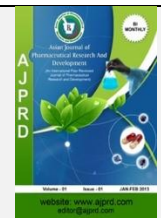


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Review Study

Between Medicines and Nutraceuticals in the Control of Diabetes Mellitus

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ABSTRACT

Diabetes is a type of metabolic disease such as insufficient insulin secretion or poor functioning. It is characterized by high blood sugar, which increases blood glucose concentration, causes various symptoms and signs due to high blood sugar, and excrete glucose from urine. Diabetes mellitus is divided into types 1 and 2, and type 1 diabetes was previously called 'juvenile diabetes', and it is a disease caused by the inability to produce any insulin. Type 2 diabetes, which is relatively deficient in insulin, is characterized by insulin resistance. Insulin treatment is required for type 1 diabetes, but type 2 diabetes is based on lifestyle correction and may require additional drug administration. In addition, many patients or people concerned about diabetes use dietary supplements to control their blood sugar, but because of the side effects of prescription drugs and the lack of definitive clinical trials of dietary supplements, it is important to choose wisely between prescription drugs and dietary supplements with the advice of a physician or expert to treat or prevent diabetes.

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INTRODUCTION

Diabetes mellitus is a type of metabolic disease characterized by high blood glucose, which is an increased concentration of glucose in the blood, resulting in a number of symptoms and signs and the excretion of glucose in the urine. Type 1 diabetes, formerly known as "juvenile diabetes," is caused by the body's inability to produce any insulin. Type 2 diabetes, which is characterized by a relative lack of insulin, is characterized by insulin resistance, which is the inability of insulin to lower blood glucose and prevent cells from burning glucose effectively. Type 2 diabetes seems to be largely caused by environmental factors such as high-calorie, high-fat, high-protein diets, lack of exercise, and stress as a result of westernization, but it can also be caused by defects in certain genes, pancreatic surgery, infections, and medications¹. In a normal body, there is a tissue called the Islet of Langerhans in the pancreas. In insulin-dependent diabetes, beta cells secrete 'insulin' to

consume glucose in the blood, but beta cells are attacked by white blood cells like allergies (type 1a) or fail to work properly due to external causes (type 1b). Since the body does not produce insulin, the only treatment for insulin-dependent diabetes is common-regulatory therapy, which involves injecting insulin into the body to maintain normal blood sugar levels in response to the correct carbohydrate intake². The most common risk factors are lack of exercise and obesity in type 2 diabetes. Lack of exercise lowers the muscle's ability to absorb glucose, and obesity causes fat deposits in the liver and muscles, which increases fat metabolism, and the byproducts of fat metabolism interfere with the action of insulin, leading to insulin resistance. The body responds by increasing the amount of insulin secreted by the pancreatic beta cells because the same amount of insulin is not enough to lower blood sugar due to less glucose uptake by the liver and muscles. This increase in blood insulin levels due to insulin resistance is called

hyperinsulinemia, and this high level of insulin breaks down fat cells, raising blood free fatty acid levels and causing fat to accumulate in the liver, leading to fatty liver. Insulin resistance causes hyperinsulinemia, and the fat deposited in the liver inhibits insulin action, creating a positive feedback loop that exacerbates insulin resistance³.

Current medicine in the control of diabetes

Type 1 diabetes requires insulin treatment. Insulin is currently available as an injectable medication and is usually administered subcutaneously, and the method of administration varies depending on the duration of action. Compared to oral medications, it has a faster blood sugar-lowering effect, can be used safely in environments where oral medications are not available, and has no dose limitations, but disadvantages include rejection of needles and difficulty in administration⁴. Insulin comes in ultra-rapid, rapid, intermediate, and long-acting varieties depending on the time of action. Ultra-rapid-acting insulins begin to take effect within 15 minutes of administration and usually last three to four hours. They are often given immediately after or just before a meal to help control postprandial blood sugar. Examples include insulin lispro, insulin aspart (NovoLog, NovoLog FlexPen, NovoPen Echo, NovoLog FlexTouch, Fiasp), and insulin glulisine (Lantus, Basaglar, Toujeo, Semglee, and Rezvoglar)⁵. Rapid-acting insulin is the type of insulin that was used to control blood sugar after meals before ultra-rapid-acting insulin became available, such as regular insulin. It usually takes effect 30 minutes to an hour after administration, and its effects usually last two to four hours. Intermediate-type insulin (NPH insulin) takes effect one to three hours after administration, with a duration of action of 12 to 16 hours and a peak effect of 6 to 8 hours after administration⁶. Long-acting insulins include insulin glargine, insulin detemir (Levemir), and degludec (Tresiba), which have a longer duration of action and more consistent effects than intermediate insulins, and are often used as basal insulin⁷. For type 2 diabetes, the treatment is based on lifestyle modification and may require additional medication. These medications are taken one to three times a day and have different dosing schedules and side effects depending on their duration of action⁸.

