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Review Article

Advanced Herbal Approaches to Diabetes and Metabolic Disorders: Current Status and Future Prospects

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ABSTRACT

Diabetes and related metabolic issues are major health problems around the world. In many cases, blood sugar is not well controlled. Insulin may not work as it should. Levels of fats in the blood can also become abnormal. Over time, oxidative stress builds up. Mild inflammation tends to continue too. Many people do benefit from common drug therapy. Even so, some medicines lead to side effects. In other cases, the response is not strong enough. Because these conditions come from more than one cause, interest in herbal options has grown. Researchers are examining plant compounds as possible supportive choices. This review explains the current status of herbal approaches. It also looks at what might happen next. Topics include the main chemicals found in these plants. It covers possible ways those chemicals may act in the body. It then summarizes what clinical studies report and how ready the evidence is for everyday use. The review also groups plant chemical types into several categories. The review covers both lab work and tests in people. It looks at medicinal plants as well as specific plant chemicals. Absorption is a key focus. Safety is discussed too, including side risks and possible clashes between herbs and drugs. Product strength is another concern. Extracts can differ a lot between one batch and the next. New ways to deliver these compounds are also included. The text mentions nanoparticles, phytosomes, liposomes, and other carriers. These systems may improve water solubility. They may also help compounds stay stable. Better uptake in the body is another point. If uptake improves, the effects in treatment could be stronger. For future work, the authors highlight multi target strategies. They also bring up metabolomics and plans that can be adjusted for each person. They suggest that artificial intelligence could aid trial design and data review. They emphasize the need for products that stay consistent and are well standardized. More toxicology studies are needed. More work on pharmacokinetics is also important. Finally, clinical trials should be planned better so herbal options for metabolic problems can be judged with solid evidence.

Keywords: Diabetes mellitus; metabolic disorders; medicinal plants; phytochemicals; herbal medicine; insulin resistance; oxidative stress; inflammation; nanocarriers; bioavailability.

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INTRODUCTION

Diabetes mellitus and other metabolic problems are not easy to pin down. They seem to be appearing more often these days. The trouble begins when the body cannot manage sugar, fats, and daily energy in a normal way. If that system stays out of balance for months or years, insulin resistance can build up. When insulin resistance rises, oxidative stress can also increase. At the same time, inflammation may not calm

down. Over time, organs may not run as efficiently as they should. That gradual change can set the stage for serious health issues later. Even though medicines have improved, worries remain. Standard treatment still does not cover every problem for every person. There are many different causes behind these conditions. Because of that, some people are turning their attention to other possibilities. Medicinal plants are one area that gets attention. Compounds from plants can act in several ways. They can also influence more than one process in the body. In addition, these plants have a record

of being used in traditional care. For these reasons, investigators believe they may help support steadier metabolic function¹.

Global burden of diabetes and metabolic disorders

Diabetes mellitus is now one of the biggest public health problems around the world. Its numbers keep going up in both rich and poorer countries. This condition is a long term metabolic disorder. It mainly involves high blood sugar that does not go away. That high level can happen because the body does not make enough insulin, because the body does not respond to insulin well, or because both issues occur at the same time. Several forces seem to drive the rise in diabetes. Urban life is more common now. Many people move less. Food habits have changed for the worse in many places. Weight gain is also common. Populations are ageing, and genetics can add extra risk. Type 2 diabetes mellitus makes up most diabetes cases. It often shows up along with excess body weight. It is also linked with abnormal blood lipids, high blood pressure, and heart and vessel problems. Other metabolic issues may be present as well. Metabolic problems can raise the risk of sickness and death, even when diabetes is not the only issue². Common examples are metabolic syndrome and obesity. People also see non-alcoholic fatty liver disease. Other frequent issues include dyslipidemia and insulin resistance. How these disorders start is not simple. Many processes are tied together. Insulin signaling can fail. Pancreatic beta cells may work poorly. Oxidative stress can rise. Low grade, ongoing inflammation can develop. Mitochondria can function abnormally. Lipid handling can go off track. Gut microbiota changes may also play a role. When the body stays out of balance over time, organ injury can build up. This can raise the chance of small vessel problems like kidney disease, nerve damage, and eye problems. It can also raise the chance of large vessel problems, including heart disease and stroke. Because of all this, the cost to health systems and society keeps growing. There is a clear need for treatments that work well and are also affordable, safe, and able to last over time³.

