Handbook of Nutraceuticals and Functional Foods

Robert E.C. Wildman, Richard S. Bruno

Nutraceutical Herbs and Insulin Resistance

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13 Nutraceutical Herbs and Insulin Resistance

Giuseppe Derosa and Pamela Maffioli

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13.1 INTRODUCTION

Insulin is a hormone produced by the endocrine pancreas, in particular by pancreatic β-cells, in response to hyperglycemia. Under normal conditions, muscle cells and fat cells are equipped with insulin receptors. After a meal, pancreatic β-cells increase insulin secretion, insulin binds to its receptors in muscle and adipose tissue with migration of glucose transport glucose 4 (GLUT4) channels, quiescent in the cellular cytoplasm, to the surface of the membrane cell, allowing glucose entrance in the cell. Also, the liver is equipped with insulin receptors: after the meal, insulin binds to hepatic receptors and with a cascade of signals inhibits glycogenolysis in favor of glycogenesis. Moreover, insulin links to its receptors in liver
cause opening of glucose transport glucose 2 channels (GLUT2), allowing glucose to enter the hepatic cell. Insulin resistance is a condition characterized by a reduced capacity of muscular, adipose, and liver cells to respond to insulin; these cells become less sensitive to the action of insulin, making more insulin needed to perform the same actions. In the initial stages, the pancreas produces more insulin to maintain normal blood glucose levels with greater work by the β-cells and hyperinsulinemia. Over time, the pancreas begins to fail to compensate for the greater need of insulin due to insulin resistance; when this happens, glycemia begins to rise, initially after meals, and then even fasting. This constant increase in fasting blood sugar can, over the years, lead to type 2 diabetes mellitus. However, insulin resistance does not only cause diabetes, because hyperinsulinemia is also considered a predictor of future cardiovascular events.\(^1\)\(^2\) Insulin resistance, in fact, can increase fibrinogen in the blood and is closely associated with hypertension in the obese and not obese.\(^3\) For this reason, prevention is certainly important; since insulin resistance is almost always linked to excessive weight, the first intervention should be an appropriate lifestyle. Lifestyle changes require the patient to be educated to follow a proper diet, in order to obtain a correction of excess body weight. An appropriate nutritional plan is based on the model of the Mediterranean diet and provides a total fat intake of less than 30%; a supply of saturated fatty acids below 10%; a supply of fibers, half soluble, exceeding 15 g/1000 kcal; a carbohydrate intake of 45%–60%; and proteins equal to 15%–20%. Patients should limit saturated fat intake to less than 7% of daily caloric needs; monounsaturated fatty acids, such as olive oil and other vegetable oils, are recommended.\(^4\) Patient should also be encouraged to increase physical activity and, in particular, to practice aerobic activity for at least 30–40 minutes, 3–4 times a week. If the patient is a smoker, he or she should be encouraged to quit. In addition to this, it is also important to address all cardiovascular risk factors (dyslipidemia, hyperglycemia, insulin resistance, and metabolic parameters).\(^5\)\(^6\) In the next pages, we will describe the main nutraceuticals with evidence of a certain action on glycemia and insulin resistance. For the description of how various nutraceuticals act, please see Table 13.1 and Figures 13.1–13.7. For a description of their chemical formula, see Table 13.2.

13.2 MEDICAL PLANTS

13.2.1 Agaricus blazei

Many edible mushrooms and traditional plants have been widely screened for use as remedies for natural products for the control of diabetes. Agaricus blazei is a common mushroom in South America and Asia, and has been widely used in traditional medicine as a remedy for certain types of cancers and diabetes.\(^7\)\(^8\)\(^9\) In Asia, including the Republic of Korea, fruiting bodies of Agaricus blazei have a considerable reputation as a potent remedy for diabetes mellitus. A preliminary study in our laboratory showed that dried culture broth from submerged cultures of Agaricus blazei inhibits \(\alpha\)-glucosidase activity in vitro and exhibits hypoglycemic action in streptozotocin-induced diabetic Sprague-Dawley rats. However, the molecule responsible for the hypoglycemic response, free of \(\beta\)-glucans and glycoproteins, is not known. Dietary supplementation with an extract of Agaricus blazei Murill has a protective effect against obesity induced by a high-fat diet. This is not due to decreased food intake but to increases in both energy expenditure and locomotor activity (especially during the dark period, which is when rodents are active), as well as decreases in pancreatic lipase activity within jejunum. As a result of the decreased body weight gain and fat mass, both plasma insulin and leptin concentrations are back to normal values.\(^10\)