There are two main types of hypoglycemic drugs: insulin secretagogues and insulin sensitizers. Insulin secretagogues are divided into the sulfonylurea and meglitinide classes. Sulfonylureas are commonly prescribed and can cause hypoglycemia. Examples include Amaryl (glimepiride), Diamicon (gliclazide), and Daonil (glibenclamide)⁹. Meglitinides, a type of insulin secretagogue, are very fast-acting medications that are taken before meals, and include Novo Norm (repaglinide), Fastik (nateglinide), and Glufast (mitiglinide)¹⁰. Insulin sensitivity enhancers are

characterized by the absence of hypoglycemia when taken alone and include metformin, a biguanide, Avandia (rosiglitazone), and Actos (pioglitazone), a thiazolidinedione. Others include Glucobay (acarbose) and Besan (voglibose), which delay the absorption of carbohydrates in the small intestine¹¹.

On the other hand, there are GLP-1 agonists, which harness the action of glucagon-like peptide-1 (GLP-1), a hormone responsible for lowering blood sugar, and include injectable medications such as exenatide and liraglutide. DPP-4 inhibitors, which inhibit the action of dipeptidyl peptidase-4 (DPP-4), an enzyme that rapidly inactivates GLP-1, are also used, including Januvia (sitagliptin), Galvus (vildagliptin), and Onglyza (saxagliptin)¹². Newer drugs include SGLT2 inhibitors, which inhibit glucose reabsorption in the kidneys and have been shown to prevent cardiovascular complications, but long-term side effects need to be monitored.

Current nutraceuticals or ingredients for diabetes

Nutraceutical products can be considered non-specific biological therapies used to promote general well-being, control symptoms, and prevent malignant processes. The term “nutraceutical” combines the two words of “nutrient,” which is a nourishing food component, and “pharmaceutical,” which is a medical drug. The name was coined in 1989 by Stephen DeFelice, founder and chairman of the Foundation for Innovation in Medicine¹³. The nutraceuticals is to focused on prevention, according to the saying by a Greek physician Hippocrates who said “let food be your medicine”. The definition of nutraceuticals and their related products generally depends on the source. These products can be classified on the basis of their natural sources, pharmacological conditions, as well as chemical constitution of the products. Most often, nutraceuticals are grouped into four categories that include dietary supplements, functional food, medicinal food, and pharmaceuticals¹⁴.

Banaba (corosolic acid)

Banaba is the common name of *Lagerstroemia speciosa*. Corosolic acid and ellagitannins are the main active constituents of banaba which play a vital role as antidiabetic agents. A clinical study showed that corosolic acid and aqueous extract of banaba leaves could improve the symptoms that are associated with the metabolic syndrome via multiple mechanisms; reduction of the gluconeogenesis, impairment in the hydrolysis of starches and sucrose and enhancement of the cellular uptake of glucose. Moreover, blood sugar level was decreased in patients who treated with 10 mg corosolic acid for 30 days¹⁵. An ellagitannin from Banaba, Lagerstroemin, appears to act as an agonist of the insulin receptor¹⁶.

