Botanicals and Nutrients to Optimize Glucose Metabolism and Support Metabolic Homeostasis

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Discussion

DIABETES INCIDENCE

Ancient Type 2 diabetes mellitus (T2D) is a chronic metabolic disease that most often results from a combination of dietary, lifestyle, and hereditary influences. Diet, physical activity, sleep, stress management, and other lifestyle issues play a primary role in the development and progression of hyperglycemic conditions or metabolic syndrome.[1] Incidence has risen from 108 million people in 1980 to 422 million in 2014.[2] About 29 million people or 9% of the US population have diabetes, and it is estimated that around 28% of those with diabetes are undiagnosed.[3] The US Department of Health and Human Services estimates that in 2012 at least 86 million US adults 20 years of age and older had prediabetes.[1]

About 5% to 10% of those with prediabetes progress to T2D while about the same percentage succeed in regaining normal glycemic indices.[4] With the onset of T2D there is progressive loss of beta-cell function, increasing beta-cell dysfunction, and sustained hyperglycemia.[4,5] Current research reports that the onset of type1 (insulin-dependent) diabetes frequently occurs in those older than 30 years of age when it can be difficult to distinguish from type 2 (non-insulin dependent) diabetes.[6]

Diabetes is one of the five leading causes of death in the world and is considered the second leading cause of preventable death in the US.[7,8] This degenerative disease can lead to serious damage in the eyes, nerves, blood vessels, and other physiological systems.[7] Diabetic complications include peripheral neuropathy, retinopathy, cardiovascular disease, coronary heart disease, cerebrovascular disease, and cataracts.[4,5,7,9] Most often, hyperglycemia and T2D occurs along with hyperlipidemia, high blood pressure, and obesity, which places people at higher risk for cardiovascular disease.[2,4,7] Hyperglycemia and dyslipidemia contribute to atherogenesis and adversely affect macrovascular and microvascular health.[9]

Diabetes is considered part of a cluster of conditions known as metabolic syndrome that includes six diagnostic criteria: hyperglycemia, insulin resistance, central obesity, hypertension, elevated triglycerides, and decreased HDL-C (high-density lipoprotein cholesterol).[9,10] The main underlying risk factors for metabolic syndrome include abdominal obesity and insulin resistance.[11]

Insulin resistance and dysfunction of pancreatic beta-cells begin long before noticeable changes in serum glucose markers occur. Insulin initiates a cellular response through binding with a transmembrane glycoprotein cellular receptor. When cell receptors in tissues of the body become unable to metabolize glucose, they become insulin-resistant. As the condition progresses, the pancreas initially produces more insulin which later results in dysfunction of the pancreatic beta- cells.[5,12] Studies find that beta-cell dysfunction is a primary factor that determines progression to T2D.[13] Beta-cells become dysfunctional due to oxidative stress, cytokine induction, and other causes which also contribute to lack of beta-cell proliferation.[13]

High blood glucose concentrations promote multiple physiological responses including inflammation, high oxidative stress, and formation of AGE (advanced glycosylated end products).[14] Hence, T2D is associated with high oxidative stress and inflammation at the cellular level.[8] ROS (reactive oxidative species) produced during hyperglycemic conditions play a key role in the progression and complications of diabetes. High glucose levels inactivate many key antioxidant enzymes including SOD (super oxide dismutase), GSH (glutathione peroxidase), and catalase (CAT) by glycating proteins. Oxidative stress is known to interfere with insulin signaling and to impair secretion of insulin from pancreatic beta-cells. Beta-cells are found to be especially sensitive to ROS, which contributes to mitochondrial damage and cell death.[5]