13.2.2 Amorphophallus konjac

Konjac extract (KE) was refined from Amorphophallus konjac K.Koch, a kind of Chinese herb. KE is a kind of white crystal grain obtained from its tuber. Its main component is Konjac glucomannan,\(^11\) which is a kind of excellent edible fiber. It was reported\(^12\)\(^13\) that this polysaccharide could decrease
<table>
<thead>
<tr>
<th>Name</th>
<th>Chemical Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fucus vesiculosus</strong></td>
<td>Fucoidan</td>
</tr>
<tr>
<td><strong>Avena sativa</strong></td>
<td>Avena sativa</td>
</tr>
<tr>
<td><strong>Berberis aristata</strong></td>
<td>Berberine</td>
</tr>
<tr>
<td><strong>Curcuma longa</strong></td>
<td>Curcumin</td>
</tr>
<tr>
<td><strong>Gymnema sylvestre</strong></td>
<td>Antrachinones</td>
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(Continued)
<table>
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<tr>
<th>Chemical Formula</th>
<th>Name</th>
</tr>
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<tr>
<td>Glycine max</td>
<td>Glycine max</td>
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<tr>
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<td><img src="image" alt="Glycine max Chemical Formula" /></td>
</tr>
<tr>
<td>Lagerstroemia speciosa</td>
<td>Corosolic acid</td>
</tr>
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</tr>
<tr>
<td>Panax quinquefolius</td>
<td>Ginsenosides</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="Panax quinquefolius Ginsenosides Chemical Formula" /></td>
</tr>
<tr>
<td>n-3 PUFAs</td>
<td>C18:3n-3 (α-linolenic acid)</td>
</tr>
<tr>
<td></td>
<td><img src="image" alt="n-3 PUFAs C18:3n-3 (α-linolenic acid) Chemical Formula" /></td>
</tr>
<tr>
<td></td>
<td>C20:5n-3 (eicosapentaenoic acid)</td>
</tr>
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<td></td>
<td><img src="image" alt="n-3 PUFAs C20:5n-3 (eicosapentaenoic acid) Chemical Formula" /></td>
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<tr>
<td></td>
<td>C22:6n-3 (docosahexaenoic acid)</td>
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<td></td>
<td><img src="image" alt="n-3 PUFAs C22:6n-3 (docosahexaenoic acid) Chemical Formula" /></td>
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<tr>
<td>α-lipoic acid</td>
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<tr>
<td></td>
<td><img src="image" alt="α-lipoic acid Chemical Formula" /></td>
</tr>
</tbody>
</table>
FIGURE 13.1  Possible mechanism of action: Stomach and bowel.

FIGURE 13.2  Possible mechanism of action: Pancreas.

FIGURE 13.3  Possible mechanism of action: Adipose tissue and muscle.
FIGURE 13.4 Possible mechanism of action: Liver.

FIGURE 13.5 Possible mechanism of action: Gut hormone and enzyme.

FIGURE 13.6 Possible mechanism of action: Nucleus.
TABLE 13.2
Mechanisms of Action

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agaricus blazei</td>
<td>It increases adiponectin increase and has a metformin-like action and an $\alpha$-glucosidase inhibition.</td>
</tr>
<tr>
<td>Amorphophallus konjac</td>
<td>It delays stomach emptying and increases adiponectin by adjusting the rate of absorption of nutrients by small bowel, thereby increasing insulin sensitivity.</td>
</tr>
<tr>
<td>Ascophyllum nodosum and Fucus vesiculosus</td>
<td>They modulate the activity of $\alpha$-glucosidase.</td>
</tr>
<tr>
<td>Avena sativa</td>
<td>$\beta$-glucan is reported to increase the viscosity of food bolus, delay gastric emptying, and lengthen intestinal transit time; slow the absorption of nutrients especially the carbohydrates; and enhance satiety. It was also reported that $\beta$-glucan could slow the appearance of glucose in plasma, resulting in longer-lasting insulin secretion, which exerts a prolonged inhibition of endogenous glucose production.</td>
</tr>
<tr>
<td>Berberis aristata</td>
<td>It improves insulin resistance partly through activation of adenosine monophosphate-activated protein kinase (AMPK) and increased phosphorylation of insulin receptor; inhibition of $\alpha$-glucosidase activity.</td>
</tr>
<tr>
<td>Cinnamomum aromaticum</td>
<td>It activates the insulin receptor by multiple mechanisms that included increased autophosphorylation of the insulin receptor, increased glucose transporter 4 receptor (GLUT4) synthesis and activation, inhibition of pancreatic and intestinal amylase and glucosidase, and increases glycogen synthesis in the liver, thus improving insulin sensitivity and glycemic control.</td>
</tr>
<tr>
<td>Cyamopsis tetragonoloba</td>
<td>Its facilitates glucose uptake into peripheral tissues. It acts as a real insulin sensitizer. It restores the activity of glucose-6-phosphatase and fructose-1,6-bisphosphatase. It decreases mass transfer and modulates intestinal absorption of glucose.</td>
</tr>
<tr>
<td>Cynara scolymus</td>
<td>It is a powerful inhibitor of glucose 6-phosphatase translocase, an essential component of the hepatic glucose 6-phosphatase system that regulates the homeostasis of blood glucose. In addition, dicaffeylochic acid derivatives can also play a hypoglycemic role in modulating the activity of $\alpha$-glucosidase and consequently the catabolism of dietary carbohydrates.</td>
</tr>
</tbody>
</table>
Recent studies indicated that KE could obviously improve glucose tolerance in diabetic patients and animals. This was confirmed by Mao et al, who showed that KE might not only improve insulin resistance and increase insulin sensitivity, but also lower fasting plasma glucose (FPG) and glycogen in liver and skeletal muscle, but it had no effect on the release of insulin. The experimental results revealed that KE might improve insulin sensitivity by increasing glucose usage of non-oxidation approach, not depending on the release of insulin.