Bitter melon (*Momordica charantia*)

A common ingredient in Southeast Asian cuisine, bitter melon is a type of gourd rich in the nutrients charantin and polypeptide-p, which have been shown to help promote healthy blood sugar levels and naturally suppress hunger cravings. While the fruit itself is bitter unless brined and cooked, research shows that taking it as a dietary supplement can yield the same benefits for glucose metabolism as consuming it raw¹⁷. Bitter melon is traditionally known for its medicinal properties such as antidiabetic, anticancer, anti-inflammation, antiviral, and cholesterol lowering effects. It contains many phenolic compounds that may have the potential as antioxidant and antimutagen¹⁸. *M. charantia* and its various extracts and components are believed to exert their hypoglycemic effects via different physiological, pharmacological and biochemical modes. The possible modes of the hypoglycemic actions of *M. charantia* and its various extracts and compounds are its hypoglycemic effect¹⁹, stimulation of peripheral and skeletal muscle glucose utilization²⁰, inhibition of intestinal glucose uptake²¹, inhibition of adipocyte differentiation²², suppression of key gluconeogenic enzymes²³, stimulation of key enzyme of HMP pathway²⁴, and preservation of islet β cells and their functions²⁵.

Cinnamon

Cinnamon is obtained from tropical evergreen trees belonging to the family *Lauraceae*. It is widely distributed in Sri Lanka, China, India, and Australia²⁶. It has long been used as a spice and in traditional herbal medicines. Available evidence suggests that cinnamon has beneficial effects on diabetes management²⁷. Multiple mechanisms have been proposed by which cinnamon improves diabetes, including enhancing insulin sensitivity through insulin receptor signaling, inhibiting the activity of carbohydrate-digesting enzymes, inhibiting glucose transport, delaying gastric emptying, and blocking glucose absorption²⁸. The liver plays a crucial role in glucose metabolism. In fact, one study in 84 people with polycystic ovary syndrome (PCOS) found that taking 1,500 milligrams (mg) of cinnamon daily led to a significant increase in antioxidant blood levels after 8 weeks²⁹. Antioxidants are important because they help the body reduce oxidative stress, a type of damage to cells that is caused by harmful free radicals³⁰. One study showed that consuming 1 gram (g) of cinnamon extract daily for 12 weeks reduced fasting blood sugar levels and improved markers of oxidative stress in people with type 2 diabetes³¹. This is significant because oxidative stress has been linked to the development of nearly every chronic disease, including type 2 diabetes³².

Chromium

Chromium is an essential mineral that plays a crucial role in supporting healthy blood sugar levels. While many

vegetables, fruits, and whole grains contain trace amounts, more than 90% of adults do not obtain enough of this key element from their diet to maintain optimal metabolic hormone sensitivity³³. Chromium (Cr), as an essential element, is directly related to the activity of glucose tolerance factor (GTF)³⁴. Cr can alleviate glucose intolerance and insulin resistance³⁵ and it is involved in the metabolism of glucose, lipid, protein, and nucleic acid³⁶. Chromium helps to maintain normal glucose metabolism and peripheral nerve function. Chromium increases insulin binding to cells, increases insulin receptor density and activates insulin receptor kinase leading to enhanced insulin sensitivity³⁷. Chromium is an essential mineral that appears to have a beneficial role in the regulation of insulin action and its effects on carbohydrate, protein and lipid metabolism. Chromium is an important factor for enhancing insulin activity. Studies show that people with type 2 diabetes have lower blood levels of chromium than those without the disease³⁸.

Alpha lipoic acid

Alpha-lipoic acid is an antioxidant that is made naturally in the body and also found in foods. It is used to break down carbohydrates and to make energy. Because alpha-lipoic acid seems to work like an antioxidant, it might provide protection to the brain and also be helpful in certain liver diseases³⁹. Alpha-lipoic acid (ALA) is a caprylic acid-derived antioxidant. The compound is synthesized in the mitochondria and is a cofactor in the enzymatic nutrient breakdown. ALA is also available in red meat, beets, carrots, potatoes, spinach, and broccoli. ALA consists of a dithiol functional group that eliminates reactive oxygen species (ROS) by reducing the oxidized forms of other antioxidants⁴⁰. Alpha-lipoic acid (ALA) is a natural compound with antioxidant and pro-oxidant properties which has effects on the regulation of insulin sensitivity and insulin secretion. ALA is widely prescribed in patients with diabetic polyneuropathy due to its positive effects on nerve conduction and alleviation of symptoms⁴¹. In skeletal muscle ALA reduce triglyceride accumulation, enhances expression of the insulin receptor substrate 1 protein and improves insulin sensitivity by activating 5'-AMP-activated protein kinase, recruits glucose transporter type 4 from its storage site in the Golgi to the sarcolemma. Prescription of ALA can have both detrimental and cytoprotective effects on pancreatic β -cells⁴².

