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Diabetes and Metabolic Disorders: An Ethnopharmacological Perspective

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20.1 Introduction

Metabolism is the process by which organisms acquire and distribute energy from food, which is composed of proteins, carbohydrates and fats. Chemicals in the digestive system break these components down into sugars and acids, the body's fuel. The body can use this fuel immediately or it can store the energy in body tissues, including the liver, muscles and body fat. A metabolic disorder occurs when abnormal chemical reactions in the body disrupt this process (National Library of Medicine, 2014).

Most metabolic diseases are rare (e.g. Gaucher's disease or hereditary hemochromatosis), but type-2 diabetes (T2D) and metabolic syndrome (MS) incidence is growing rapidly worldwide. All metabolic diseases are linked to genetic factors, but T2D and MS are also correlated with lifestyle, obesity and a lack of physical activity. The International Diabetes Federation (IDF) estimates that as of 2013, worldwide more than 382 million people have diabetes and that this number will increase to 592 million by 2035 (International Diabetes Federation, 2014). WHO estimates that 347 million people currently have diabetes and that by 2030 it will be the seventh leading cause of death (World Health Organization, 2014). The IDF also estimates that approximately one quarter of the world's adults have MS. The clustering of cardiovascular disease (CVD) risk factors that typify metabolic syndrome is now considered a driving force for a new CVD epidemic (International Diabetes Federation, 2014).

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The use of medicinal plants to treat various diseases is common practice worldwide. In countries such as India, China and Mexico, traditional medicine plays an important role in official or unofficial healthcare systems. Such medicinal plants are used primarily in unprocessed forms. In developed countries such as Germany, the UK and France, traditional medicine now plays an important role as part of the official health system, primarily in the form of phytomedicines.

Ethnopharmacological research, in countries where traditional medicine plays an important role in the health system, can provide us with new compounds or new phytomedicines for the management of metabolic disorders.

In this chapter we present an ethnopharmacological perspective on the main metabolic disorders: T2D and MS.

20.2 Type-2 diabetes

Diabetes mellitus is defined as an elevated blood glucose level associated with absent or inadequate pancreatic insulin secretion, which may occur with or without the impairment of insulin signalling. T2D is characterized by tissue resistance to insulin combined with a relative deficiency in insulin secretion. A given individual may exhibit either increased insulin resistance or increased β-cell deficiency, and these abnormalities may be mild or severe. Although in these patients insulin is produced by β cells, their production is inadequate to overcome insulin resistance, and blood glucose therefore increases. Impaired insulin signalling also affects fat metabolism, resulting in increased free fatty acid flux, elevated triglyceride levels and reciprocally low levels of high-density lipoprotein (HDL) (Expert Committee, 2003).

T2D is a polygenic disorder; the additive effects of an as-yet unknown number of genetic polymorphisms (risk factors) are required for its development, and they may not be sufficient in the absence of environmental (acquired) risk factors. The most important risk factors are those that influence insulin sensitivity: obesity (visceral obesity), physical inactivity, high-fat/low-fibre diets, smoking, and low birth weight (Alsahli and Gerich, 2012).

The onset of T2D, then, depends on two types of factors: (i) genetic factors that affect obesity, β-cell potential or insulin resistance, and (ii) environmental factors such as inactivity and excess in food intake or in inadequate food. These two causes lead to insulin resistance, which is initially compensated by β cells. The β cells will then work too hard, which reduces their mass and creates glucose intolerance and glucotoxic effects on the cells. Further decreases in their mass create more severe glucotoxicity and decomposition with severe hyperglycemia.

The long-term complications of diabetes include retinopathy with a potential loss of vision, nephropathy leading to renal failure, peripheral neuropathy with risk of foot ulcers, amputations, and Charcot joints, autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms, and sexual dysfunction (Expert Committee, 2003).

The pathophysiology of these diseases is complicated; many metabolic pathways and cell types are involved. Herein, we provide a short description of the main metabolic aspects.

20.2.1 Insulin

Insulin-like signalling integrates the storage and release of nutrients with somatic growth during development and in adulthood. It is a feature of all metazoans, revealing a common mechanism used by animals to integrate metabolism and growth with environmental signals (White, 2012).