### 13.2.3 Ascophyllum nodosum and Fucus vesiculosus

Ascophyllum nodosum and Fucus vesiculosus are brown seaweed species harvested off the coast of Sea Nord that are commercially available as a nutritional supplement and feed additive. The polyphenolic composition is represented by phlorotannins, able to inhibit α-amylase and α-glucosidase with an...
important hypoglycemic action in vivo\textsuperscript{16,17} and in particular post-prandial glucose (PPG). Phlorotannins slow carbohydrate absorption with a noncompetitive (not focused on catalytic site in competition with the substrate) and reversible mechanism of inhibition of the enzymes involved in carbohydrate degradation.\textsuperscript{16} The inhibiting action toward the activity of these enzymes results, in animal models (rats), in a reduction of glycemia and insulinemia after administration of amids and glucose.

Derosa et al. conducted a study about the effects of a hypoglycemic nutraceutical containing \textit{Ascophyllum nodosum} and \textit{Fucus vesiculosus} in a ratio of 95/5 and chromium picolinate.\textsuperscript{18} Also, \textit{Ascophyllum nodosum} and \textit{Fucus vesiculosus} act in an acarbose-like mechanism, and also, in this case, we recorded a similar reduction of glycated hemoglobin (HbA\textsubscript{1c}), FPG, PPG, and HOMA-IR compared to placebo, suggesting that reducing glucose absorption can be a valid option to prevent diabetes.

13.2.4 \textit{Avena sativa}

Oats, which are considered unique among the cereals, belong to the Poaceae family and are known as “Jai” or “Javi” in the Indian subcontinent. In the mid-1980s, oats were recognized as a healthy food, helping prevent heart disease, and then became more popular in human nutrition. The common oat (\textit{Avena sativa}) is the most important crop among the cultivated oats. Oats are suitable for human consumption as oatmeal, rolled oats, and other oat-enriched products. Recent studies in food and nutrition have revealed the importance of the various components of oats, such as dietary fiber, especially \(\beta\)-glucan, minerals, and other nutrients.\textsuperscript{19} Oats and oat-enriched products have been proven to control blood glucose concentrations and to be helpful in the treatment of diabetes. Several studies have suggested that oats and oat-enriched diets can significantly decrease insulin responses, FPG, and PPG in overweight and type 2 diabetic subjects,\textsuperscript{20–25} which is mainly attributed to the markedly functional properties and enormous importance of \(\beta\)-glucan in human nutrition. \(\beta\)-glucan is a kind of high-molecular-weight polysaccharide exhibiting high viscosity at relatively low concentrations, which can reduce mixing of the food with digestive enzymes and delay gastric emptying. Increased viscosity also retards the absorption of glucose.