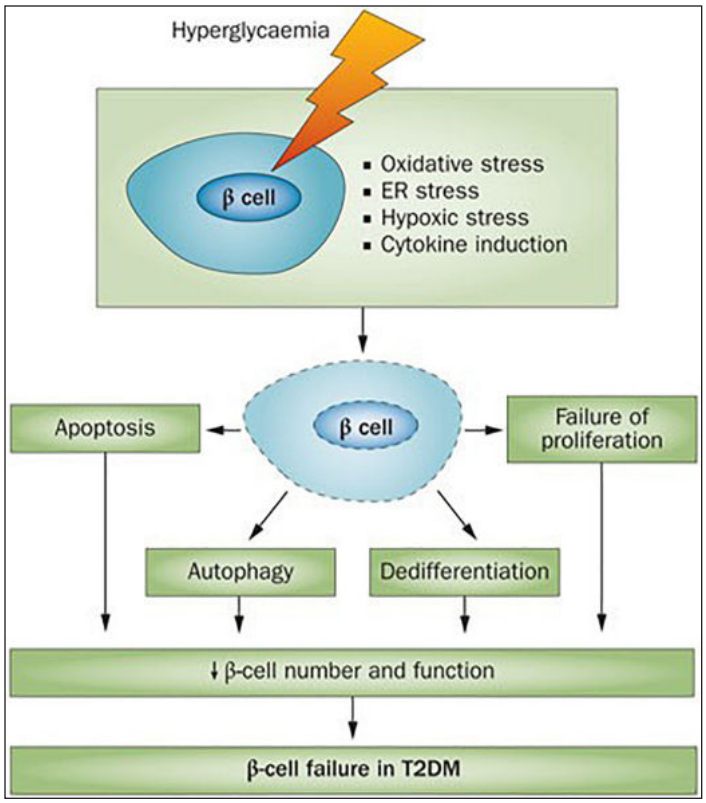


Image Source: *See reference #12*

Conditions of overweight and obesity are associated with metabolic disorders including T2D. The prevalence of obesity has risen 100% in the last decade and is commonly associated with T2D. Adipose tissue functions as an endocrine organ that plays a key role in regulating obesity, metabolism, insulin resistance, and other processes.[8]

Homocysteinemia (HC) – elevated serum homocysteine – is thought to promote insulin resistance and beta-cell dysfunction. HC provokes oxidative stress and systemic inflammation that promotes insulin-resistance in the liver, skeletal muscle, and vascular endothelium. HC, which contributes to dysfunctions of insulin-mediated glucose metabolism, is associated with a 3.6-fold increase in T2D risk. Folic acid, B6, and B12 are found to support healthy homocysteine levels.[15]

DIET AND MICRONUTRIENTS

While it is well-known that diet, nutrition, and lifestyle help prevent and slow the progression of most metabolic conditions, many patients are not compliant. Micronutrients, including vitamins and minerals, are required in small amounts for specific physiological functions. Most often they act as essential coenzymes and cofactors for metabolic processes including energy production and maintenance of life.[17] Some of those found to be most influential in modulation of glucose metabolism include chromium, vanadium, zinc, and members of the B-complex.

