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REVIEW

Novel nutraceutic therapies for the treatment of metabolic syndrome

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Abstract

Nutraceutic therapies such as berberine, bitter melon, *Gymnema sylvestre*, *Irvingia gabonensis*, resveratrol and ursolic acid have been shown to help control metabolic syndrome (MetS). The effect of berberine on glucose and lipid metabolism, hypertension, obesity and MetS has been evaluated in animal models and humans. Most clinical trials involving bitter melon have been conducted to evaluate its effect on glucose metabolism; nevertheless, some studies have reported favorable effects on lipids and blood pressure although there is little information about its effect on body weight. *Gymnema sylvestre* helps to decrease body weight and blood sugar levels; however, there is limited information on dyslipidemia and hypertension. Clinical trials of *Irvingia gabonensis* have shown important effects decreasing glucose and cholesterol concentrations as well decreasing body weight. Resveratrol acts through different mechanisms to decrease blood pressure, lipids, glucose and weight, showing its effects on the population with MetS. Finally, there is evidence of positive effects with ursolic acid in *in vitro* and *in vivo* studies on glucose and lipid metabolism and on body weight and visceral fat. Therefore, a review of the beneficial effects and limitations of the above-mentioned nutraceutic therapies is presented.

Key words: Nutraceutics; Metabolic syndrome; Berberine; Bitter melon; *Gymnema silvestre*; *Irvingia gabonensis*; Resveratrol; Ursolic acid

Core tip: Metabolic syndrome (MetS) is a cluster of endocrine problems including obesity, dysglycemia, dyslipidemia, and hypertension. Unfortunately, there is no unique treatment to control it. Nutraceutic therapies such as berberine, bitter melon, *Gymnema sylvestre*, *Irvingia gabonensis*, resveratrol and ursolic acid have demonstrated some improvement in anthropometric parameters and cardiometabolic risk factors and could

be considered as treatment for patients with MetS. This review attempts to demonstrate the beneficial effects and limitations of some of these novel nutraceutic therapies.

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INTRODUCTION

Metabolic syndrome (MetS) is a cluster of endocrine disturbances including typically obesity, dysglycemia, dyslipidemia, and hypertension, predisposing individuals to increased risk for atherosclerosis, cardiovascular events, and eventually type 2 diabetes mellitus (T2DM)[1]. However, a number of other parameters that appear to be related to MetS, including non-alcoholic fatty liver disease, should be evaluated in some specific cases to help determine the risk of complications[2,3]. Prevalence of MetS is increasing significantly and is becoming a worldwide health problem[4]. Unfortunately, there is no a single treatment to control MetS; frequently, the option is to treat each component separately. Therefore, any substance that helps to control all the characteristic disturbances of MetS must be considered and studied in depth[5]. Nutraceutic therapies such as berberine, bitter melon, *Gymnema sylvestre* (*G. sylvestre*), *Irvingia gabonensis* (*I. gabonensis*), resveratrol and ursolic acid, which are currently being studied in our Research Institute, among many therapies, have demonstrated to improve some anthropometric parameters and cardiometabolic risk factors. In this regard, they could be considered as treatment for patients with MetS. The aim of this review is to show the beneficial effects and limitations of some of these novel nutraceutic therapies.

BERBERINE

Berberine is an isoquinoline quaternary alkaloid (or a 5,6 dihydrodibenzo[*a,g*]quinolizinium derivative) isolated from many medicinal plants such as *Hydrastis canadensis*, *Berberis aristata*, *Coptis chinensis*, *Coptis rhizome*, *Coptis japonica*, *Phellondendron amurense* and *Phellondendron chinense schneid*[6]. Berberine is traditionally used for its supposed antimicrobial effects and as treatment for diabetes in traditional Chinese, Indian and Middle Eastern folk medicine[7] and has definite potential as a drug included in a wide spectrum of clinical applications.

During approximately 500 A.D., Hongjing Tao recorded the anti-diabetes activity of Rhizoma coptidis for the first time in a book entitled "Note of Elite Physicians". In 1988, the hypoglycemic effect of berberine was revealed when berberine was used to treat diarrhea in diabetic patients in China. Since that time, many physicians in China have used berberine as an anti-hyperglycemic agent. There are a substantial number of clinical reports regarding the hypoglycemic action of berberine in Chinese literature reports[8]. A meta-analysis of berberine reported beneficial effects on blood glucose control in the treatment of T2DM patients similar to those obtained with conventional oral antidiabetic treatments[9]. One study confirms that administration of berberine (0.5 g three times/d) at the beginning of each major meal was able to reduce fasting blood glucose as well as postprandial blood glucose in adult patients with newly diagnosed T2DM. Glycated hemoglobin A1c (A1C) level was decreased by 2.0% with berberine treatment, which is comparable to that of metformin. In poorly controlled diabetic patients[8], berberine regulates glucose metabolism possibly through multiple mechanisms and signal pathways such as increasing insulin sensitivity, activating the adenosine monophosphate- (AMP-) activated protein kinase (AMPK) pathway, modulating gut microbiota, inhibiting liver gluconeogenesis, stimulating glycolysis in peripheral tissue cells, promoting intestinal glucagon-like protein-1 secretion, upregulating hepatic low-density lipoprotein receptor mRNA expression, and increasing glucose transporter[10].