Limitations of current therapeutic approaches

Diabetes and metabolic disorders are treated in several ways. Most plans start with changes in daily habits. Clinicians may also use pills for blood sugar control. Some people need injections, and many also take medicines to lower lipids or blood pressure. If needed, insulin is added to the regimen. These steps can help bring glucose levels down. They can also improve other metabolic problems. Still, they do not always stop the illness from moving forward. Some patients also develop long term issues despite treatment. Results can differ a lot from one person to the next. That is because diabetes is not one single condition⁴. It involves many different body processes and signaling routes. Over time, drug therapy can bring its own problems. Some people do not tolerate certain medicines. Treatment can feel hard to manage. Side effects may appear. Taking medicines every day can also be difficult. Another concern is that many standard drugs focus on one pathway at a time. Diabetes often involves more than one disturbed mechanism at once. For instance, insulin resistance can show up along with oxidative stress. In the same patient, inflammation may be present too. There may also be dyslipidemia, problems with the vessel lining, and changes in mitochondrial

function. Because of this, some researchers look for treatments that can affect several targets at the same time⁵.

Rationale for herbal and phytochemical interventions

Medicinal plants have long been part of how people handled diabetes and other metabolic problems. They are still used in many places as part of local health care. A big reason these plants attract attention is the mix of natural chemicals they contain. Flavonoids, phenolic acids, alkaloids, terpenoids, saponins, tannins, polysaccharides, and other compounds can all play a role. Plant compounds often work in more than one way. This is different from many single drug targets. Some constituents can affect blood sugar control and also touch insulin action, fat balance, stress from free radicals, and inflammation. They may also support cell survival signals. Many studies point to several ways these effects can happen. Some compounds slow enzymes in the gut that break down carbs⁶. Others can help insulin release. Still others may make the body respond better to insulin. They can also support glucose uptake and shift how glucose moves into cells. GLUT4 is one transport related protein that is often discussed. Some phytochemicals also act through pathways such as PI3K/Akt and AMPK. Another point is that some plant chemicals may lower oxidative stress. They may do this by changing levels of reactive oxygen species and by turning related regulators on or off. Signals linked to NF- κ B and Nrf2 are often mentioned. Some herbal constituents have also been linked to protection of key organs. Examples include liver, heart, kidney, and nervous system effects. This matters because diabetes can lead to damage in these areas over time⁷.

Herbal medicines have clear benefits. Still, using them as therapy brings major problems. The results can shift a lot from batch to batch. Plant type may change. The place where the plant grew can differ. Soil and farming methods also matter. Even when the same herb is used, harvest timing and how it is handled after picking can vary. Extraction is another weak point. Different steps can pull out different chemicals. Storage can also reduce or alter phytochemicals over time. This can change both chemical profiles and biological effects. Many active compounds also face practical limits. Some do not dissolve well in water. They may break down easily. They can absorb poorly in the gut. The body may process them fast. As a result, only small amounts may reach the bloodstream and tissues. Because of this, researchers are testing delivery tools to help. Examples include nanoparticles, liposomes, phytosomes, and nanoemulsions. Other carriers are also used. These methods aim to protect herbal compounds and keep them stable. They are also meant to raise absorption and improve how compounds spread through tissues. In the end, these strategies may help move older herbal treatments toward forms that are more consistent and supported by careful testing⁸.

This review looks at how herbal treatments may work for diabetes and other related metabolic problems. It also considers where the field may go next. We highlight key medicinal plants and the main groups of plant chemicals that have been tested for effects on blood sugar and metabolism. The focus is on what these compounds might do inside the body, at the level of cell pathways. Attention is given to how glucose and fat are handled in the body. We also discuss

insulin signaling and how herbal agents may influence it. Other targets include oxidative stress and inflammation. Mitochondrial function is reviewed as well, since it links to energy use and metabolic balance. The review pulls together evidence from lab studies, animal work, and human trials. It weighs what is known about effect size, and it also notes safety concerns. Pharmacokinetic points are summarized for selected herbal options, along with how well they may translate to real clinical use. Because many traditional herbal products have limits, the review includes a section on new delivery methods. Nanotech based systems are mentioned as one way to improve uptake and consistency. It also covers major obstacles. These include standardizing plant material, controlling quality, and improving bioavailability. Possible toxicity is discussed, along with risks from herb-drug interactions. We also address regulatory approval issues and the need for stronger clinical validation⁹.