Insulin exerts critical control over carbohydrate, fat and protein metabolism; β cells in the islets of Langerhans are the only cells in the body that produce a meaningful quantity of insulin to maintain glucose levels within a range from 70 to 150 mg/dl in normal individuals. The β cells release insulin in two phases. The first phase release is rapidly triggered in response to increased blood glucose levels, and the second phase is a sustained, slow release of newly formed vesicles triggered independently of sugar. Other substances known to stimulate insulin release include the amino acids arginine and leucine, the parasympathetic release of acetylcholine (via phospholipase C), sulfonylurea, cholecystokinin (CCK, via phospholipase C) and the gastrointestinally derived incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide.

20.2.2 Insulin effects in peripheral tissues

Insulin activity in the peripheral tissues is mediated via the insulin receptor, which on hormone binding initiates a cascade of intracellular protein phosphorylation. The intracellular subunit of the receptor is a tyrosine-specific kinase that auto-phosphorylates and catalyses the phosphorylation of several proteins that in turn promotes the multifaceted effects of the hormone. Different tissues are known to respond distinctly to insulin; tissue sensitivity correlates with the levels of insulin receptors expressed on the plasma membrane. Insulin stimulates glucose turnover, favouring its influx into cells, followed by oxidative metabolism to release energy, produce lipids or store glucose as glycogen via non-oxidative metabolism. Insulin-stimulated glucose transport is observed only in skeletal muscle, adipose cells and the heart because these tissues express the insulin-dependent glucose transporter, GLUT4. In the liver and kidney, insulin inhibits gluconeogenesis because of the tissue-specific expression of hormone-sensitive metabolic enzymes involved in this process. Insulin simultaneously stimulates lipid synthesis while preventing lipolysis in adipose cells, skeletal muscle and liver. Insulin promotes protein synthesis in almost all tissues. Insulin acts as a mitogen via increased DNA synthesis and the prevention of programmed cell death, or apoptosis. In addition, insulin stimulates ion transport across the plasma membrane of multiple tissues. There is increasing evidence for a direct role of insulin, acting through the insulin or insulin growth factor (IGF) receptors, in the regulation of pancreatic β-cell growth, survival and insulin release (White, 2012).

The most prominent abnormality in T2D is an impairment of glucose-induced insulin secretion, which is more severe in the first phase than in the longer second phase of secretion. In contrast, β-cell responses to non-glucose secretagogues, such as GLP-1 or sulfonylureas, remain intact; β cells exposed to abnormally high glucose concentrations lose the differentiation that normally equips them with the unique metabolic machinery needed for glucose-induced insulin secretion (Gordon *et al.*, 2012).

20.2.3 Insulin resistance (skeletal muscle and adipose tissue)

Insulin resistance occurs when cells in the body (liver, skeletal muscle and adipose tissue) become less sensitive and eventually resistant to insulin, and occurs when normal hormone concentrations produce a substandard biological response. T2D mellitus is characterized in almost all cases by insulin resistance. This has been clearly demonstrated by the glucose clamp technique, in which glucose clamps were performed in normal subjects, subjects with impaired glucose tolerance (IGT) and subjects with T2D. Despite similar steady-state insulin levels, the glucose disposal rate was decreased by 24% in the subjects with IGT and by 58% in those with T2D compared with normal controls. In the basal state, 30% of glucose uptake is insulin

mediated, whereas in the post-prandial state insulin-mediated glucose disposal increases by 85%. Studies have shown that 80–90% of this increased insulin-mediated glucose disposal is into skeletal muscle. Consequently, in insulin-resistant states an inability to respond to insulin stimulation with an adequate increase in glucose disposal largely contributes to post-prandial hyperglycemia (Courtney and Olefsky, 2003).

20.2.4 Liver

Glucose metabolism in the liver is controlled by the pancreatic hormones insulin and glucagon. A high insulin:glucagon ratio in the post-prandial state favours glucose storage and disposal, glycogen synthesis and glycolysis, whereas a low ratio in the fasted state favours glucose production, glycogenolysis and gluconeogenesis. This tightly regulated control of hepatic glucose metabolism is disrupted in diabetes, leading to inappropriate increases in glucose production by the liver (Clark and Newgard, 2003).