The effects of berberine on lipid metabolism have been evaluated in animals and humans. A systematic review and meta-analysis of randomized controlled trials with berberine show that its administration produced a significant reduction in total cholesterol (mean difference -0.61 mmol/L; 95%CI: -0.83 to -0.39), triglycerides (mean difference -0.50 mmol/L; 95%CI: -0.69 to -0.31), and low-density lipoprotein cholesterol (LDL-C) (mean difference -0.65 mmol/L; 95%CI: -0.76 to -0.54) levels, with a remarkable increase in high-density lipoprotein cholesterol (HDL-C) (mean difference 0.05 mmol/L; 95%CI: 0.02 to 0.09)[11]. The lipid-lowering effect of berberine appears to be mainly due to stabilization of hepatic LDL receptor (LDL-R) in an extracellular signal-regulated kinase (ERK)-dependent manner and also by increasing transcriptional activity of LDL-R promoter by c-Jun N-terminal kinase (JNK) pathway. Berberine also activates AMPK while blocking the AMPK/ERK pathway, resulting in inhibition of lipid synthesis[7].

Few reports in the literature affirm that berberine is able to decrease blood pressure in humans; however, vasorelaxant effects of berberine have been observed in different rat models[7]. Vasodilatator effect of berberine is the result of its action on both endothelium and vascular smooth muscle. Other mechanisms suggested to be involved in the vasorelaxant effect of berberine are angiotensin-converting enzyme (ACE) inhibitor effect and direct release of nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) from rat aortic rings, α_1-adrenoreceptor antagonistic action in rat and rabbit aorta, potentiation of acetylcholine, activation

of K^+ channels and inhibition of intracellular calcium release, and blocking of L-type calcium channels[7]. A recent study showed that berberine could delay the onset and attenuate the severity of hypertension as well as to ameliorate hypertension-induced renal damage in spontaneously hypertensive rats (SHR). Furthermore, berberine could inhibit the activities of the renin-angiotensin system and pre-inflammatory cytokines such as interleukin (IL)-6, IL-17 and IL-23, which are involved in the pathophysiology of hypertension[12].

Several clinical studies have reported the effect of berberine on obesity indicators such as body weight reduction, waist circumference or body mass index (BMI). A study in 116 patients with T2DM and dyslipidemia showed that berberine (1.0 g daily) compared with placebo for 3 mo decreased body weight from 68.7 ± 11.3 to 66.4 ± 11.8 kg[13]. This effect could be due to an inhibition of adipogenesis that may contribute to the anti-obesity activity of berberine. Since then, it has been shown to suppress adipocyte differentiation and reduce lipid accumulation in (3T3-L1) adipocytes. In cells treated with berberine, expression of several lipogenic genes including peroxisome proliferator-activated receptor gamma (PPARγ), enhancer-binding protein alpha (EBPα), sterol regulatory element-binding protein 1 (SREBP-1c), fatty acid synthase, acetyl coenzyme A carboxylase, acyl-CoA synthase, lipoprotein lipase, and cluster of differentiation 36 were all suppressed[8].

The above-mentioned findings show that berberine has excellent potential for prevention and treatment of MetS. A randomized, double-blind, placebo-controlled clinical trial carried out by our research group in 24 patients with a diagnosis of MetS showed that, after berberine administration, patients had a remission of 36% (P = 0.037) in the presence of MetS and a significant decrease in waist circumference in females (106 ± 4 cm *vs* 103 ± 3 cm, $P < 0.05$), systolic blood pressure (123 ± 7 mmHg *vs* 115 ± 9 mmHg, $P < 0.01$), and triglycerides (2.4 ± 0.7 mmol/L *vs* 1.4 ± 0.5 mmol/L, $P < 0.01$) in female and male patients[14].

There is no effective dose for berberine; however, the therapeutic dosage for most clinical situations is 0.2-1.5 g/d for the treatment of various diseases, especially for T2DM[7].

Berberine has been shown to be safe in the majority of clinical trials. In a low percentage of patients, berberine has been reported to cause nausea, vomiting, constipation, hypertension, respiratory failure and paresthesias; however, clinical evidence of such adverse effects is not often reported in the literature[7].

The diverse pharmacological properties exhibited by berberine indicate that the alkaloid has definite potential as a drug in a wide spectrum of clinical applications that include MetS.