DIABETES AND METABOLIC DISORDERS: PATHOPHYSIOLOGICAL BASIS

Diabetes mellitus and metabolic disorders are examples of polygenic diseases that include many different metabolic disorders of glucose and lipids metabolism, the functioning of insulin, the formation of energy, inflammation, and redox systems. The most common form of diabetes is T2DM that is mainly characterized by insulin resistance and dysfunction of pancreatic beta-cells. These disorders are usually accompanied by such health problems as obesity, dyslipidemia, hypertension, non-alcoholic fatty liver, metabolic syndrome that increases the risk of such serious disorders as cardiovascular, renal, hepatic, and others. It is important to reveal the reasons of developing these disorders in order to find means of their treatment. Many of these disorders can be affected by plants components¹⁰.

Insulin resistance and β -cell dysfunction

One of the pathologies associated with T2DM is resistance to insulin. In other words, target organs develop lower sensitivity to insulin metabolism. Normally, binding of insulin to insulin receptors triggers insulin receptor substrates phosphorylation as well as activation of different signaling cascades such as PI3K/Akt. The mentioned processes result in increased glucose uptake, glycogen synthesis, and inhibition of hepatic glucose production. However, in the state of insulin resistance, impairment of the PI3K/Akt signaling pathway results in decreased glucose uptake and compensatory hyperinsulinemia in early stage of T2DM. Insulin deficiency appears because of progressive β -cell dysfunction and apoptosis, leading to impaired glucose uptake, persistent hyperglycemia, and deterioration of metabolic homeostasis. Chronic hyperglycemia further promotes oxidative stress, inflammation, and advanced glycation, thereby creating a vicious cycle that accelerates β -cell damage and insulin resistance. Consequently, the progressive interaction between insulin resistance and β -cell dysfunction plays a central role in the onset and progression of type 2 diabetes mellitus and its associated metabolic complications¹¹.

Glucose and lipid metabolism

Interconnection between carbohydrate and lipid metabolism is high, and disturbance of this mechanism results in numerous metabolic disorders. Once ingested, carbohydrates

are turned into glucose, and the activation of insulin secretion from pancreas follows. The hormone promotes the entrance of glucose into muscle and fat cells, stimulates glycogen synthesis, and inhibits processes of gluconeogenesis and glycogenolysis. In the case of T2DM, insulin resistance results in inadequate absorption of glucose by peripheral tissues and poor suppression of glucose production by the liver, which consequently provokes hyperglycemia. Besides, disturbances in the process of glucose regulation, the disorder in lipid metabolism is another feature of metabolic syndrome and T2DM. Insulin resistance increases lipolysis in adipose tissue and high concentrations of free fatty acids. Free fatty acids are transported to the liver, where triglycerides can be synthesized, and lipids accumulated¹². Consequently, individuals with metabolic syndromes may exhibit high levels of triglycerides, high LDL cholesterol levels, and low HDL cholesterol levels. Such a syndrome may lead to endothelial dysfunction, atherosclerosis, and coronary diseases. The control of glucose and lipid metabolism is controlled by several cellular pathways that include AMPK, PPARs, SREBPs, and PI3K/Akt signaling pathways. AMPK serves as the energy sensor and increases glucose uptake as well as fatty acids oxidation and inhibits lipid synthesis. As such, regulation of metabolic pathways by means of action of these compounds from plants can form a possible mechanism behind the anti-diabetic and lipid reducing effect of these herbs. Plant compounds with the ability to reduce blood glucose and lipids can operate through various pathways¹³.

Oxidative stress and chronic inflammation

Oxidative stress is one of the most important features of the pathogenesis of diabetes and metabolic disorders. High blood sugar levels lead to excessive ROS generation through mitochondrial dysfunction, glucose autooxidation, advanced glycation end products production and stimulation of metabolic stresses. Disproportion between the production of ROS and the activities of antioxidants leads to oxidative modification of lipids, proteins, DNA, mitochondria and cell membranes. Among other targets of oxidative stress in patients with diabetes mellitus are pancreatic β -cells that do not have appropriate defense against oxidative stress¹⁴. ROS can interfere with the process of insulin release, disturb the functioning of mitochondria and induce β -cell death. Besides, oxidative stress can worsen insulin resistance because of disturbance of insulin signaling pathway and inflammation development. Adipose tissue expansion in obese subjects promotes infiltration and activation of immune cells, namely macrophages. As a result, an increase in tumor necrosis factor- α , interleukin-6, and other pro-inflammatory cytokines is observed. Activation of inflammatory responses, such as activation of the nuclear factor- κ B pathway, is responsible for the development of insulin resistance and metabolic injury. The close connection between oxidative stress and inflammation results in a vicious circle accelerating the development of metabolic disorders. For this reason, antioxidants with anti-inflammatory activities may have more effective action. Numerous phytochemicals, such as polyphenols, flavonoids, terpenoids, and others, which are found in various plants, have shown their ability to influence oxidative stress and inflammatory signaling. These compounds may decrease