The liver contributes to glucose homoeostasis through the rapid postprandial clearance of glucose from the portal vein in the absorptive state after a meal; when blood glucose falls below normal concentrations, glycogen is mobilized and glucose is produced via gluconeogenesis. When the blood glucose concentration increases, hepatic glucose uptake increases proportionally, stimulating glucokinase and glycogen synthesis. Elevated blood glucose concentrations normally increase insulin release and reduce glucagon release, thus increasing the insulin to glucagon ratio, which in turn inactivates glycogen phosphorylase (inhibiting glycogenolysis), activates glycogen synthase (stimulating glycogen synthesis) and increases the concentration of fructose-1,6-bisphosphate. These events reduce the hepatic production of glucose and increase the hepatic storage of glucose as glycogen. The main enzymatic targets for controlling the elevation of blood sugar levels are the inhibition of glucose-6-phosphatase, the inhibition of fructose-1, 6-bisphosphatase and the inhibition of glycogen phosphorylase (Andrade-Cetto, 2012).

20.2.5 Gut

Incretins are hormones released by the gut in response to food ingestion that augment insulin release by what is known as the incretin effect. Two primary incretins are GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). Other gut hormones that influence glucose homeostasis include ghrelin and peptide YY. Ghrelin acts on the hypothalamus to stimulate appetite and also inhibits insulin secretion. The incretin effect can be measured because there is a greater insulin response after oral than intravenous glucose delivery despite comparable glycemia (Alsahli and Gerich, 2012).

The α-glucosidase enzyme is located in the brush border of the small intestine and is required for the breakdown of carbohydrates to absorbable monosaccharides. The α-glucosidase inhibitors (AGIs) delay but do not prevent the absorption of ingested carbohydrates, reducing the postprandial glucose and insulin peaks (Andrade-Cetto *et al.*, 2008).

20.3 Metabolic syndrome

MS is a cluster of conditions with the most dangerous effect being an increased risk of heart attack; the main risk factors are elevated fasting plasma glucose (>110 mg/dl but <126 mg/dl) and abdominal (or central) obesity, which is defined by having a waist circumference of at least 102 cm for men and 89 cm for women, although these values can vary by ethnicity.

The underlying cause of MS continues to challenge experts, but both insulin resistance and central obesity are considered significant factors. Genetics, physical inactivity, ageing, a pro-inflammatory state and hormonal changes may also be causative, but the role of these factors can vary depending on the ethnic group. Central obesity is associated with insulin resistance and MS; it contributes to hypertension, high serum cholesterol, low HDL-c and hyperglycemia, and it is independently associated with higher CVD risk.

According to the IDF, for a person to be defined as having MS, they must have central obesity (defined by waist circumference, with ethnicity-specific values) along with any two of the following four predispositions: elevated triglycerides (≥150 mg/dl), reduced HDL cholesterol (<40 mg/dl in males, <50 mg/dl in females), elevated systolic blood pressure (BP) (≥130) or diastolic BP (≥85 mm Hg) and elevated fasting plasma glucose (≥100 g/dl) (http://www.idf.org).

People with metabolic syndrome are at increased risk of

- atherosclerosis, peripheral vascular disease and other diseases related to fatty build-ups in artery walls (these blockages narrow the arteries and restrict blood circulation throughout the body but are especially dangerous when they affect the arteries leading to the brain, heart, kidneys and legs)
- coronary heart disease and heart attack
- stroke, which occurs when the blood supply to a part of the brain is interrupted by a blocked or burst blood vessel, depriving the brain of oxygen and nutrients
- T2D (American Heart Association, 2014).

In obesity, plasma free fatty acids (FFAs) are elevated, causing insulin resistance in muscle, liver and endothelial cells, and this contributes to the development of T2D, hypertension, dyslipidemia and non-alcoholic fatty liver disease. Elevated FFA levels cause insulin resistance in skeletal muscle and liver, which contributes to the development of T2D and MS (Boden, 2006).