BITTER MELON

Bitter melon, also known as *Momordica charantia*, is a common tropical vegetable that has also been used in traditional medicine. The plant grows in tropical areas of Asia, Amazon, East Africa, India and the Caribbean[15]. Approximately 228 different compounds with possible medicinal properties have been isolated from bitter melon fruit, seeds, leaves, pericaps and endosperm. Among these, the most actively studied constituents shown to improve glycemic control include charantin, vicine, momordicin, and polypeptide-p. Polypeptide-p closely resembles bovine insulin with the exception of one extra amino acid, methionine[16].

Several mechanisms of action have been proposed for its effects on glucose, lipids and blood pressure. Studies have shown that bitter melon inhibits the absorption of glucose by inhibiting α-glucosidase, reduces Na^+/K^+-dependent absorption of glucose by the intestinal mucosa and also suppresses disaccharidase activity in the intestine[15,17]. Bitter melon repairs damaged β-cells, stimulates insulin secretion, and enhances insulin sensitivity. Enhancement in insulin sensitivity may be due to multiple factors such as inhibition of protein tyrosine phosphatase 1B (PTP-1B) activity in skeletal muscle, increase in the number and translocation of glucose transporter type 4 (GLUT4) receptors, increase in the rate of phosphorylation of insulin receptor substrate and enhancement in the activity of AMPK. AMPK inhibits cholesterol synthesis in liver by activating 3-hydroxy-3-methylglutaryl-coenzyme reductase. It also stimulates the synthesis and release of thyroid hormones and adiponectin[17]. Other proposed mechanisms for actions include decreased hepatic gluconeogenesis and increased hepatic glycogen synthesis[18]. PPARs are nuclear receptors that control lipid and carbohydrate metabolism. These receptors are regarded as important targets for treating MetS. In animal models, bitter melon upregulated PPARγ- and PPARα-mediated pathways[18].

The hypoglycemic, hypolipidemic and antihypertensive effects of bitter melon have been reported in animal models and clinical trials. Male db/db mice (an animal model of obesity, diabetes, and dyslipidemia) were given sterile tap water as a control or bitter melon daily at a dosage of 150 mg/kg body weight for 5 wk. A1C levels were higher in control mice compared with the bitter melon-treated mice. Additionally, bitter melon reduced PTP-1B activity in skeletal muscle cytosol[19]. Normal and streptozotocin-induced diabetic rats were fed either with basal diet or a diet containing 10% bitter melon powder. Specific activities of intestinal disaccharidases were significantly increased during diabetes. Bitter melon supplementation in the diet clearly indicated amelioration in the activities of maltase and lactase during diabetes[20]. The effect of bitter melon at 10% level in the diet was evaluated in streptozotocin-induced diabetic rats. Amelioration of approximately 30% in fasting blood glucose was observed[21]. The aqueous extract powder of the fruit of bitter melon at a dose of 20 mg/kg body weight was also found to reduce fasting blood glucose by 48% in diabetic rats[22].

To date, most published human clinical trials on bitter melon have focused on blood glucose control. A randomized, double-blind, active-control trial was conducted to assess the efficacy and safety of three doses of bitter melon compared with metformin. Patients were randomized into four groups to receive bitter melon 500 mg/d, 1000 mg/d, and 2000 mg/d or metformin 1000 mg/d. All patients were followed for 4 wk. There was a significant decline in fructosamine in the metformin group (16.8 ± 40.6 μmol/L) and the bitter melon 2000 mg/d group (-10.2 ± 23.3 μmol/L)[23]. After adding bitter melon (800-1600 mg/d) to the current regimens (sulfonylureas and/or metformin) of 42 diabetic patients, fasting plasma glucose was reduced by 26.9 ± 40.8 mg/dL ($P < 0.001$)[24].

The effect of bitter melon on blood pressure and lipids has been evaluated in several experimental studies and only one clinical trial has aimed to investigate its effects on MetS. Acute intravenous administration of bitter melon aqueous extract produced dose-dependent, significant reductions in systemic arterial blood pressure and heart rates of normal and hypertensive Dahl salt-sensitive rats[25]. In another study, normal Sprague Dawley rats were divided into control and three test groups. Rats were administered one of three bitter melon preparations in food for 52 d: Chinese or Indian commercial preparations or an extract of bitter melon. All test groups lowered systolic, but not diastolic, blood pressure. Only the group with the extract significantly lowered ACE activity[26]. The methanol extract of bitter melon fruit was administered to diabetic rats for 30 d. A significant decrease in triglyceride and LDL-C and a significant increase in HDL-C were observed[27]. Bitter melon lowered plasma apolipoprotein B-100 and apolipoprotein B-48 levels in mice fed a high-fat diet and inhibited lipogenesis by downregulating lipogenic gene expression in adipose tissue of diet-induced obese mice[17].