13.2.5 \textit{Berberis aristata}

Berberine is a standardized extract of \textit{Berberis aristata}, an Indian medicinal plant of the Berberidaceae family, an isoquinolinic alkaloid that has been shown to decrease glucose levels and improve insulin resistance through activating of MAP-kinase and increasing the phosphorylation of insulin receptors. In addition to a positive effect on glucose metabolism, berberine also regulates the expression of the receptor for low-density lipoproteins, leading to a 30% decrease in total cholesterol and 25% in LDL cholesterol. The extract of \textit{Berberis aristata} is present in various combinations and also available with the extract of \textit{Silybum marianum}, a potential inhibitor of enterocyte-associated glycoprotein and known hepatoprotector. \textit{Berberis aristata}, in fact, is easily absorbed at the intestinal level, but is characterized by poor oral bioavailability, as it is the substrate of several ABC transporters, such as P-glycoprotein, which causes enteroctic re-extrusion. The extract of \textit{Silybum marianum}, being a P-glycoprotein inhibitor, is able to allow berberine to bypass P-glycoprotein and be absorbed at a higher concentration. The patented combination of \textit{Berberis aristata/Silybum marianum} based on 588 mg of Berberis extract aristata titrated to 85% in berberine (equivalent to 500 mg of berberine) and 105 mg of extract of \textit{Silybum marianum} titrated to 65% in flavanolignanes has shown good efficacy in reducing insulin resistance in several studies. A first study was conducted by Di Pierro et al.;\textsuperscript{26} it was a single-blind, randomized, controlled, 4-month trial, conducted on 69 normcholesterolemic patients with type 2 diabetes mellitus and non-optimal glycemic control (HbA\textsubscript{1c} between 7.0% and 9.0%). Patients were randomized to \textit{Berberis aristata} at a dose of two tablets/day, corresponding to 500 mg of berberine, or to \textit{Berberis aristata/Silybum marianum} at a dose of two tablets/day for 120 days. The therapy taken before enrollment was not changed. Both \textit{Berberis aristata} and \textit{Berberis aristata/Silybum marianum} reduced FPG (−19.05%,
and $-18.13\%$, respectively) and HbA$_{ic}$ ($-7.18\%$ and $-12.35\%$, respectively), with a better effect of \textit{Berberis aristata}/\textit{Silybum marianum} on HbA$_{ic}$. The results are not surprising since it has been said above that Silymarin serves to increase the bioavailability of berberine, so a combination of these is more effective. Although the data of Di Pierro et al. suggest that there is an improvement in insulin resistance due to the improvement of glyco-metabolic control, the first study to directly evaluate the improvement of insulin resistance with \textit{Berberis aristata}/\textit{Silybum marianum} was conducted by Derosa et al.\textsuperscript{27} This randomized, placebo-controlled, 14-month, double-blind, randomized study was conducted on 105 overweight, normotensive Caucasian patients aged $\geq 18$ years, euglycemic and hypercholesterolemic, with cholesterol values between 200 and 240 mg/dL and triglycerides (Tg) $< 400$ mg/dL. The patients underwent an initial period of diet and exercise, after which they were randomized to placebo or \textit{Berberis aristata}/\textit{Silybum marianum}, two tablets/day for 3 months, followed by a 2-month wash-out period, followed by another 3 months with the resumption of the same therapy before the wash-out. In addition, to a marked improvement in the lipid profile with the \textit{Berberis aristata}/\textit{Silybum marianum} combination, there was a reduction in fasting insulin (FPI) and insulin resistance (HOMA-IR) index 3 months after randomization. After the wash-out period, a growth of FPI and HOMA-IR was observed, which again decreased with the reintroduction of the treatment with \textit{Berberis aristata}/\textit{Silybum marianum}. The data were strengthened by the fact that the retinol-binding protein-4 (RBP-4), an adipocytokine secreted by adipocytes, contributing to insulin resistance, and resistin, a hormone produced by adipose tissue, which results in insulin resistance, decreased after 3 months of treatment with \textit{Berberis aristata}/\textit{Silybum marianum}. These values grew during the wash-out period and decreased again when the nutraceutical was reintroduced. On the other hand, adiponectin, a protein hormone whose levels are inversely related to the percentage of fat in the adult body, was increased after 3 months of \textit{Berberis aristata}/\textit{Silybum marianum}.

13.2.6 \textbf{CINNAMOMUM AROMATICUM}

Cinnamon bark oil has been used for centuries in Western and traditional Eastern medicine, such as Indian Ayurvedic and Unani systems, to treat many conditions. The German Commission E recognizes the use of two cinnamon species (\textit{Cinnamomum verum} and \textit{Cinnamomum aromaticum}) to treat loss of appetite, dyspeptic complaints, bloating, and flatulence. Cinnamon (Cinnamomum) has been suggested to help patients with type 2 diabetes mellitus to achieve better glycemic control, although conclusions from meta-analyses are mixed.\textsuperscript{28} Some \textit{in vitro} and \textit{in vivo} studies have suggested that a compound or compounds in the aqueous extract of cinnamon activated the insulin receptor by multiple mechanisms that included increased autophosphorylation of the insulin receptor, increased glucose transporter-4 receptor synthesis and activation, inhibition of pancreatic and intestinal amylase and glucosidase, and increased glycogen synthesis in the liver, thus improving insulin sensitivity, glycemic control, and lipid levels.\textsuperscript{29}

13.2.7 \textbf{CYAMOPSIS TETRAGONOLOBA}

\textit{Cyamopsis tetragonoloba} is also known as cluster bean. It is a drought-resistant annual herb ranging from 2 to 4 feet in height cultivated in semi-arid regions throughout India. \textit{Cyamopsis tetragonoloba} beans are consumed as food; the gum acquired from the endosperm of the seeds is beneficial for health. Polyphenol composition of the plant includes gallic acid, caffeic acid, gallotannins, genistein, catechol, rutin, myricetin-7-glucoside-3-glycoside, chlorogenic acid, ellagic acid, quercetin, daidzein, rutin, catechin, naringenin, kaemferol, 2,4,3,-trihydroxy benzoic acid, texasin-7-O-glucoside, hydroxycinnamic acid, and p-coumaroylquinic acid. \textit{Cyamopsis tetragonoloba} beans have been reported to possess hypoglycemic and hypolipidemic effects in and alloxan-induced insulin-deficient animal model, and researchers have also reported antihyperglycemic properties of \textit{Cyamopsis tetragonoloba} beans in alloxan-induced hyperglycemic rats.\textsuperscript{30,31}
13.2.8 Cynara scolymus