20.4 Case studies

It is important to embed such an ethnopharmacological perspective in a discussion on the use of plants in traditional medicine to treat these diseases. As we can deduce from the background information presented here, the diagnosis of T2D and MS is quite difficult in a traditional medicine-based framework. For T2D, the blood glucose level is necessary to establish a diagnosis, and MS is not even considered among many of the traditional medicines worldwide. Central obesity can be easily observed, but insulin resistance, HDL-c and triglyceride levels are difficult to detect without laboratory testing. The plants that are primarily used to treat T2D are selected by diabetic patients once they have a diagnostic examination performed by a physician. For MS, the patients look for plants used to treat obesity, T2D or hypertension, and thus fewer plants with centuries of use and evaluation exist to treat these increasingly modern-day problems. In many parts of the world, diabetic patients or people with obesity are trying new plants at their own risk.

20.4.1 Liver targeting

In South and Central Mexico as well as Guatemala traditionally the dry leaves (15 g) of *Cecropia obtusifolia* Bertol. (Cecropiaceae) are boiled in water (c. 500 ml) and the resulting infusion is cooled and filtrated, with the cold infusion being consumed over the day or

when people are thirsty (Andrade-Cetto and Heinrich, 2005). Studies have assessed its hypoglycemic effects in animal models and T2D patients.

An open, controlled clinical trial was conducted with 12 recently diagnosed (2 ± 0.8 years) T2D patients, eight women and four men with an average age of 48 ± 4 years, who controlled their diabetes with diet and exercise. None of the patients had ever taken any hypoglycemic drug. Over a 34-week period the patients received daily an aqueous leaf extract. Glucose, cholesterol, triglycerides and insulin levels were determined every 15 days, and HbA1c was measured monthly. A significant reduction in the glucose levels was detected after 4 weeks of administration, and HbA1c was significantly reduced after 3 months of treatment. No significant effect on cholesterol, triglycerides or insulin could be observed (Revilla-Monsalve *et al.*, 2007).

C. obtusifolia contains chlorogenic acid (CA) and isoorientin. CA is an inhibitor of glucose-6-phosphate translocase (Figure 20.1) and thus the authors proposed that the hypoglycemic effects of the plant were due at least in part to this inhibition. They proposed that glucose-6-phosphate translocase inhibition would inhibit gluconeogenesis and reduce hepatic glucose production. To test this hypothesis, they measured the effects of plant extracts on gluconeogenesis (*in vivo*) and glucose-6-phosphate translocase enzyme activity (*in vitro*). A pyruvate tolerance test (2 g/kg) was performed in 18-h fasted n5-STZ rats to determine whether inhibition of gluconeogenesis occurred *in vivo*. The effect of the extracts on glucose-6-phosphatase translocase activity was assayed *in vitro* in intact rat liver microsomes. The diabetic rats treated with plant extracts had a lower glucose curve; the extracts reduced the elevation in glucose blood levels and inhibited glucose-6-phosphatase translocase activity with IC_{50} values of 224 g/ml for *Cecropia obtusifolia* aqueous extract, 160 g/ml for *C.obtusifolia* butanolic extract and 254 g/ml for chlorogenic acid. The authors concluded that the administration of the plant could improve glycemic control by blocking hepatic glucose output, especially in the fasting state (Andrade-Cetto, 2012).

20.4.2 Gut targeting

An aqueous extract from the aerial parts of *Brickellia cavanillesii* (Cass.) A. Gray (Asteraceae), orally administered to normal and diabetic mice, showed significant hypoglycemic effects.

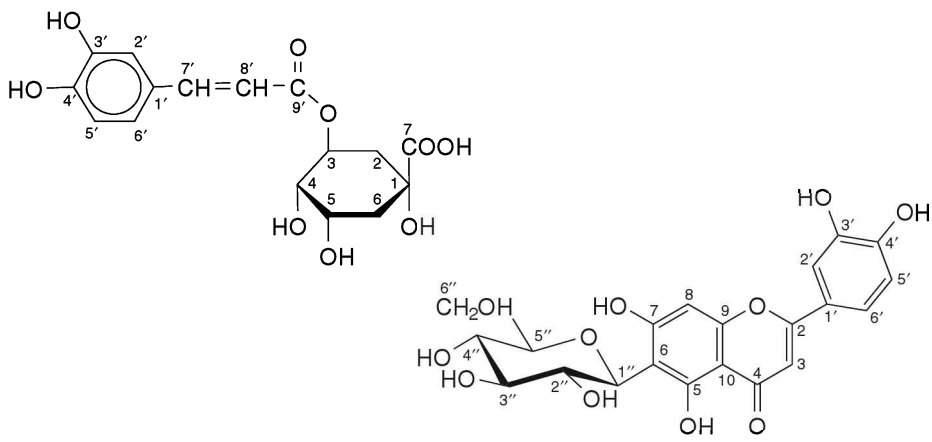

Figure 20.1 Chlorogenic acid (left) and isoorientin (right) isolated from *Cecropia Obtusifolia*.