A preliminary open-label, single arm, uncontrolled supplementation trial was carried out in 42 participants to evaluate the effect of bitter melon supplementation (4.8 g/d for 3 mo) on MetS. Decrease in the incidence of MetS rate at the end of the supplementation period was significantly different from that at baseline (19.0%, $P = 0.021$). The difference remained significant for 1 mo after cessation of supplementation ($P = 0.047$). Except for waist circumference (-2.09 cm, $P < 0.05$), the remaining four risk factors of MetS did not show significant decreases after bitter melon supplementation[18].

An effective dose for bitter melon has not been established. In animal models the dose range has oscillated from 20 to 150 mg/kg body weight, whereas in clinical trials the dose has varied from 500 mg to 4800 mg per day[18,19,22,24].

Few side effects have been associated with the use of bitter melon. The most commonly observed adverse effects include mild diarrhea and abdominal pain, which subside after discontinuation. Bitter melon use is also contraindicated during pregnancy because of its abortifacient properties[16].

Although the effect of bitter melon on glucose, blood pressure and lipids has been evaluated in several studies with significant results, only one clinical trial has assessed its effect on waist circumference as a primary outcome. Therefore, its effects on body weight remain to be studied in future clinical trials. The multiple mechanisms behind the hypoglycemic, hypolipidemic and antihypertensive effects of bitter melon and the results reported in previous studies provide a firm base for further well-designed randomized controlled trials to evaluate the efficacy of bitter melon on MetS.

G. SYLVESTRE

G. sylvestre is a medicinal plant belonging to the Asclepiadacea family popularly known as "gurmar" in Hindi, which means "sugar destroying". It is a woody climber that grows in tropical forests in India and South East Asia. Its leaves exhibit a broad range of therapeutic effects due to its active ingredients referred to as gymnemic acids. These are a mixture of at least 17 different saponins, acidic glycosides and anthroquinones[28]. In Indian medicine it is used for its main antidiabetic effects; however, other important metabolic effects have emerged from various studies with potential for treating MetS[29,30].

G. sylvestre helps to promote weight loss possibly through its ability to reduce cravings for sweets and also controls blood sugar levels. Chewing the leaves, rinsing the mouth with aqueous extracts, or topical application to the tongue selectively and reversibly inhibit the sensation of sweetness. Some investigations have suggested that gymnemic acid binds to the receptor located on the taste buds of the tongue and prevents activation by sugar molecules as well as suppressing sugar uptake, presumably by blocking sucrose receptors by one of its molecules, the gurmarin peptide[31,32].

G. sylvestre has also been found to be useful against obesity in accordance with recent preclinical studies in a murine model of obesity where the anti-obesity effect of ethanolic or water-soluble fraction of *G. sylvestre* extract (120 mg/kg, orally for 21 d) was demonstrated in a high-fat diet (HFD)-induced murine model of obesity[33]. Another study with a standardized ethanolic *G. sylvestre* extract (200 mg/kg) administered for 28 d resulted in a significant reduction of BMI, organ weight and visceral fat pad weight, among other metabolic parameters[34]. *G. sylvestre* has also shown a decrease in body weight without rebound on Otsuka Long-Evans Tokushima Fatty rats[35]. Decreasing body weight in humans has been demonstrated in studies using *G. sylvestre* only in combination with various dietary supplements. Therefore, the resulting weight loss cannot be attributed to only *G. sylvestre*[36,37].

Researchers have recently established that *G. sylvestre* does not block only sweet receptors on the taste buds of the mouth. It has the same inhibitory

activity on sodium-dependent glucose transporter 1 found in high levels in brush-border membranes of intestinal epithelial cells[38].

The ability of *G. sylvestre* to lower blood glucose concentrations has been tested as a hypoglycemic agent in combination with insulin in humans, with encouraging results. A preliminary study shows that administration of 200 mg/d of *G. sylvestre* extract decreased the required insulin dose by 50% and lowered A1C in both type 1 and T2DM. It also increased the number of beta cells in the pancreas and therefore the internal production of insulin. When 400 mg/d of this extract is taken with conventional hypoglycemic drugs such as glyburide or tolbutamide, some patients were able to reduce the dose of the drug or even discontinue its use[39,40]. *In vivo* studies with oral administration of an extract of *G. sylvestre*, Om Santal Adivasi (OSA®) (1 g/d for 60 d) induced a significant increase in circulating insulin and C-peptide, which were associated with significant reductions in fasting and postprandial blood glucose. *In vitro* measurements using isolated human islets of Langerhans demonstrated direct stimulatory effects of OSA® on insulin secretion in human cells, consistent with an *in vivo* mode of action through enhancing insulin secretion. As a result, it also stabilizes blood sugar and decreases insulin doses. In fact, one patient with a disease duration of 10 years and another patient with a duration of 2 years and who were both using a total of 20 U of insulin a day were able to completely discontinue insulin at this point in the study[41].

Individual chemical components of extract of *G. sylvestre* have also been shown to be potent and selective antagonists *in vitro* and *in vivo* for the β isoform of liver X receptor[42] in rats in whom *G. sylvestre* was administered at a dose of 200 mg/kg. Significant reductions in lipid levels and an increase in HDL-C have been reported[43].