BOTANICALS TRADITIONALLY USED FOR DIABETES

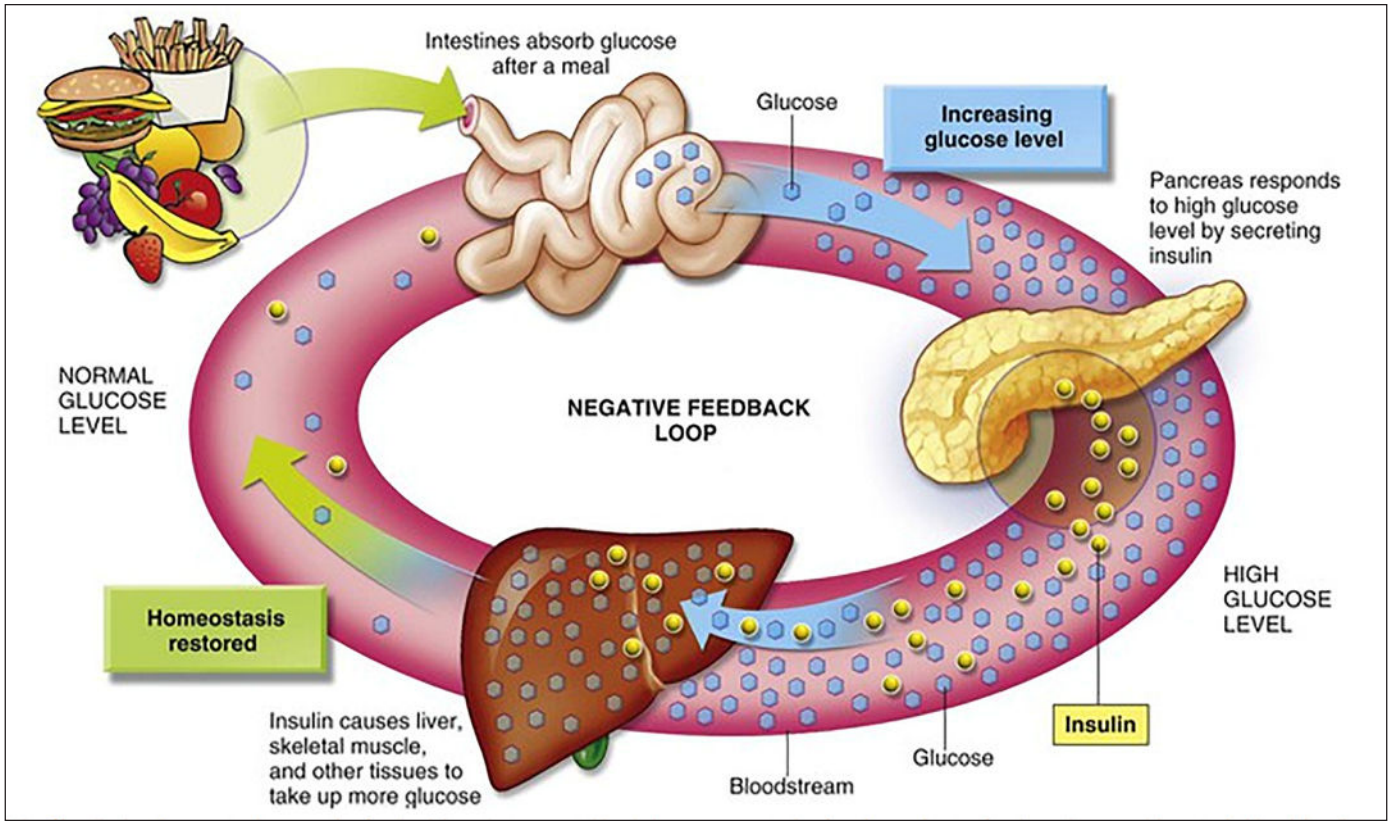
Chinese and Ayurvedic medicines have successfully treated metabolic disorders, including diabetes and obesity, for thousands of years with botanicals. Worldwide, most cultures have traditionally used medicinal plants to prevent and control metabolic and blood sugar conditions. Practitioners combine specific botanicals in formulations according to a detailed understanding of the progression and stages of the disease. Currently, it is estimated that one-third of those with diabetes use some form of alternative medicine.[7]

Many of the herbs used have a long history of safety and efficacy and are widely studied today. Scientists are interested in botanicals for their ability to act through multiple pathways to modulate physiological processes.[5,10,15] Clinical trials with botanicals demonstrate significant benefits to those with metabolic syndrome, obesity, and insulin resistance.[11]

Through their multiple actions, specific botanicals facilitate healthy glucose and lipid metabolism through modulation of numerous pathways to help restore metabolic homeostasis. Many of these including Momordica, Salacia, Gymnema, Berberine, Fenugreek, Pterocarpus, and Cinnamon inhibit or modulate glucose absorption through various pathways. Some of the herbs, such as Gymnema, Fenugreek, and Pterocarpus help stimulate the release of insulin. Herbs such as Gymnema stimulate the beta-cells and increase the affinity of insulin-binding receptors to insulin, thereby enhancing optimum glucose levels.[5]