pro-inflammatory mediators production, stimulate endogenous antioxidant system, increase insulin sensitivity, and prevent tissues from metabolic and oxidative damage. Hence, medicinal plants containing multifunctional phytochemicals may be considered promising sources for the treatment of insulin resistance associated with obesity and related metabolic diseases¹⁵.

Gut microbiota and metabolic dysfunction

It has become clear that the gut microbiota is an important player in regulation of metabolic homeostasis and is being implicated as the reason for diabetes, obesity and metabolic syndrome. The intestinal tract is inhabited by a diverse community of microorganisms that interact with the host metabolism and diet. Alterations in the community of microorganisms, known as gut dysbiosis, have been associated with the development of insulin resistance, glucose intolerance, obesity and inflammation. The gut microbiota can influence the metabolism of the host through production of short chain fatty acids (SCFAs), regulation of the intestinal barrier integrity, bile acid metabolism and modulation of immune and endocrine signaling pathways. The effect of herbal drugs and the chemicals derived from plants can have positive impact on gut microbiota through stimulation of the growth of the beneficial bacteria, production of short chain fatty acids, reduction in the number of pathogens, and enhancement of the intestinal barrier functions. Furthermore, certain chemical compounds of herbs that cannot be absorbed by the body can undergo biotransformation in the presence of gut microbiota and produce new biological compounds¹⁶.

Major diabetic and metabolic complications

Prolonged metabolic disturbances can lead to damage of many organs and tissues. Chronic hyperglycemia leads to formation of advanced glycation end products, oxidative stress, inflammation, endothelial dysfunction, and abnormalities of intracellular signal transduction pathways, contributing to the formation of complications of diabetes. Diabetic microvascular complications include retinopathy, nephropathy, and neuropathy, while macrovascular complications include atherosclerosis, coronary artery disease, peripheral artery disease, and cerebrovascular disease. Metabolic dysfunction-associated steatotic liver disease is one of the most frequent types of hepatic complications seen in diabetes, related to excessive fatty liver and insulin resistance. Cardiovascular disease is one of the major causes of morbidity and mortality in diabetes, as a result of dyslipidemia, endothelial dysfunction, inflammation, oxidative stress, and vascular remodeling. In addition, cognitive and neurological complications can develop from vascular dysfunction, neuroinflammation, oxidative stress, and metabolic disturbances of neurons¹⁷. This multifactorial etiology requires therapy that would be able to target several pathogenic factors at the same time. Herbal medicine formulations that have several

bioactive components can be utilized in such multilevel therapy due to their antioxidative, anti-inflammatory, insulin sensitizing, hypolipidemic, hepatoprotective, nephroprotective, and cardioprotective properties. Use of such herbs in clinical practice entails a thorough study of the efficiency, safety, pharmacokinetic aspects, standardization, and interactions of such herbs with other medications. Furthermore, identification and characterization of the active ingredients of such herbs, understanding of their mode of action, and determination of proper dosage are crucial for successful utilization in therapeutic interventions. Systematic analysis of such herbs can contribute to the creation of evidence-based herbal formulations as complementary or alternative treatment of diabetes and metabolic complications¹⁸.