The extract attenuated postprandial hyperglycemia in diabetic mice during oral glucose and sucrose tolerance tests. The extract also showed potent inhibitory activity (IC_{50} = 0.169 mg/ml vs 1.12 mg/ml for acarbose) towards yeast α-glucosidase. The bioassay-guided fractionation of the active extract using the α-glucosidase inhibition assay led to the isolation of several compounds, including three chromenes, three sesquiterpene lactones, several flavonoids and a coumarin. One of these chromenes is a new chemical entity and was identified by spectroscopic techniques. Moreover, all the compounds were tested *in vitro* against α-glucosidase activity; the active products were a flavonoid (isorhamnetin), a sesquiterpene lactone (calein C) and the new chromene (Figure 20.2) (IC_{50} = 0.16, 0.28 and 0.42 mM, respectively, vs 1.7 mM for acarbose). Enzyme kinetic analysis of these compounds revealed that calein C (*Ki* 1.91 mM) and isorhamnetin (*Ki* 0.41 mM) behaved as mixed inhibitors, whereas the new chromene (Ki 0.13) was a non-competitive inhibitor. Docking analysis predicted that the flavonoids and sesquiterpene lactones but not the chromene bind to the enzyme at the catalytic site (Mata *et al.*, 2013).

20.4.3 Insulin targeting

The fruit of *Momordica charantia* L. (bitter gourd, Cucurbitaceae) is used in the Ayurveda for treating diabetes. Unripe fruits, seeds and aerial parts of the plant have a widespread use as a phytomedicine in various parts of the world to treat diabetes. Several clinical studies have been performed with the plant since the 1970s. Rahman *et al.*, 2009 compared the effects of the plant juice (55 ml/day for 5 months) and rosiglitazone, in 25 patients. The results showed that the plant was more effective in the management of fasting blood glucose and total cholesterol, and in some diabetes-related complications (retinopathy and myocardial infarction) than rosiglitazone.

The plant's effects on glucose uptake were assessed in adipose tissue, a key link between obesity (as observed in MS) and diabetes. Additionally, uptake was assessed in the classic insulin target tissues – hepatocytes, adipose tissue and skeletal muscle – as these tissues play important roles in glucose homeostasis after glucose uptake. A protein extract of the fruit at 5 and 10 μg/ml was tested in perfused islet cells, incubated C2C12 myocytes and 3T3-L1

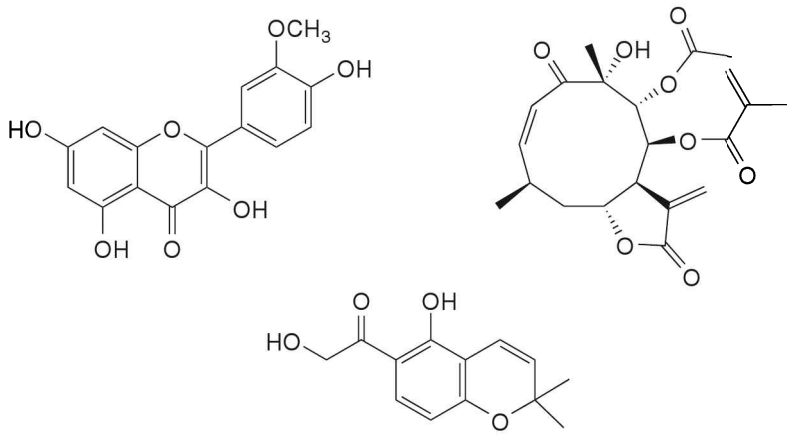

Figure 20.2 Isorhamnetin, calein C and the 6-hydroxyacetyl-5-hydroxy-2 2-dimethyl-2-chromene isolated from *Brickellia cavanillesii*.

adipocytes, and the authors reported an increase in insulin secretion and an increase in glucose uptake in myocytes and adipocytes (Yibchok-anun *et al.*, 2006).

