; 3:1-8.
105. Ghule BV, Ghante MH, Saoji AN, Yeole PG. Antihyperlipidemic effect of the methanolic extract from Lagenaria siceraria stand. Fruit in hyperlipidemic rats. J Ethnopharmacol. 2009; 124:333-337.
106. Mali VR, Bodhankar SL. Cardioprotective effect of Lagenaria siceraria (LS) fruit powder in isoprenalin-induced cardiotoxicity in rats. Eur J Integr Med. 2010; 2:143-149.
107. Mali VR, Mohan V, Bodhankar SL. Antihypertensive and cardioprotective effects of the Lagenaria siceraria fruit in NG-nitro-L-arginine methyl ester (L-NAME) induced hypertensive rats. Pharm Biol. 2012; 50(11):1428-35