HERBAL MEDICINES AND BIOACTIVE PHYTOCONSTITUENTS FOR DIABETES AND METABOLIC DISORDERS

The phytoconstituents of medicinal plants are multitargeted bioactive molecules that may be potentially used for the treatment of diabetes and metabolic disorders because of their multitargeting effect on the glucose and lipid metabolism, insulin resistance, oxidative stress, inflammation, and cell dysfunctions. The main classes of phytochemicals include: flavonoids, polyphenols, alkaloids, terpenoids, saponins, tannins, and polysaccharides. The flavonoids and polyphenols, such as quercetin, resveratrol, curcumin, catechins, and EGCG may have some impact on the glucose tolerance, glucose uptake, insulin signaling and oxidative and inflammatory processes due to the activation of AMPK, PI3K/Akt, Nrf2 and NF- κ B. The alkaloids, such as berberine, can regulate the glucose and lipid metabolism and activate AMPK. The terpenoids and saponins, such as ginsenosides, diosgenin, and ursolic acid, participate in the regulation of glucose utilization, lipid metabolism and reducing oxidative and inflammatory stresses¹⁹.

There are a number of medicinal plants that have proven to provide beneficial effects in the context of antidiabetic, hypolipidemic, antioxidant, and anti-inflammatory activity based on experimental and clinical studies (**Table 1**). These plants include *Momordica charantia*, *Trigonella foenum-graecum*, *Gymnema sylvestre*, *Berberis* spp., *Curcuma longa*, *Panax ginseng*, *Cinnamomum* spp., *Azadirachta indica*, *Allium sativum*, *Syzygium cumini*, *Camellia sinensis*, and *Nigella sativa*. Generally, herbal drugs may be viewed as potentially effective and multitarget strategies that might help in preventing and treating the disease and its metabolic consequences. The wide range of bioactive substances may exert their influence on human body via different ways of action such as regulation of glucose and lipid metabolism, enhancement of insulin sensitivity, protection from oxidation, and anti-inflammatory effect. Nevertheless, more clinically-oriented trials need to be conducted in order to confirm their efficacy, safety, dosage, and possible interaction with antidiabetic drugs²⁰.

Table 1: Representative medicinal plants and bioactive phytoconstituents investigated for diabetes and metabolic disorders

Medicinal plant	Major bioactive constituents	Major reported mechanisms	Potential metabolic effects	Ref.
<i>Momordica charantia</i> (Bitter melon)	Charantin, polypeptide-p, cucurbitane triterpenoids	Enhances glucose uptake; modulates AMPK and insulin signaling; inhibits carbohydrate metabolism	↓ Blood glucose; ↑ insulin sensitivity	[21]
<i>Trigonella foenum-graecum</i> (Fenugreek)	4-Hydroxyisoleucine, diosgenin, galactomannan, saponins	Enhances insulin secretion; delays carbohydrate absorption; improves lipid metabolism	↓ Hyperglycemia; ↓ cholesterol and triglycerides	[22]
<i>Gymnema sylvestre</i>	Gymnemic acids, gymnemasaponins	Modulates intestinal glucose absorption; supports β -cell function; influences glucose utilization	↓ Blood glucose; improved glycemic control	[23]
<i>Berberis</i> spp.	Berberine, berbamine, other alkaloids	Activates AMPK; improves insulin signaling; regulates hepatic glucose and lipid metabolism	↓ Glucose; ↓ insulin resistance; improved lipid profile	[24]
<i>Curcuma longa</i> (Turmeric)	Curcumin, demethoxycurcumin, bisdemethoxycurcumin	Antioxidant and anti-inflammatory effects; modulates AMPK, Nrf2, and NF- κ B	Improved insulin sensitivity; reduced inflammation and oxidative stress	[25]
<i>Panax ginseng</i>	Ginsenosides, polysaccharides	Modulates AMPK, PI3K/Akt and glucose transport; antioxidant activity	Improved glucose utilization and insulin sensitivity	[26]
<i>Cinnamomum verum</i> / <i>C. cassia</i>	Cinnamaldehyde, polyphenols, procyanidins	Enhances insulin signaling and glucose uptake; antioxidant effects	↓ Blood glucose; improved insulin sensitivity	[27]
<i>Murraya koenigii</i> (Curry leaf)	Carbazole alkaloids, flavonoids, phenolics	Antioxidant activity; inhibition of carbohydrate-digesting enzymes; metabolic regulation	↓ Hyperglycemia; potential lipid-lowering activity	[28]
<i>Withania somnifera</i>	Withanolides, alkaloids, phenolic compounds	Anti-inflammatory and antioxidant effects; metabolic stress modulation	Potential improvement in insulin sensitivity and metabolic health	[29]
<i>Camellia sinensis</i> (Green tea)	EGCG, catechins, polyphenols	AMPK activation; antioxidant activity; modulation of lipid and glucose metabolism	Improved glucose and lipid homeostasis	[30]
<i>Nigella sativa</i>	Thymoquinone, nigellidine, alkaloids	Antioxidant and anti-inflammatory effects; modulation of insulin signaling	↓ Hyperglycemia; improved metabolic parameters	[31]
<i>Ginkgo biloba</i>	Flavonoids, terpenoids, ginkgolides	Antioxidant and anti-inflammatory activity; vascular protection	Potential cardiometabolic protection	[32]
<i>Hibiscus sabdariffa</i>	Anthocyanins, phenolic acids, flavonoids	Antioxidant activity; modulation of lipid and glucose metabolism	Potential ↓ glucose, blood pressure and lipids	[33]