Compounds from the leaves of *G. sylvestre* may act as an endothelial synthase (eNOS) agonist. To further confirm the results, animal studies were performed with *G. sylvestre* leaves to demonstrate its future usefulness, not only in controlling blood glucose levels in diabetic patients but also to help avoid diabetic complications such as vascular diseases that occur due to decreased availability of NO[44]. One of the most active constituents of *G. sylvestre* is deacyl gymnemic acid (DAGA), which is associated with decreases in homeostasis model asesment (HOMA) insulin resistance, a surrogate marker of insulin resistance, suggesting treatment with DAGA at a dose of 200 mg/kg has beneficial effects on improvement in insulin sensitivity[30]. Conversely, in another study, systolic blood pressure was increased in SHR fed a high sucrose diet, but the clinical importance of this finding is unknown[37].

Clinical studies investigating antidiabetic effects have typically used 200-1000 mg extract daily, standardized to contain 25% gymnemic acids[30,39,41].

Adverse effects have not been reported in long-term studies in patients with type 1 diabetes[45]. However, at high doses, hypoglycemia, weakness, excessive sweating and muscular dystrophy may occur[46]. On the other hand, due to its lipophilic character, *G. sylvestre* may inhibit intestinal absorption of oleic acid[47]. However, the United Nations Organizations has reported only one case of toxic hepatitis due to the use of *G. sylvestre*. Additional studies are needed to support its toxic effect[48]. The above-mentioned evidence supports the possibility of treating MetS with *G. sylvestre*, although more studies are needed.

I. GABONENSIS

I. gabonensis belongs to the family Irvingiaceae. The tree of Irvingia, commonly known as mango bush, wild bush, dikanut or African mango, is native to Central and Occidental Africa[49]. Both the fruit and seeds of *I. gabonensis* are widely consumed in Africa as part of its gastronomy. It has recently been reported that roots, leaves and an extract of the seeds have medicinal properties.

I. gabonensis has been used for the treatment of diarrhea and to shorten the time of lactation in women. It is also administered for the treatment of colicky pain and dysentery. The tree bark has antibiotic properties and helps to heal dermal wounds produced by burning. It has also been administered for the treatment of toothache.

The use of an extract of *I. gabonensis* seeds has been studied as a source of dietary fiber useful to decrease glucose and cholesterol concentrations in diseases such as diabetes mellitus. Gastric emptying is delayed and absorption of glucose at the intestinal level is reduced, leading to better insulin sensitivity in tissues. This extract has also demonstrated to modify distribution of phospholipids, which lowers the plasma concentrations of total cholesterol and triglycerides[50]. Although the use of the extract of *I. gabonensis* has increased, no pharmacokinetic data have been reported.

Different studies have been carried out to determine the composition, antioxidant capacity, mechanism of action and effects of *I. gabonensis.* One study that aimed to identify the principal components of an extract of *I. gabonensis* seeds through high-resolution liquid chromatography coupled to mass spectrophotometry demonstrated that its principal components are ellagic acid, mono-, di-, and tri-O-methyl-ellagic and some long-chain glucosides[51].

In relation to its antioxidant activity, a study was carried out to evaluate the antioxidant capacity of 14 species from Cameroon including *I. gabonensis*. Using different methanol extracts and two different assays to determine antioxidant capacity - the Folin assay and the ferric reduction potential assay - it was found that *I. gabonensis* has an elevated antioxidant concentration of approximately 202 mmol/100 g[52].

Another experimental study was carried out with the aim of investigating the effect of an extract of *I. gabonensis* on inhibition of intracellular triglycerides

and the activity of the enzyme glycerol-3-phosphate in adipocytes 3T3-L1 of a murine model. Expression of some proteins typical of adipogenesis, leptin and adiponectin was also studied. Adipocytes were cultivated for 8 d after initiation of their differentiation and were treated with 0-250 μmol/L of *I. gabonensis* for 12 and 24 h at 37 ℃ in an incubator with humidity at 5%. The results showed that *I. gabonensis* significantly inhibits adipogenesis in adipocytes. This effect appears to be mediated through a decrease in the expression of the PPARγ ($P < 0.05$) and leptin ($P < 0.05$). An increase in adiponectin expression was also found ($P < 0.05$)[53].

An experimental study carried out in diabetic rats fed for 4 wk with a typical rat diet supplemented with *I. gabonensis* or cellulose found that both types of diets significantly reduced glucose, cholesterol and triglycerides concentrations and also increased HDL-C ($P < 0.05$[54].

These results agree with results reported in another experimental study where the potential of a seed extract of *I. gabonensis* was studied to decrease hyperglycemia and hyperlipidemia in a group of diabetic rats administered a diet supplemented with *I. gabonensis* for 4 wk. The results showed a significant decrease in glucose concentrations, food intake, total cholesterol, triglycerides and LDL-C levels. A significant increase in HDL-C was also reported ($P < 0.05$)[49].