*Cynara scolymus*, better known as artichoke, has been shown to increase body weight control and positively influence glucose and lipid metabolism both in animal models and in humans. Cynara scolymus derivatives, such as mono- and dicaffeoylchicnic acid compounds and glycosidic flavonoids (cyanoside and scolimoside), have recently been shown to influence glucose and lipid metabolism. This effect seems to be related mainly to the presence of chlorogenic acid. This compound is a potent inhibitor of glucose 6-phosphate translocase, an essential component of the hepatic glucose 6-phosphatase system, which regulates the homeostasis of blood glucose. In addition, dicaffeoylchicnic acid derivatives can also play a hypoglycemic role in modulating the activity of α-glucosidase and consequently the catabolism of dietary carbohydrates.

13.2.9 Curcuma longa

Curcuma is obtained from the *Curcuma longa* plant: its main constituent, curcumin, is a polyphenol with the ability to modulate numerous signal transmission mechanisms. Curcumin can act positively on all components of the metabolic syndrome, including insulin resistance. Thanks to its antioxidant and anti-inflammatory action, curcumin can also improve endothelial dysfunction, adipocytokine imbalances, and hyperuricemia. A recently published study has shown that supplementation with Curcuma for 8 weeks leads to an increase in adiponectin and a reduction in leptin levels in patients with metabolic syndrome. In particular, the ratio serum leptin/adiponectin was significantly reduced in the group treated with curcumin compared to placebo. The ratio leptin:adiponectin is considered an index of insulin resistance and atherogenic risk in both diabetic and non-diabetic patients. There are also studies showing an association between ratio leptin:adiponectin and low degree of inflammation, mean intimal thickness, first cardiovascular event, arterial stiffness, and different components of the metabolic syndrome.

Some previous studies revealed that curcumin could decrease insulin resistance by increasing the oxidation of fatty acids. Curcuma improved insulin resistance in skeletal muscles through the activation of MAP-kinase and the oxidation of fatty acids. Moreover, Curcuma has a hypoglycemic and insulin-sensitizing effect: It is able to reduce plasma glucose and to reduce the production of hepatic glucose and inflammation-induced hyperglycemia; it stimulates glucose entry into cells with the over-expression of GLUT4, GLUT2, and GLUT3 and the activation of MAP-kinase. Furthermore, curcumin promotes the activity of PPAR ligand, stimulating the secretion of insulin by pancreatic tissue, improving the functionality of pancreatic cells and reducing insulin resistance.

13.2.10 Gymnema sylvestre

*Gymnema sylvestre* is a medicinal plant belonging to the Asclepiadaceae family, popularly known as “gurmar” in Hindi, which means “sugar destroyer.” It is a climbing plant that grows in tropical forests in India and Southeast Asia. Its leaves present a wide range of therapeutic effects thanks to its active ingredients, gymnemic acids, a mixture of at least 17 different saponins, glycosides, and antherocinonic acids. In Indian medicine, it is used for its hypoglycemic properties, but various studies have also shown a potential of this plant in the treatment of metabolic syndrome. *Gymnema sylvestre* helps to promote weight loss through its ability to reduce the desire for sweets, and also controls blood glucose levels. Chewing the leaves, rinsing the mouth with watery extracts, or applying an extract topically on the tongue selectively inhibit the feeling of sweetness. Some studies have suggested that gymnemic acid binds to the receptor located on the taste buds of the tongue and prevents their activation by the sugar molecules. *Gymnema sylvestre* also suppresses the absorption of sugars, presumably by blocking the sucrose receptors through one of its component, the peptide gurmarin. It would seem, moreover, that not only does this plant block the receptors at the level of the mouth, it also acts, with the same inhibitory activity, on the sodium-dependent glucose transporters expressed at high concentrations on the intestinal cell brush.
Gymnema sylvestre’s ability to lower blood glucose concentrations was tested using it as a hypoglycemic agent in combination with insulin in humans, with encouraging results. A preliminary study shows that the administration of 200 mg/day of Gymnema sylvestre extract reduced the required insulin dose by 50% and reduced the value of HbA1c both in type 1 diabetics and in type 2 diabetics. Also, the number of ß-cells in the pancreas increased and, consequently, the endogenous production of insulin increased. When 400 mg/day of this extract was added to conventional hypoglycemic agents such as glibenclamide or tolbutamide, some patients were able to reduce the dose of the drug or even discontinue it. In vivo studies, oral administration of a Gymnema sylvestre extract (1 g/day for 60 days) showed a significant increase in insulin and circulating C-peptide, which were associated with significant reductions in FPG and PPG.