Alpha-glucosidase enzymes in the small intestines are essential for the breakdown of complex carbohydrates into glucose and monosaccharides. Inhibition of these enzymes is found to benefit post-prandial and fasting glucose levels.[5] Studies find that many herbs including Fenugreek and Salacia have the ability to inhibit or modulate alpha-glucosidase enzymes in the small intestines.

In addition to their antidiabetic influence through multiple pathways, two herbs are noted in research for their restorative capacities. Gymnema and Pterocarpus are both found to be insulinotropic. Gymnema is able to help increase the number of beta-cells. Pterocarpus is found to exert a regenerative and protective influence on the beta-cells with the ability to reverse beta-cell damage.



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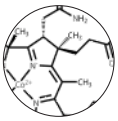
Botanicals and Nutrients to Optimize Glucose Metabolism and Support Metabolic Homeostasis



Vitamin B Complex

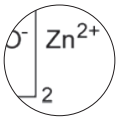
The water-soluble B-complex vitamins act as co-factors in enzyme reactions that facilitate numerous biochemical responses and play key roles in metabolic pathways. Studies report that serum levels of B vitamins are significantly lower in adults with T2D.[14]

Thiamin (vitamin B1) is a coenzyme in the formation of enzymes essential for metabolism of carbohydrates, amino acids, and fatty acids.[18-20] Thiamine and its metabolites are found to help prevent the formation of AGEs.[19]

Riboflavin (B2) is a precursor of coenzymes involved with redox reactions and influences the metabolism of B6, folate, niacin, and iron.[21] Niacin (B3) is essential for metabolic pathways involved with energy production and redox functions.[22] Pantothenic acid (B5) is a precursor in the biosynthesis of coenzyme A, which is essential for energy generation at the cellular level.[23]

Vitamins B6 and B12 play key roles in pathways for cellular energy production and in the hepatic methylation system. B6 and B12 are the most influential members of the B complex in supporting healthy homocysteine levels.[14] Many human enzyme systems that involve protein metabolism (catabolism/anabolism) or enzyme production require vitamin B6 for proper function.[24] B12 plays a key role in DNA synthesis, optimal haemopoesis, methylation, and neurological functions, among other essential functions. Vitamin B12 deficiency is found to be highly prevalent in T2D.[25]

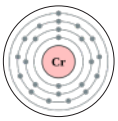
Zinc



Zinc, a non-toxic, biologically-essential trace mineral, is vital for almost all physiological processes. The only metal that is a coenzyme to all classes of enzymes, zinc is a key component of over 300

metalloenzymes. Zinc is essential for over 2000 transcription factors that are involved with gene transcription and regulation of lipid, protein, and nucleic acid metabolism.[26-32] About 10% of the human genome encodes for proteins that can bind zinc.[33] Necessary to maintain the structural integrity of DNA, zinc also plays a role in cellular metabolism.[26-33] Zinc exerts antioxidant influence, improves insulin signaling, and enhances cellular uptake of glucose.[34]

Chromium as Nicotinate Glycinate Chelate



Chromium is an essential micronutrient that potentiates insulin sensitivity and functions as a cofactor in all insulin-related activities. This trace element is vital for normal glucose metabolism and helps regulate carbohydrate and lipid metabolism.[16,34-37] The signs of chromium deficiency are similar to those of metabolic syndrome.[38] Chromium supplementation is found to improve glucose function and to increase the number of insulin receptors, facilitate the binding of insulin to insulin receptors, and to activate cellular insulin receptors in the presence of insulin.[16,34,37]