A study in which the effect of the administration of a viscous presentation of *I. gabonensis* seeds in diabetic rats was evaluated for 3 wk at a dose of 2 g/kg every 12 h showed that the extract decreased glucose concentrations ($P < 0.05$), decreased activity of the enzymes pyruvate kinase and lactate dehydrogenase ($P < 0.05$) and increased the activity of the enzyme glucose-6-phosphatase ($P < 0.05$) compared with the control group[55].

Another experimental study was carried out to evaluate the long-term effect of an aqueous extract of the bark of *I. gabonensis* administered daily to rabbits for 24 wk. At the end of the study, glucose concentration and body weight significantly decreased ($P < 0.05$)[56].

Some clinical trials have been conducted to determine if *I. gabonensis* has an effect on body weight, glucose and lipid concentrations. A double-blind clinical trial carried out in 40 obese subjects who received *I. gabonensis* or placebo at a dose of 1.05 g three times/d for 1 mo showed that the administration of the extract of *I. gabonensis* decreased on average 5.25 kg of body weight ($P < 0.001$). The subjects also showed a significant decrease of total cholesterol, LDL-C and triglycerides concentrations and increased their HDL-C[57].

Another clinical trial was conducted in 102 overweight or obese subjects who were randomized into two groups: One group who received 150 mg of *I. gabonensis* 30 min prior to breakfast and dinner and the other received placebo at the same dose for 10 wk. The results showed a significant diminution on body weight, fat mass and waist circumference. Significant differences were also found in plasma concentrations of total cholesterol, LDL-C, glucose, C-reactive protein, leptin and a significant increase was shown for adiponectin and HDL-C concentrations in the *I. gabonensis* group *vs* placebo[58].

An approved dose has not yet been established for its use. A systematic review of three randomized controlled trials that evaluated the efficacy of *I. gabonensis* supplementation in the management of overweight and obesity found that the daily dosages differed from approximately 200 mg to approximately 3150 mg[59].

Adverse events reported in some clinical trials regarding the use of *I. gabonensis* are headache, dry mouth, diarrhea, sleep disturbances, and constipation[60]. Acute toxicity studies have not reported any deaths after the 7-d administration of *I. gabonenis* at a dose of 1600 mg/kg in rats[59].

The different studies performed either in animal models or as clinical trials suggest that the administration of *I. gabonensis* may be a promising option for the prevention and treatment of MetS.

RESVERATROL

As a chemical compound, resveratrol (3,5,4-trihydroxystilbene) has been described since the 1940s when it was isolated for the first time from the roots of a white hellebore. Years later, it was extracted from the dried roots of a plant called *Polygonum cuspidatum,* which is often used in traditional Chinese medicine[61].

Today it is known that resveratrol can be found in different quantities in > 70 plants and is also present in some foods and beverages such as nuts, berries, grapes, peanuts and their derivatives such as red wine. The quantity of resveratrol depends of different factors such crop type, geographical origin, and climate[62].

In plants, resveratrol acts as a phytoalexin, a toxic compound produced by plants as a defense mechanism in response to the presence of pests and other stressful situations such as climate.

Resveratrol can be found in two different isomeric forms: *cis* and *trans*, the *cis* form being the more common used form due to its pharmacological properties[63].

Despite the multiple therapeutic effects attributed to resveratrol, its pharmacokinetic characteristics are not favorable because of its poor bioavailability. It is rapidly metabolized and excreted[64].

There is no evidence of the existence of specific receptors for resveratrol. However, resveratrol seems to accumulate in different tissues, mainly related with its absorption and metabolism such as duodenum, colon, liver and kidney[65-67].

Although most of the studies carried out with resveratrol are in regard to its cardioprotective effect, there is evidence that resveratrol has other pharmacological properties in a wide range of chronic diseases such as cancer, T2DM, and degenerative diseases such as Alzheimer's as well as having antithrombotic,

antiosteoporotic and antimicrobial effects[63,67]. Resveratrol acts through different mechanisms. Similar to other polyphenols, resveratrol has an important antioxidant activity and interacts with different receptors, kinases and enzymes[68]. Some studies carried out in *in vivo* models reveal that resveratrol activates sirtuin 1 (SIRT1) and AMPK, both molecules implicated in metabolism regulation; therefore, resveratrol could be a new alternative for the prevention and treatment of MetS[69].

Activation of SIRT1 by resveratrol decreases the activity of PPARγ and therefore adipogenesis, which decreases the number of adipocytes and thus obesity. Resveratrol also increases phosphorylation of the coactivator type 1α of PPAR (PGC-1α) and cyclic adenine monophosphate (cAMP), which increases lipolysis. Resveratrol also enhances the activity of AMPK, which decreases the activity of acetyl CoA carboxylase by its phosphorylation, resulting in a decrease of lipogenesis that contributes to the control of obesity and dyslipidemia. Increase of the activity of AMPK stimulates phosphorylation of the myocyte enhancer factor 2 (MEF2), which results in a higher expression of GLUT4 and therefore a lower resistance to insulin and a diminution of glucose.