13.2.11 Glycine max

Glycine max, or soya bean, is a species of legume native to East Asia, widely grown for its edible bean, which has numerous uses. Soybeans and pulses are known to be beneficial for diabetes management due to their low glycemic index, defined as producing a relatively low rise in blood glucose following their consumption. Soybeans are the best-known source of isoflavones, including the major isoflavone aglycones, genistein, daidzein, and glycitein, and their respective glycoside conjugates, genistin, daidzin, and glycitin. Their proposed anti-diabetic activity is reportedly due to their ability to attenuate insulin resistance and improve insulin secretion, with evidence to support these claims found in various clinical trials.

13.2.12 Ilex paraguariensis

Ilex paraguariensis, also known as mate tea, is a very popular beverage in vast regions of South America, and its use has been expanding to Europe and the United States in the past decades. It is very rich in polyphenols. Notably, it has one of the highest concentrations of chlorogenic acids among the popular beverages and teas. It has been observed that consumption of Ilex paraguariensis improves the glycemic and lipid profile in patients with type 2 diabetes mellitus treated with oral hypoglycemic agents (metformin and sulfonylureas), and also induces a decrease of some anthropometric parameters in overweight subjects.

13.2.13 Lagerstroemia speciosa

Lagerstroemia speciosa, commonly known as banaba, is a tropical plant found in many parts of Southeast Asia. In the Philippines, dried banaba leaves are used for the treatment of diabetes and kidney diseases. Many in vivo and in vitro studies have confirmed the anti-diabetic activity of banaba. The mechanisms involved include increased glucose entry into cells, altered hydrolysis of sucrose and starches, and reduced gluconeogenesis. These activities are attributed to the corosolic acid and ellagitannins and mediated by the PPAR receptor, MAP-kinase, and other signal transducer factors. Supplementation with banaba has proven to be safe and well tolerated.

Banaba standardized to 1% of corosolic acid was tested in a randomized study involving 32 patients with type 2 diabetes mellitus. Patients received banaba 32 or 48 mg or placebo for 2 weeks. Banaba significantly reduced blood sugar levels without any particular side effects.

13.2.14 Momordica charantia

Momordica charantia L. (Cucurbitaceae) has been used in the management of hyperglycemia and early signs of diabetes since ancient times in some countries. Ma et al. showed that Momordica charantia can ameliorate insulin resistance in type 2 diabetic rats. This effect may be related to the regulation of mRNA and protein levels of SOCS-3 and JNK.
13.2.15 **Morus alba**

*Morus alba* L. belongs to the family Moraceae; it is native to China and also widely cultivated in Japan and Korea. The species is a fast-growing tree, which can reach up to 20 meters in height. In Korea and Japan, patients with diabetes consume mulberry leaves as an anti-hyperglycemic supplement. Studies reported in literature seem to suggest that the leaf extract has significant post-prandial hypoglycemic effect, possibly through the inhibition of α-glucosidase and glucose transport.\(^6\)

13.2.16 **Opuntia ficus-indica**

The cactus opuntia, also known as nopal, is native to Central Mexico and the pads are eaten as a vegetable. Cactus plants have long served as a source of food for people, and they have long been used in traditional Mexican medicine for treating diabetes. Nopal is considered a functional food because it is a proven source of dietary fiber and bioactive compounds with antioxidant activity, such as flavonoids, flavonols, carotenes, and ascorbic acid, in addition to being low in calories.\(^62\)–\(^64\)

13.2.17 **Panax quinquefolius**

The only study that evaluated the effects of *Panax quinquefolius* on humans involved 84 patients with ischemic coronary artery disease and patients with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), or type 2 diabetes mellitus. Patients were randomized to take *Panax quinquefolius* for 4 weeks or placebo. After treatment, FPG was lowered more with *Panax quinquefolius* (25.80 ± 12.72% vs. 20.89 ± 17.12%), but without statistical significance. No changes in HOMA-IR were observed; however, a statistically significant increase in HOMA-β was observed, indicating higher insulin sensitivity, with *Panax quinquefolius* compared to the control group (from 3.48 ± 0.76 to 4.19 ± 0.79) (\(p < 0.01\)). From these preliminary data, therefore, it would appear that the use of *Panax quinquefolius* can help to improve β-cell function in cardiac patients with dysglycemia.\(^65\)

13.2.18 **Phaseolus vulgaris**

*Phaseolus vulgaris* (kidney bean) was shown to increase the body weight control and to influence positively glucose and lipid metabolism both in animal models and in humans.\(^32\) The mechanism of action that could explain the reducing effect on food intake, body weight, and glycemia of *Phaseolus vulgaris* is linked to the concomitant presence of two glycoproteins: α-amylase inhibitors and phytohaemoagglutinin. The inhibition of pancreatic α-amylase decreases starch metabolism and consequently glycemia after carbohydrate intake;\(^32\) moreover, it slows down gastric emptying, thus inducing satiety. Phytohaemoagglutinins bind to the intestinal brushborder and stimulate the release of cholecystokinin (CCK) and glucagon-like peptides that control food intake.\(^66\) These observations are consistent with their traditional use as antidiabetic products in Central America and even Europe prior to the discovery of insulin.