The saponin-rich fraction (125 μg/ml) of the total ethanolic extract from *M. charantia* stimulated insulin secretion in MIN6 pancreatic β-cells and monodesmoside, and a bidesmoside (Figure 20.3) and cucurbitanes (0.05 and 0.010 mg/ml) were identified as active substances. The plant lowers blood glucose by promoting insulin secretion and this mechanism may contribute substantially to the plant's overall hypoglycemic effect (Keller *et al.*, 2011).

Cinnamomun cassia J. Presl. (Lauraceae) also targets insulin, possibly linked to enhanced insulin action, increased phosphorylation of the insulin receptor and overall facilitation of the insulin signalling system, inhibition of α-glucosidase activity and a possible activation of peroxisome proliferator activated receptors. The main active ingredients are procyanidin type-A polymers. A meta-analysis of clinical trials involving 282 people indicated that doses of 1–6 g/day of *C. cassia* resulted in decreased fasting glucose and lipid levels. Furthermore, a 3-month study in 102 people with T2D found a significant decrease in Hb1Ac of 0.83% using 1 g/day. A meta-analysis of six clinical trials involving 435 patients found that the plant improved fasting glucose by 15 mg/dl and only slightly decreased Hb1Ac in short-term studies. It remains controversial whether the whole powdered spice has an effect because a possibly combination of different types of cinnamon or an aqueous extract will be used (Shane-McWhorter, 2013).

20.4.4 Obesity and insulin resistance

Cordyceps species (Hypocreaceae) (a genus of endoparasitic ascomycete fungi, mainly on insects and other arthropods) have a long history of use in traditional medicine. One of the earliest clear records is a 15th-century Tibetan medical text, and there are claims of thousands of years of use in TCM (Winkler, 2008). *Cordyceps* has been used in tonics and stimulants to enhance energy, thus revealing potential effects on energy metabolism. Clinical trials have suggested beneficial effects on lipid metabolic disorders such as hyperlipidemia. The effect of *Cordyceps militaris* on metabolic parameters using obese C58BL/6J mice induced by a high-fat diet were studied, including body and organ weight measurements, stained sections of epididymal adipose tissue, fat accumulation in frozen liver sections and the plasma biochemical parameters (Kim *et al.*, 2014). Two active new compounds, cordyrroles A and B (Figure 20.4), together with 12 known compounds, including pyrrole alkaloids and nucleotide derivatives, were identified. The administration of the extract (100 mg/kg and 300 mg/kg) the body weight gain and food efficiency ratio induced by the diet. The amount of epididymal fat and the size of adipocytes were also decreased. Liver weight and fat deposition in the liver

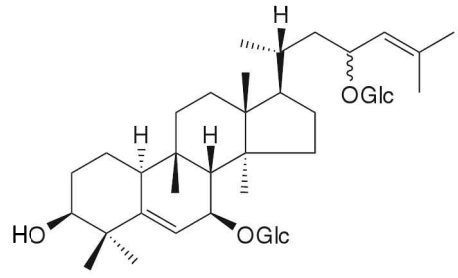

Figure 20.3 Kuguaglycoside isolated from *Momordica charantia*.

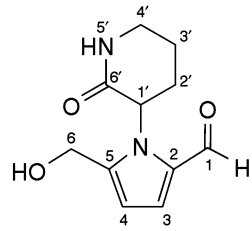

Figure 20.4 Cordyrrole A isolated from *Cordyceps militaris*.

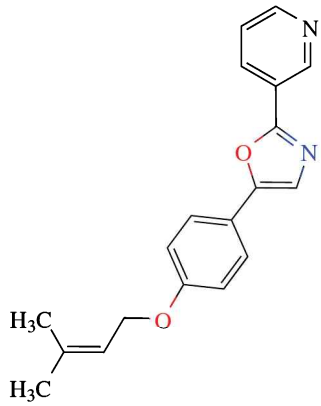

Figure 20.5 (3,3-dimethylallyl) halfordinol isolated from *Aegle marmelos*.

were dramatically reduced, and the lipid profiles were also reduced. Among the isolated compounds, cordyrrole A significantly inhibited adipocyte differentiation in 3T3-L1 preadipocytes and pancreatic lipase activity, whereas cordyrrole B was more effective at inhibiting pancreatic lipase. Cordycepin, a characteristic compound of *Cordyceps militaris*, decreased the rate of adipocyte differentiation.