Berberine

Berberine is a chemical found in some plants, including a group of shrubs called *Berberis* and a bitter-tasting and yellow-colored chemical. Technically, it belongs to a class of compounds called alkaloids. It's yellow and is often used as a dye. Berberine is a supplement that has been associated with several potential health benefits. In particular, berberine has been shown to lower blood sugar, increase weight loss, and improve heart health. It

also stimulates glycolysis, improving insulin secretion, and inhibits gluconeogenesis and adipogenesis in the liver; by reducing insulin resistance. In a 2008 study of 116 people with diabetes, taking 1 gram of berberine per day lowered fasting blood sugar by 20%⁴³. It also lowered hemoglobin A1c (HbA1c), a marker of long-term blood sugar regulation, by 12% and improved levels of blood lipids such as cholesterol and triglycerides⁴⁴. According to an older review of 14 studies, berberine may be as effective as certain oral diabetes drugs, including metformin, glipizide, and rosiglitazone⁴⁵.

CONCLUSIONS

Scientific evidence on the effectiveness of dietary supplements in treating diabetes is short. Dietary supplements are stuffs that claim to have beneficial effects on many chronic diseases, including diabetes. However, there is no good evidence that dietary supplements can help people with diabetes control their blood sugar levels or prevent the development and progression of type 2 diabetes. There has been limited research on how well these products work and whether they are safe for long-term use. Better quality and quantity of scientific evidence is needed to support the use of dietary supplements to treat diabetes. There are several steps to improve the quality and quantity of scientific evidence on the effectiveness of dietary supplements in treating diabetes. Researchers need to be more diligent in data collection and analysis. More studies in randomized controlled trials are needed. Nutraceuticals should also be evaluated for their long-term effects. Over the past several years, nutraceuticals have attracted considerable interest due to their potential nutritional, safety, and therapeutic effects. These products could have a role in a plethora of biological processes, including antioxidant defenses, cell proliferation, gene expression, and safeguarding of mitochondrial integrity.

Therefore, nutraceuticals may be used to improve health, prevent chronic diseases, postpone the aging process, and in turn increase life expectancy, or just support the functions and integrity of the body. These products are considered to be healthy sources for the prevention of life-threatening diseases such as diabetes, renal and gastrointestinal disorders, as well as different infections. A wide range of nutraceuticals has been shown to impose crucial roles in immune status and susceptibility to certain disease states. Nutraceuticals also exhibit disease-modifying indications related to oxidative stress including allergies, Alzheimer's disease, cardiovascular diseases, cancer, eye conditions, Parkinson's diseases, and obesity.

Currently, diabetes medications prescribed worldwide have various effects and are well used, but the biggest problem is that they can cause side effects when taken long-term. Although they are helping to control blood sugar and improve HbA1c, there are of course individual

differences, but there are many problems caused by side effects.

Metformin is the first-line medication for diabetes and is often the first medication started. One of the side effects of diabetes medications is low blood sugar, and this drug rarely causes low blood sugar. It also maintains or slightly reduces body weight. It also reduces insulin resistance in the body and has been shown to reverse diabetes itself. It causes mild gastrointestinal disorders such as indigestion and diarrhea, but it is a necessary medication, so it is often taken in combination with medications that improve the above symptoms. Metformin is the most commonly used drug for the initial treatment of diabetes. This drug lowers blood sugar levels by inhibiting the production of glucose by the liver. It also improves insulin resistance by lowering insulin levels. Metformin is effective in stabilizing blood sugar levels and preventing weight gain. However, it can have a small number of side effects, including digestive upset, abdominal discomfort, and anemia⁴⁶.