Finally, resveratrol increases the activity of endothelial eNOS and therefore the NO concentrations, which contributes to the vasodilation and indirectly to decreased blood pressure[70]. All these effects have been confirmed in different studies, both in animal models and in clinical trials.

A clinical trial was conducted in 11 males with obesity but without any other metabolic alteration. Patients received resveratrol or homologated placebo at a dose of 150 mg/d for 30 d. Results show that resveratrol activated AMPK at the muscular level and increases levels of SIRT1 and PGC-1α, resulting in higher lipolysis of adipose tissue. A decrease in glucose, insulin and HOMA index was also demonstrated[71]. A meta-analysis carried out with 11 clinical trials found that resveratrol administrated at different doses for at least 2 wk in patients with diabetes decreases fasting glucose, insulin, A1C and insulin resistance evaluated through HOMA index, but this meta-analysis did not find any differences in patients without diabetes[72].

Although the information obtained about the effects of resveratrol on cholesterol and triglycerides concentrations is inconclusive, some studies performed in animal models with MetS have shown that resveratrol at different doses reduces atherosclerotic plaque formation, total cholesterol and triglycerides[73,61]. Clinical trials reported in obese patients have not found any significant differences in lipid profile after resveratrol administration[71,74].

Our research group[75] conducted a randomized, double-blind, placebo-controlled clinical trial in 24 patients with a diagnosis of MetS in accordance with the International Diabetes Federation modified criteria. Resveratrol or homologated placebo was administrated for 90 d at a dose of 500 mg three times per day. After resveratrol administration, significant differences were found in total weight (94.4 ± 13.2 kg *vs* 90.5 ± 12.3 kg, $P = 0.007$), BMI (35.6 ± 3.2 kg/m^2 *vs* 34.3 ± 3.0 kg/m^2, $P = 0.006$), fat mass (41.2 ± 7.9 kg *vs* 38.8 ± 6.0 kg, $P = 0.001$), and waist circumference (109 ± 9 cm *vs* 105 ± 10 cm, $P = 0.004$). There were also significant differences in area under the curve (AUC) of insulin (48418 ± 22707 pmol/L *vs* 26473 ± 8273 pmol/L, $P = 0.003$) and total insulin secretion evaluated through insulinogenic index (0.48 ± 0.22 pmol/L *vs* 0.28 ± 0.08 pmol/L, $P = 0.004$).

An approved dose has not yet been established for its use. In a meta-analysis where the effect of resveratrol on glucose control and insulin sensitivity was evaluated, a dose range from 8 to 1500 mg/dL was found[72].

Some adverse effects reported due to the use of resveratrol are headache, abdominal pain and general malaise[75]. At high doses (2000 mg twice daily for 1 wk), a clinical trial reported statistically, but not clinically significant, increased serum bilirubin and potassium concentrations[76]. Daily dosing of 100 mg for 4 wk did not change these values[77].

These results lead to the conclusion that resveratrol could be an option for the treatment of MetS due to the decrease of obesity and by controlling the hypersecretion of insulin characteristic of this group of patients.

URSOLIC ACID

Ursolic acid is a pentacyclic triterpene carboxylic acid present as a free acid or as an aglycone part of saponins[78] and can be obtained naturally or synthetically[79]. It is also known as urson, prunol, micromerol or malol[80]. This compound was considered inactive; however, in recent years interest has been sparked due to the multiple and varied effects of ursolic acid[79,81]. Evidence for this substance appears promising for the treatment of MetS.

The main sources of ursolic acid include components of certain fruits, herbs and plants. Ursolic acid is found in apple peel, cranberry juice and grape skin. It is also found in some common spices like rosemary, thyme and oregano and has been identified in Ayurvedic herbs such as Holy Basil, some traditional Chinese medicinal herbs including Jujuba zizyphus, and in yerba mate and sage. Ursolic acid also is found in some herbs that have attributed antidiabetic effects and is found in small amounts in the leaves of some plants[82,83].

Ursolic acid is formed by 30 carbons distributed in five rings of six carbons and has an hydroxyl group at carbon 3, a carboxyl group at carbon 28 and a double bond at carbon 12 and 13. Its chemical formula is $C_{30}H_{48}O_3$[84]. Some structurally related compounds of ursolic acid include its isomer, oleanolic acid, in addition to corosolic, maslinic, latanolic, pomolic, camarinic and pomolic acids[85]. These compounds share common characteristics of pentacyclic triterpenoids with

apparently similar effects, although differing from each other in strength[85].