Momordica charantia

The fruit of Momordica, a climbing perennial grown throughout the world, is revered as a powerful medicinal in traditional medical systems.[39] Known as bitter melon, Momordica fruit (MF) has been used as a vegetable and herb for at least 600 years in Southern China.[10] Over 100 modern studies find MF beneficial in diabetes and its complications.[39] MF extract is well-known for its ability to alleviate diabetes, decrease blood glucose, and benefit dyslipidemia.[7,8,10,39-41] MF also possesses immumo-modulatory influence.[40,41]

Both MF extract and several of its constituents demonstrate the ability to lower blood sugar in hyperglycemic subjects through various pathways in both animal and human studies. It is found to inhibit glucose absorption, to promote glucose utilization in the liver, and to benefit both glucose and lipid metabolism. It is shown to influence energy balance through its effect on lipid metabolism.[42] MF is reported to facilitate cellular uptake of glucose, promote insulin release, and potentiate the effects of insulin. It demonstrates the ability to increase the number of insulin-producing cells in the pancreas of diabetic animals. MF is noted to be protective of pancreatic beta-cells.[7,41-43]

MF is found to stimulate peripheral and skeletal glucose utilization, inhibit intestinal glucose uptake, and to suppress key gluconeogenic enzymes. Research finds that MF juice seems to regulate glucose metabolism through the same intracellular signaling pathways as does insulin.[4]

MF contains a unique insulin-like polypeptide,[42] charantin, which is a triterpenoid found to exert antidiabetic activity.[4] It is known as p(plant)-insulin, which is biochemically similar to bovine insulin.[7,41]

MF is highly studied for its ability to reduce obesity and adiposity and to lower serum lipid markers.[8,10,40-42,44] MF is thought to influence the mechanisms for fatty acid transport into intracellular organelles. MF is found to exert an anti-obesity effect via pathways involving lipid oxidation and energy uncoupling.[40] MF juice inhibits membrane lipid peroxidation and the saponins component of MF exert lipid-lowering influence.[41] It also inhibits lipogenesis and stimulates lipolysis in human adipocytes.[8] In addition, MF inhibits adipocyte differentiation[7,40] and regulates adipogenic transcription factors and adipocytokine gene expression.[8] Adipocytokines influence both fat metabolism and energy homeostasis.[40]

This nutrient-dense fruit is a good source of dietary fiber and contains many beneficial compounds along with minerals, vitamins, and antioxidants.[7,41] MF is rich in vitamins A, C, E and contains vitamins B1, B2, B3, and folate. Its high mineral content includes potassium, calcium, zinc, magnesium, phosphorus, and iron. MF contains phenols, flavonoids, isoflavones, terpenes, anthroquinones, and glucosinates, which contribute to its high antioxidant activity.[7,41] The abundance of phenolics and flavonoids in MF pulp contribute to its antioxidant influence and ability to inhibit lipid peroxidation.[45]

Traditionally, MF and Fenugreek seed are combined for diabetic and blood sugar conditions. Animal studies find this combination helps normalize glucose levels, exert antioxidant activity, and helps protect vital organs against damage from diabetes-induced oxidative stress.[46]

Salacia reticulata

Salacia, which grows as a shrub or small tree, is highly valued in traditional Ayurvedic (Indian) and Unani (Greek) medicines to treat hyperglycemia and obesity.[9,47-49] *S. reticulata*, the most widely studied of the Salacia species, contains a wide range of constituents that vary with geographical place of origin and species.[48]

Modern studies find that, like most botanicals, Salacia works through multiple pathways to help normalize hyperglycemia and dyslipidemia.[9] Salacia extracts are found to modulate pathways and enzyme systems that influence carbohydrate and lipid metabolism.[48] Salacia is found to significantly lower blood glucose levels in animal studies.[47] Human studies show Salacia extracts decrease plasma glucose and insulin levels, decrease HbA1c (hemoglobin A1C), and modulate serum lipid levels.[48] In double-blind, randomized, placebo studies

with T2D patients, those receiving *S. reticulata* tea for three months had significant reduction in HbA1c.[48]