13.2.19 **Plantago ovata**

*Plantago ovata*, also known as *Plantago psyllium* or psyllium, belongs to the category of gel-forming fibers and acts positively against constipation as well as with a mass action, even at the metabolic level: Influencing, that is, the transformation and use of nutrients to varying degrees. The fibers, in fact, are fermented in the colon, producing healthy bacteria and short chain fatty acids (SCFAs), which in turn improve the flora and reanimate intestinal peristalsis, improving in this way all intestinal functions and thus countering more complete constipation, preventing relapses, especially if appropriate and well-planned therapies are performed. Furthermore,
the gel of the gel-forming fibers softens feces and facilitates their expulsion. Even in subjects suffering from hemorrhoids, therefore, the combined actions performed by the gel-forming fibers are able to provide a better therapeutic and prophylactic action than insoluble fibers, which give almost exclusively mass action, provided that the subject takes on large quantities of water. Several studies have been published in the literature on the positive effects of psyllium; for example, Derosa et al. published a 6-month study where 141 overweight and hypertensive subjects were randomized to take psyllium or guar gum 3.5 g three times a day 20 minutes before main meals or standard diet. Both fibers significantly improved body mass index (BMI), glycemia and FPI, HOMA-IR, HbA1c, LDL cholesterol, and Apo B levels, but only psyllium led to significant improvement of the Tg and pressure values. Furthermore, a meta-analysis published in 2012 showed that supplementation with psyllium led to a significant improvement in the frequency of defecation compared to placebo (OR = 1.19; 95% CI: 0.58–1.80, p < 0.05). The number of discharges per week increased in the psyllium-treated group compared to placebo (OR = 1.19; 95% CI: 0.58–1.80, p < 0.05).

Another meta-analysis evaluated the hypoglycemic effects of psyllium: data showed that psyllium administered before meals led to an improvement in FPG (−37.0 mg/dL; p < 0.001) and HbA1c value (−0.97%; p = 0.048). What is interesting is that the effects on glycemia were proportional to FPG levels: there were no significant effects in euglycemic subjects, but there was a modest improvement in subjects with pre-diabetes and a greater improvement in overt diabetic subjects.

13.2.20 *Stevia rebaudiana*

*Stevia rebaudiana* is one such herb of the genus Stevia, widely grown for its sweet leaves. Its glycosides are stevioside and rebaudioside, which are 250–300 times sweeter than sucrose, heat stable, pH stable, and non-fermentable. Stevia has several beneficial effects, such as helping in weight control, the management of diabetes, control of dental caries, anti-fungal and antibacterial properties, a healing effect on blemishes and cuts, blood pressure management, and aiding immune modulation. It is completely safe and non-toxic.

The possible glucose-lowering action may be due to the direct impact of steviosides on pancreatic beta cells to secrete more insulin and to improve their function in gluco-toxicity. It can also impose its hypoglycemic effect, as it enhances the first phase insulin response and concomitantly suppresses the glucagon levels.

13.2.21 *Trigonella foenum-graecum*

Fenugreek is a herb that is widely used in cooking and as a traditional medicine for diabetes in Asia. It has been shown to acutely lower PPG levels. Animal studies have shown that fenugreek seed extracts have the potential to slow enzymatic digestion of carbohydrates, reduce gastrointestinal absorption of glucose, and thus reduce post-prandial glucose levels. In addition, fenugreek stimulated glucose uptake in peripheral tissues and had insulinotropic properties in isolated rat pancreatic cells. In humans, fenugreek seeds acutely reduced PPG and insulin levels.

In addition, several longer-term clinical trials showed reductions in FPG and PPG levels and HbA1c.

13.2.22 *Syzygium cumini*

*Syzygium cumini* (L.) Skeels belongs to the Myrtaceae family, and it has been intensively studied as an antidiabetic agent. It has been recommended as an adjuvant for the treatment of type 2 diabetes mellitus. In Brazil, most people use an infusion or decoction of dry leaves in an average dilution of 2.5 g/L (0.2–6.9) for *Syzygium cumini*. Moreover, experimental data revealed the potential hypoglycemic activity of leaf extract, seed, and bark extracts and also seed kernels and fruits of *Syzygium cumini*. 
13.3 PHYTOCONSTITUENTS