Physicochemical properties of ursolic acid give it great stability. Ursolic acid has a molecular weight of 456.70032 g/mol. Its melting point is 269-271 ℃. It has an optical activity of +34° at a concentration of 0.20 g/100 mL in methanol and a molar solubility in pure water at pH 7 and 25 ℃ of 1.11 × 10^{-5} mg/L[80,84].

Evidence demonstrates positive effects *in vitro* and *in vivo* through various mechanisms in glucose and lipid metabolism as well as in body weight and visceral fat usually altered in MetS.

Ursolic acid inhibits the enzyme PTP1B, promoting phosphorylation of the insulin receptor *in vitro*, thereby stimulating glucose uptake[86,87]. PTPB1 is an enzyme associated with the endoplasmic reticulum and plays a key role in signaling metabolic pathways that interacts and dephosphorylates insulin receptor and leptin, causing downregulation signaling of both receptors in modulating the mitogenic actions of insulin[88].

Translocation of GLUT4 is increased by ursolic acid as part of the action on the insulin receptor and manages to improve glucose uptake. GLUT4 is the principal glucose transporter protein and thus plays a key role in regulating whole body glucose homeostasis[88].

Ursolic acid appears to inhibit the α-amylase enzyme, an enzyme that hydrolyzes α-links of large polysaccharides such as starch and glycogen to yield glucose and maltose. Inhibition of α-amylase has been shown to lower blood glucose levels due to lowering the breakdown and absorption of starch[89].

Ursolic acid reduces the activity of aldose reductase and sorbitol dehydrogenase[90,91]. These enzymes catalyze the reduction of hexoses. In the presence of hyperglycemia, aldose reductase converts glucose to sorbitol. The latter is metabolized to fructose by sorbitol dehydrogenase. During this process, the production of sorbitol and fructose occurs. Reduced nicotinamide adenine dinucleotide phosphate is decreased and nicotinamide adenine dinucleotide phosphate is increased[91]. Sorbitol increases intracellular osmotic pressure and damages tissues by cell edema; fructose causes protein fructosylation[90].

The increase in the glyoxalase system produced by ursolic acid represents the decrease of cytotoxicity and chronic complications caused by methylglyoxal, a toxic metabolite produced as a by-product of metabolism. This detoxification reaction is carried out by the glyoxalase system[92].

Administration of ursolic acid was associated with decreased adipocyte differentiation[93]. Adipocytes synthesize and release a wide variety of peptide and non-peptide substances and also store and mobilize triglycerides, cholesterol and retinoids. Lipid-laden adipocytes can be emptied and extended, forming cells that resemble their predecessors not only in appearance but also for its potential for multiplication. This change reflects fully differentiated adipocyte regression to an earlier or less mature, but complete, stage[93].

Overregulation of the c-Cbl associated protein (CAP) was observed in adipocytes treated with ursolic acid[94]. CAP is expressed only in insulin-sensitive tissues (adipose, liver and muscle). Increase in transcription of CAP is directly related to greater sensitivity to insulin in adipocytes. It is postulated that CAP would facilitate phosphorylation of c-Cbl by the insulin receptor, allowing the union of c-Cbl to the insulin-dependent tyrosine kinase. The relationship of CAP is an example of a direct molecular link between PPARγ sensitivity and insulin in adipose tissue[94].

Through the activation of protein kinase A, ursolic acid appears to increase lipolysis *in vitro* as well as to decrease hormone-sensitive lipase and perilipin activity[93]. Lipolysis favors the production of energy from fatty acids into the mitochondria, enabling the generation of free fatty acids from triglycerides stored in adipocytes of white adipose tissue. As a result, there is an activation of fatty acids as well as a translocation to the mitochondria from tissues such as muscle and brown adipose tissue. As a final result, the production of energy occurs from β-oxidation of fatty acids in mitochondria and in some cases in the peroxisome[93].

There is no established dose for ursolic acid. Animal studies have found benefits with ursolic acid at 0.05%-0.2% of the diet[86-93], which is about 10-40 mg/kg based on their weight and food intake. In clinical trials, a 150-mg dose one to three times a day has been used, providing a maximum of 450 mg and revealing some biological activity.

No adverse effects have been associated with ursolic acid in humans. However, studies in animals have reported that ursolic acid at very high doses resulted in a decrease of sperm motility, cell death and DNA damage[95]. Due to the beneficial effects of ursolic acid on several components of the MetS, its clinical administration should be further studied.

CONCLUSION

Nutraceutic therapies such as berberine, bitter melon, *G. sylvestre, I. gabonensis,* resveratrol and ursolic acid have demonstrated substantial scientific information regarding their safety and beneficial effects to be comprehensively considered for treating patients with MetS. Berberine and resveratrol, which already have been studied in patients with MetS, have demonstrated valuable results. For the remainder of the nutraceutics presented in this review, it may be necessary to perform more in-depth studies to be clinically recommended.

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