Salacia contains triterpenoids, quinones, phenolic acids, proanthocyanidins, flavonoids, catechins, tannins, sterols, and natural sugars. These compounds are all found to contribute to the potent antidiabetic activity of Salacia.[5,47,50]

Mangiferin, considered one of the primary compounds responsible for the antidiabetic influence of Salacia, is shown to inhibit enzymes involved with sugar digestion (sucrose, isomaltase, and others) and is widely studied.[48] Salacia contains potent alpha-glucosidase inhibitors that reduce the rate of digestion of complex carbohydrates in the small intestines.[47,49] Studies find Salacia reduces postprandial glucose levels and improves fasting glucose levels because of its inhibitory influence.[5,47-49] Postprandial hyperglycemia is a risk factor for microvascular and macrovascular complications in both patients with T2D and in those with impaired glucose tolerance.[49]

Salacia also exerts hepato-protective, antimicrobial, anti-inflammatory, antioxidant, and anti-obese activity.[47,48] It is found to suppress pancreatic lipase activity[47], which is attributed to its mangiferin, catechin, tannin, and proanthocyanadin constituents.[5,47,48]

Gymnema sylvestre

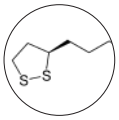
Gymnema is a climbing woody plant native to India where it has been successfully used for thousands of years to treat honey urine (as referred to in Ayurvedic medical texts) and high blood sugar conditions.[51-53] Currently, Gymnema is well-known for its ability to normalize serum glucose and serum lipids in both animal and human studies.[51,52,54] Studies find that Gymnema benefits blood sugar homeostasis, controls sugar cravings, and promotes regeneration of pancreatic beta-cells.[55-60] It also benefits body weight, serum cholesterol, and triglyceride levels.[55] Gymnema exerts antimicrobial, hepatoprotective, and anti-inflammatory influence.[51]

Gymnema leaves are rich in minerals including calcium, iron, magnesium, manganese, and zinc.[57] They contain terpenoids, flavonoids, phenolics, glycosides, and coumarins, along with other bioactive constituents known to reduce serum glucose levels.[51,52,55] Studies find Gymnema benefits blood sugar levels in T2D patients through multiple actions. Gymnema is found to help decrease sugar cravings through blocking the ability to taste sweetness. With a molecular structure similar to glucose, it also occupies receptors in intestines, which prevents sugar absorption from the small intestines.[51,55,56]

Gymnema is found to increase beta-cell numbers, stimulate insulin release, increase cell permeability to insulin, and benefit beta-cell function.[5] Gymnema is found to increase activity of enzymes that influence glucose uptake and utilization. In a controlled study with type 1 diabetics, insulin requirements decreased along with significant decrease in HbA1C.[52]

Gymnema leaf extract contains insulinotropic agents including gymnemic acids (triterpenoid saponins).[53] Gymnemic acid (GA), considered to be the plants active constituent, is found to increase pancreatic beta-cells.[51,52] The GS4 fraction of gymnemic acid is highly studied for its ability to help normalize serum glucose and to enhance endogenous insulin, likely through its ability to increase and revitalize pancreatic beta-cells.[53,56,58,59] GS4 is found to exert potent anti-diabetic activity and to play a significant role in regulation of both type 1 and type 2 diabetes.[53,60] The GS4 extract, used clinically to treat T2D, is found to stimulate insulin release from beta-cells and from islets.[53,56]