Insulin secretion stimulators (sulfonylureas, meglitinides) act on the pancreas in our body, and in the case of diabetics, insulin is not regulated because the action of insulin is not smoothly regulated due to insulin resistance rather than low insulin secretion. Because it forcibly increases the amount of insulin, blood sugar drops according to the secretion of insulin, so hypoglycemia easily occurs and weight gain occurs. It lowers blood sugar but may cause weight gain and hypoglycemia. Sulforaphane is a drug that lowers blood sugar by stimulating insulin secretion. It is commonly used to treat type 2 diabetes and has the effect of stabilizing blood sugar levels. It can cause side effects in some users, including digestive upset, itching, and low blood sugar. Glipizide is a medication that lowers blood sugar by stimulating insulin secretion. It is used primarily to treat type 2 diabetes and has been shown to stabilize blood sugar levels. It can cause side effects in some users, including digestive upset, itching, and weight gain⁴⁷.

Alpha-glucosidase inhibitors (Acarbose, Voglibose) are characterized by regulating blood sugar by acting in the intestine. It has the effect of improving postprandial blood sugar by regulating the absorption of carbohydrates. It has the disadvantage that it must be taken after every meal (3 meals), and the suppressed sugar passes into the large intestine, causing high-glucose liquid to pass into the large intestine and ferment, causing a lot of farting and diarrhea. In severe cases, irritable bowel syndrome can also occur (less common these days)⁴⁸.

Thiazolidinediones (Actos, Avandia, Alogliptin/pioglitazone) are characterized by their action on visceral fat. They reduce insulin resistance and secretion. Side effects can be weight gain and severe edema. They make

you gain more subcutaneous fat than visceral fat. Not everyone will gain weight, but about 3% compared to those who don't take it. There is a low risk of heart failure, fractures, and even bladder cancer. However, it protects the cardiovascular system, reducing complications, and protects the pancreas, preventing hypoglycemia⁴⁹.

SGLT-2 inhibitors (Brenzavvy, Invokana, Farxiga, Jardiance, Steglatro) are newer drugs that move blood sugar to the kidneys for reabsorption, but this drug prevents reabsorption and causes it to be excreted in the urine. Excellent for weight loss, reduces blood pressure and inflammation, and protects the kidneys. Side effects include cystitis and vaginitis. If they persist, it's impossible to use the drug. It can also cause an increase in urine output, which can lead to dehydration⁵⁰.

DPP-4 inhibitors (Sitagliptin, Saxagliptin, Linagliptin, and Alogliptin) reduce fasting blood sugar, decrease appetite, and prevent sugar absorption in the small intestine. Nasopharyngeal cancer, urinary system infections, and respiratory system infections occur very rarely, and headache and diarrhea may occur. Highly effective, low side effects, and expensive. Diabetes medications are drugs used to treat diabetes and help control blood sugar levels. There are many different types of medications, each with different effects and side effects⁵¹.

Finally, Insulin is a medication administered by injection to treat diabetes. Insulin is used to effectively control blood sugar levels, and is primarily used in people with type 1 diabetes and people with type 2 diabetes who have difficulty controlling their blood sugar. Insulin works quickly to lower blood sugar, but it can cause side effects in some users, including low blood sugar, weight gain, and pain at the injection site⁵².

The effects and side effects of diabetes medications can vary from person to person and depend on the type and dose of the medication, so it's important that patients who are prescribed diabetes medications take them exactly as directed by their doctor and consult their doctor immediately if they experience any side effects or unusual symptoms.

This review paper has given you an understanding of diabetes medications and health supplements. The most important thing is that if you use dietary supplements for blood sugar control or treatment, you must consult with your doctor or specialist and use them with caution in terms of dosage and other intake, and if you experience side effects from diabetes medications, you should stop taking them and consult your doctor to determine the nature of the side effects, switch to other prescription medications, or take other measures.

Diabetes should be recognized as a concept of control rather than a cure, and it is judged that it is right to aim

for treatment and improvement for a long time without side effects by improving lifestyle.

CONFLICTS OF INTEREST

Authors should disclose any personal or financial relationships that could be viewed as potential conflicts of interest in relation to the publication on manuscript file just before references section.

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