13.3.1 α-LIPOIC ACID

α-lipoic acid is the treatment of choice for diabetic neuropathy, in combination with symptomatic therapy and physical treatment. α-lipoic acid, however, also plays the main role of antioxidant and takes part in some enzymatic reactions involved in glucose metabolism. Studies aimed to confirm the effects of α-lipoic acid on glycemic control and on antioxidant parameters in humans are lacking, but recently, Derosa et al. published a study to evaluate the effects of a dietary supplement based on α-lipoic acid versus placebo on glyco-metabolic control and on some oxidative stress markers in type 2 diabetic patients. One hundred and five diabetic patients were randomized to α-lipoic acid 600 mg supplementation, L-carnosine 165 mg, 7.5 mg zinc, and vitamin B, or placebo, for 3 months. Body mass index, FPG, PPG, HbA1c, FPI, HOMA-IR, lipid profile, high sensitivity C-reactive protein (Hs-CRP), superoxide dismutase, glutathione peroxidase (GSH-Px), and malondialdehyde were evaluated. There was a reduction in FPG, PPG, and HbA1c with the food supplement based on α-lipoic acid compared to baseline and placebo. Regarding the lipid profile, we observed a reduction of LDL-C and Tg with the food supplement, both compared to baseline and compared to placebo. There was a reduction of hs-CRP with the α-lipoic acid-based food supplement, both compared to baseline and placebo. An increase in SOD and GSH-Px and a decrease in MDA were achieved with the food supplement containing α-lipoic acid, both from baseline and placebo. From the data obtained, it can be concluded that the dietary supplement containing α-lipoic acid, L-carnosine, zinc, and B vitamins improved glycemic control, lipid profile, and oxidative stress markers.

13.3.2 ESSENTIAL FATTY ACIDS (n-3 PUFAs)

The n-3 PUFAs are components of the cell membranes of organs and tissues, able to modulate, even at moderate concentrations, complex biological processes, influencing the functionality of different systems (cardiovascular, nervous, immune) and the progression of some of the most significant diseases. Studies on the use of n-3 PUFAs such as eicosapentaenoic acid and docosahexaenoic acid on insulin resistance have given interesting data, so much so that supplementation with n-3 PUFAs seem to be a promising therapeutic strategy to prevent diabetes and improve insulin resistance. The metabolic precursor of EPA and DHA is a fatty acid mainly present in plants, α linolenic acid (ALA), a minor component of our diet, which is contained at relevant concentrations in green leafy vegetables, such as spinach, but above all in walnuts and canola, linseed, and soya oils. Like the homologue of the omega 6 series, linoleic acid, a precursor of arachidonic acid, ALA is an essential fatty acid, essential for the organism, which is not able to synthesize it de novo and must necessarily introduce it with the diet. Scientific evidence has shown that supplementation with n-3 PUFA leads to a beneficial effect on insulin resistance and glucose homeostasis, with a reduction in insulin resistance in the muscle, adipose, and liver, a possible reduction of insulin secretion and a consequent potential prevention of the development of type 2 diabetes. This was confirmed by a randomized controlled trial conducted by Derosa et al.: the aim of this study was to evaluate whether high doses of n-3 PUFA, compared to placebo, could regress the condition of impaired blood glucose in patients with IFG and IGT. Two hundred and eighty-one overweight/obese subjects were randomized with IFG or IGT; 138 subjects were randomized to n-3 PUFA, 1 g 3 times a day, and 143 to placebo for 18 months. Patients underwent an oral glucose load curve (OGTT) at the start and end of the study. A reduction in FPG and the HOMA-IR index with n-3 PUFA was observed, compared to baseline and placebo. Insulin levels were reduced with n-3 PUFA, while they were increased with placebo. The most interesting finding, however, is the fact that after the OGTT performed at the end of the study, a higher percentage of patients had a regression from IGT to IFG or from IFG to euglycemia in the group that took n-3 PUFA compared than that treated with placebo, where instead there have been several cases of progression in diabetes. Other data on the efficacy of n-3 PUFA on insulin resistance come from another study conducted by
the same research group:91 in this randomized, placebo-controlled study, the effects of n-3 PUFA were evaluated on insulin resistance markers in patients with fasting dyslipidemia and after an oral fat curve (OFL), which has been shown to be a reliable method for simulating post-prandial lipemia. The study showed that n-3 PUFA treatment not only improved the lipid profile in a basic situation, but also improved all insulin resistance parameters in a post-prandial situation simulated with an OFL. In particular, the Tg value obtained with n-3 PUFA was lower, while the levels of high-density lipoprotein and adiponectin were higher than placebo. After the OFL, comparing the OFL performed at baseline with that performed at the end of the study, there was a reduction in the value of Tg, resistin, and RBP-4 and an increase in adiponectin with 3-PUFA compared to placebo. Supplementation with n-3 PUFA, therefore, seems to lead to an improvement of the lipid profile and an improvement of insulin resistance parameters.

13.4 CONCLUSIONS

Insulin resistance is the common soil of cardio-metabolic pre-risk factors, as pre-hypertension, dysglycemia (pre-diabetes), and dyslipidemia. In people with insulin resistance, an appropriate lifestyle is certainly important for losing weight and improving insulin sensitivity. Adhering to a healthy lifestyle, however, is not always easy, the patient is often lazy and struggling to follow an adequate diet, so the use of nutraceuticals can help to achieve the goal.72 The fact that nutraceuticals are natural substances, however, does not mean that all substances are equal or that everyone can take them. Nutraceuticals should be taken under medical prescription and should be associated with an appropriate lifestyle.

REFERENCES