Alpha Lipoic Acid



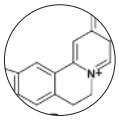
Alpha lipoic acid (ALA), also called thiotic acid, is well-known for its wide spectrum of activity including as an antidiabetic agent, powerful antioxidant, and anti-glycosylation influence. ALA, found to support healthy blood sugar metabolism, is shown to be beneficial for many aspects of diabetes. Studies report that ALA shows potential as an antidiabetic agent with insulin-sensitizing activity.[61] ALA can increase glucose uptake by a range of normal muscle types, improve the response to insulin by insulin-resistant skeletal muscles, and enhance efficient disposal of glucose.[62]

There is evidence for an association between oxidative stress and insulin resistance, possibly due to downregulation of insulin signaling.[63] ALA helps lessen the impact of oxidative damage caused by dysregulation of glucose metabolism.[64] ALA is found to lower lipid peroxidation in animals with insulin resistance.[65] It is able to quench free radicals in both aqueous and lipid domains. ALA demonstrates the remarkable ability to recycle other antioxidants including glutathione, coenzyme Q10, vitamins C and E, and even itself.

A potent redox-coupling agent, ALA works with glutathione in a cyto-protective role. It has the ability to raise levels of intracellular glutathione. It also functions as a coenzyme essential for ATP production and contributes to cellular health. For these and other reasons, ALA is often called a universal antioxidant.[66,67]

ALA exerts a powerful anti-glycosylation effect. Glycation reactions, accelerated in the diabetic patient, contribute to the development of diabetic complications. Sugar-damaged proteins called advanced glycation end-products (AGE) are a major factor in the aging process. AGE may lead to premature signs of aging and cause damage to tissues and organs.[68] ALA

is shown to control the formation of AGE and reduce protein damage from glycation in both humans and animals. This is found to benefit diabetic neuropathy, which is influenced by glycation and protein oxidation by glucose (glyco-oxidation).[69] Diabetic neuropathy is a complication of diabetes that results from many factors, including prolonged high blood glucose, oxidative stress, and decreased circulation. ALA is shown to alleviate diabetic neuropathy, along with its attendant pain and numbness.[70,71]



Berberine Sulfate

Berberine is a botanical alkaloid found in the root, rhizome, and bark of several medicinal botanicals commonly used specifically for infections, diabetes, and other conditions.[9] Berberine exerts powerful antioxidant and antidiabetic activity.[10,72] Some studies find it significantly helps reduce HbA1C comparable to metformin.[10] Berberine is shown to stimulate glucose uptake independent of insulin activity.[10] In animal studies, berberine is found to help reduce weight gain, enhance insulin sensitivity, and decrease blood glucose in those with T2D.[10]

Berberine is found to influence lipid metabolism. It inhibits adipogenesis and is shown to suppress adipocyte differentiation and reduce lipid accumulation in certain adipocytes through influencing specific genes and enzymes.[10]

AMPK (AMP-activated protein kinase) is a vital energy-sensing and -signaling system in mammalian cells. When activated, it can increase mitochondrial function and insulin sensitivity. Part of berberine's ability to regulate glucose metabolism is attributed to the fact that it targets and activates AMPK possibly through influencing the AMP/ATP ratio and through inhibition of the mitochondria. Studies suggest that moderate inhibition of mitochondrial function may benefit insulin sensitivity.[10]

Fenugreek (*Trigonella foenum-graecum*)

One of the oldest medicinal plants, originating in India and Northern Africa, Fenugreek seed is traditionally used in China, India, and the Mediterranean region as a culinary spice and powerful medicinal herb. Egyptians used Fenugreek seed flour for cooking along with maize and wheat flour. The seeds are known for their carminative, tonic influence and have long been used to treat diabetes.[78,79] Fenugreek seed powder and extracts are well-known for their hypoglycemic and anti-hyperlipidemic properties as demonstrated in human and animal studies.[73-77]

Fenugreek seed powder is found to enhance glucose tolerance, decrease insulin levels, and to significantly reduce glycosylated hemoglobin.[77] Fenugreek exerts its anti-hyperglycemic influence through multiple pathways. In humans, it is found to stimulate glucose-dependent insulin secretion from beta-cells and to inhibit intestinal enzymes.[74]