Molecular Mechanisms of Herbal Antidiabetic and Metabolic Actions

The characteristics of diabetic pathology and metabolic disorders include the presence of a number of factors caused by insulin deficiency, insulin resistance, problems in carbohydrate and lipid metabolism, oxidative stress, inflammation, impairment of mitochondrial functioning, and alterations in gut microbiota. The current treatment of diabetes is aimed at addressing one specific target; in turn, natural products contain a complex of compounds that allow them to regulate several metabolic pathways simultaneously³³. Main categories of phytochemicals, namely flavonoids, phenolic acids, alkaloids, terpenoids, saponins, stilbenes, polysaccharides, and coumarins have the impact on carbohydrate breakdown, pancreatic β -cells, insulin signaling, glucose absorption, lipid metabolism, inflammation, and gut microbiota³⁴.

Inhibition of α -amylase and α -glucosidase

Inhibition of the degradation of carbohydrates via digestive enzymes in the intestine is the one of the first mechanisms of

action of phytochemicals in lowering postprandial hyperglycemia. First of all, dietary starch is broken down by α -amylase enzymes into oligosaccharides and carbohydrate molecules. Afterward, oligosaccharides are digested into monosaccharides, which are then absorbed into the body by brush-border α -glucosidases such as maltase, sucrase and other. Numerous phytochemicals found in plants affect these enzymes by means of hydrogen bonding, hydrophobic effects, π - π interactions, and enzyme-substrate interaction³⁵. Flavonoids like quercetin, catechins, rutin, as well as other polyphenols have been proven to inhibit activity of carbohydrate hydrolases through interaction with amino acid residues in or close to the enzyme active site. Inhibition of α -amylase and α -glucosidase results in decrease in glucose liberation from complex carbohydrates, hence gradual and limited increase in postprandial blood glucose. Such mechanism of action not only contributes to the reduction in excess production of insulin but also is beneficial in cases of impaired glucose tolerance. It needs to be noted that the level of enzyme inhibition depends on phytochemical structure, hydroxylation, glycosylation, size and concentration of the compounds³⁶.

Regulation of insulin secretion and sensitivity

The phytochemicals of herbs can be of great importance in controlling insulin secretion from the β -cells of the pancreas and insulin sensitivity peripherally. Phytochemicals like flavonoids, polyphenols, alkaloids, terpenoids, and saponins can help to protect the pancreatic β -cells from the stress of oxidation, dysfunction of mitochondria, endoplasmic reticulum stress, and chronic inflammation that result in impairment of insulin secretion. Some phytochemicals are capable of increasing the secretion of insulin through the modulation of ATP-sensitive potassium (K_{ATP}) channels, voltage-dependent calcium channels, intracellular Ca^{2+} signaling, and cAMP signaling pathway, resulting in exocytosis of insulin granules³⁷. Furthermore, the phytochemicals of herbs can enhance the action of insulin through stimulation of IR, IRS, PI3K, and Akt signaling pathways. These pathways activate the GLUT4 translocation, glycogen synthesis, and glucose uptake, while inhibiting the glucose production by the liver. The herbal phytochemicals have the ability to block the mediators of inflammation and oxidative signaling pathways that cause disruption of the insulin signaling and insulin resistance in muscle, fat tissue, and liver. Thus, the maintenance of β cell function and insulin signaling pathway is an important molecular mechanism responsible for antidiabetic activity of herbal medicines³⁸.