A plant widely used in South-East Asia for the treatment of T2D and obesity is *Aegle marmelos* Correa. (Rutaceae). Lipolytic and antiadipogenic effects of (3,3-dimethylallyl) halfordinol (Hfn) (Figure 20.5) isolated from the leaves have only been shown recently (Saravanan *et al.*, 2014). The authors measured the intracellular lipid accumulation by Oil Red O staining and glycerol secretion. They analysed the expression of genes related to adipocyte differentiation by reverse transcriptase-polymerase chain reaction (PCR). The isolated compound dose-dependently (5–20 μg/ml) decreased intracellular triglyceride accumulation and increased glycerol release in differentiated 3T3-L1 adipocytes. Furthermore, they tested Hfn in high-fat diet-fed C57/BL 6J mice; treatment with 50 mg/kg for 4 weeks reduced plasma glucose, insulin and triglyceride levels, and significantly reduced total adipose tissue mass by 37.85% and visceral adipose tissue mass by 62.99%.

The PCR analyses indicated that Hfn decreased the expression of peroxisome proliferator-activated receptor γ (PPARγ) and CCAAT enhancer binding protein α (CEBPα) and increased the expression of sterol regulatory enzyme binding protein (SREBP-1c), peroxisome proliferator-activated receptor α (PPARα), adiponectin and glucose transporter protein 4 (GLUT4) compared to the high-fat diet group. These results suggested that Hfn decreased

adipocyte differentiation and stimulated the lipolysis of adipocytes. The main conclusion of this study was that Hfn showed lipolytic and antiadipogenic effects in *in vitro* and *in vivo* models. The reduced adipocyte size and decreased circulating triglyceride levels showed decreased insulin resistance in the treated animals.

20.5 Conclusions

T2D and MS are rapidly growing worldwide health problems. Although the aid of a physician and laboratory testing are required for diagnosis, patients seek alternative treatments, including traditional medicines. Why? Because when people realize that they will need extended treatment for these perpetual conditions, they look for treatments they believe will be less harmful. It is beyond the scope of this chapter to discuss the side effects of medicinal plants, but certainly if a plant has a pharmacological effect, it will also have side effects.

As we saw in the examples, flavonoids, coumarins, alkaloids, terpenes and nearly all types of structures have been reported to possess hypoglycemic effects.

The good news is that at least one compound, n,n-dimethylguanidine, isolated from the European lilac *Galega officinalis* L., was used to produce metformin, a modern first-line treatment of choice for T2D, especially in overweight and obese individuals (MS). This provides hope for the discovery of new natural compounds or chemically well-characterized extracts with a therapeutic profile similar to metformin.

There are many options for the treatment of T2D and MS, and several possible targets. We can increase the incretin levels in the gut or inhibit the enzymes that destroy them to increase insulin levels. We can instead delay the ingestion of carbohydrates by inhibiting alpha glucosidases; these only represent a broad approach to gut targeting. We can target the liver via several enzymatic and genetic targets to limit excessive glucose production due to the lack of insulin activity, or we can improve the insulin resistance in the liver.

There is a close relationship between obesity and T2D, and insulin resistance bridges them. It is important to note that not all patients with insulin resistance and obesity become diabetic; these conditions can be lifelong and accompanied by blood sugar levels in normal ranges. However, this relationship provides us with the tools for the study of new compounds in nature. Even if traditional medicine does not recognize MS, we can look for plants traditionally used to reduce glucose levels (hypoglycemic) and/or plants used to control weight (obesity), and there certainly are examples from traditional medicines for such uses.

Until now, there has been no phytomedicine available to treat MS or T2D, so ethnopharmacological field studies in places where medicinal plants are still at the top range of use can provide us with opportunities for discovering unknown hypoglycemic agents. More and better clinical studies are needed on the hypoglycemic plants discussed here.

As a final reflection, why must we search for treatments for people with T2D and MS? We know that the origin of these problems is in many cases obesity produced by poor nutrition. Why do we not learn to eat correctly instead? Perhaps, in time, we can stop this growing epidemic in a better and more far-reaching way.

Acknowledgments

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