Fenugreek acts at the site of insulin receptors[78] and animal studies suggest that Fenugreek's ability to lower blood glucose is comparable to that of insulin.[79] It is found to increase the metabolic clearance rate of glucose and to increase erythrocyte insulin receptors.[78]

Through its action in the gastrointestinal tract, Fenugreek seed is shown to reduce fasting and postprandial blood glucose in T2D.[78] This activity is attributed to its high content of saponins and fiber, which help slow postprandial glucose absorption.[73,74] The fiber-rich, defatted portion of the seed has a significant level of saponins. Defatted Fenugreek seed is shown to reduce fasting and post-prandial glucose, glucagon, and insulin.[75]

Pterocarpus marsupium

Pterocarpus marsupium (PM) is native to areas of the Indian continent and Sri Lanka. Ayurvedic medicine utilizes all parts of the tree for medicinal properties. The heartwood is known as an astringent, traditionally used for treatment of inflammation and diabetes.[80,81] PM demonstrates anti-hyperglycemic activity. It is found to possess potent insulinotropic and insulin-like properties.[82] PM is also found to exert regenerative and protective influence on pancreatic beta-cells. In animal studies, PM reversed the damage to beta-cells and repopulated the pancreatic islets with resultant restoration of normal insulin secretion.[83-89]

The antidiabetic influence of PM is attributed to its polyphenolic compounds, particularly pterostilbene and epicatechin, both present in the bark. Its constituent epicatechin is found to be insulinogenic. Studies find it stimulates oxygen uptake in fat cells and in the tissues of various organs and increases glycogen content as glucose uptake increases.[87-90]

The phenolic compound pterostilbene is a naturally-occurring analogue of resveratrol. It is found to exert multiple influences including antioxidant, anti-inflammatory, antidiabetic, and anti-proliferative capacity.[91,92] Silbinol®, a concentrated extract, is standardized for a minimum of 5.0% pterostilbene and 0.01% epicatechin. It is carefully prepared from the heartwood and bark of PM.

Cinnamon (*Cinnamomum cassia*)

Cinnamon bark is a renowned and valued culinary spice and botanical medicine, traded worldwide for millennia. Traditional medicines, including Ayurveda and Chinese, revere it for its warming, tonic properties and include Cinnamon bark in many types of formulations. Modern studies find that Cinnamon bark

improves fasting blood glucose.[93] Cinnamon extract is shown to regulate glucose transport and insulin-signaling gene expression.[94] A human study showed a significant decrease in HbA1c in those with poorly-controlled T2D given two grams of Cinnamon daily for 12 weeks.[95] In a 40-day study with T2D patients, Cinnamon helped significantly reduce serum glucose, triglyceride levels, and serum lipid markers.[96]

Water extracts of Cinnamon are found to increase in vitro glucose uptake, increase glycogen synthesis, and increase phosphorylation of the insulin receptors. Cinnamon is thought to help trigger the insulin cascade system.[97] Polyphenols in Cinnamon are found to influence insulin signaling and glucose control. Studies find Cinnamon polyphenols help improve insulin sensitivity in in vitro, animal, and human studies.[97]

Vanadium Nicotinate Glycinate Chelate

Vanadium is a trace element that has multiple functions in human physiology. It is shown to exert a beneficial influence on insulin response and glucose metabolism in diabetics. Vanadium contributes to balanced tissue levels of reactive oxygen species and enhances healthy glucose and lipid metabolism.[17,98-100] Vanadium is considered an insulin-mimetic agent and exerts multiple influences in insulin activity. Vanadium enhances insulin activity and increases insulin sensitivity when insulin is still present. It is found to influence insulin-signaling pathways and the upregulation of insulin receptors.[17]

For more information on any of the ingredients listed here, including extensive research or individual monographs compiled by Donnie Yance, please email info@naturaedu.com.

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