Modulation of GLUT4 and glucose uptake

The gut microbiota is considered an essential regulatory element in glucose and lipid metabolism, which establishes the functional link between the intestine, liver, pancreas, fat tissue, and the brain. The occurrence of diabetes and obesity is typically accompanied by changes in the microbial diversity, intestinal permeability, microbial metabolites, and bile-acid metabolism. Phytochemicals from herbs can change the microbial population and metabolic activity of the intestinal microflora, while microbial biotransformation of the plant chemical can form metabolites with a unique biological profile. One of the effects of the microbiota modulation is the production of SCFA such as acetate, propionate, and butyrate that can be capable of activation of G-protein coupled receptors GPR41/FFAR3 and GPR43/FFAR2³⁹. Metabolites are involved in hormone release from the intestines, immune response, energy metabolism, insulin sensitization, and GLP-1 secretion. The herbs may increase the integrity of the intestinal barrier through modulating tight-junction proteins such as occludin, claudins, and ZO-1, leading to a reduction in endotoxin lipopolysaccharide translocation from bacteria. Modulation of microbial bile-acid metabolism influences the FXR and TGR5 signaling, thus affecting glucose regulation, lipid metabolism, energy expenditure, and incretin release⁴⁰.

AMPK, PI3K/Akt, and insulin-signaling pathways

The phytochemicals in herbs can influence the metabolism of glucose and energy through various signaling pathways, specifically through the AMPK, PI3K/Akt, and the insulin-signaling pathway. The role of AMPK is significant in the process of sensing the cellular energy levels and, when activated, stimulates glucose uptake and fatty acid oxidation and, on the other hand, prevents gluconeogenesis in the liver and fat formation. Plant-based substances can activate

AMPK using upstream activators such as LKB1 and CaMKK β to increase the efficiency of energy metabolism. Simultaneously, the PI3K/Akt pathway is an insulin-signaling pathway wherein insulin binds to the receptor leading to the activation of IRS-1/2 and the PI3K. The Akt pathway is then activated to help with the translocation of GLUT4 and glucose uptake, glycogen synthesis, and inhibition of gluconeogenesis by way of inhibiting FOXO1 and downstream gluconeogenic enzymes such as PEPCK and glucose-6-phosphatase. Herbal phytochemicals can help increase the efficiency of these signaling pathways as well as reduce oxidative stress and inflammatory signaling that affect the function of the insulin receptors⁴¹⁻⁴².

Modulation of Oxidative Stress, Inflammation, Lipid Metabolism, and Gut-Metabolic Signaling

Plant-based phytochemicals have a multi-target effect on metabolism by regulating oxidative stress, inflammation, lipid metabolism, and gut-metabolism interplay, which are closely related to the pathogenesis of diabetes and metabolic disorders. Polyphenols, flavonoids, terpenoids, alkaloids, and other active plant components are capable of reducing oxidative stress by neutralizing reactive oxygen species (ROS) and up-regulating endogenous antioxidants via Nrf2/ARE pathway, thus increasing the expression of superoxide dismutase, catalase, glutathione peroxidase, heme oxygenase-1, NAD(P)H quinone dehydrogenase 1, and other enzymes. On the other hand, herbal substances are able to decrease chronic inflammation by preventing the activation of NF- κ B, MAPK, TLR4, and NLRP3 inflammasome signaling, hence decreasing the production of pro-inflammatory cytokines, such as TNF- α , IL-1 β , IL-6, and, as a consequence, improving insulin sensitivity⁴³. Additionally, herb-based phytochemicals affect lipid metabolism by suppressing hepatic lipogenesis via regulation of SREBP-1c, acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), and stearoyl-CoA desaturase-1 (SCD1) and stimulation of fatty-acid oxidation by way of AMPK, PPAR α , and CPT-1 signaling pathways. The mentioned mechanisms could result in the reduction of triglyceride accumulation, hepatic steatosis, and lipid-induced insulin resistance. Moreover, herbal interventions can influence the composition of gut microbiota, stimulating the growth of healthy bacteria and regulating the production of short-chain fatty acids⁴⁴.

PRECLINICAL AND CLINICAL EVIDENCE OF HERBAL INTERVENTIONS

The antidiabetic and metabolic role of herbs have been explored through a series of studies using in-vitro, animal and human approaches. *In-vitro* data from enzyme inhibition assays and cellular experiments have shown that herbal extracts and their phytochemicals are capable of inhibiting enzymes α -amylase and α -glucosidase, enhancing glucose uptake, promoting insulin release, protecting β -cells of pancreas and regulating pathways related to oxidative stress, inflammation and lipid metabolism. The animal experiments using induction of diabetes by streptozotocin and alloxan, induction of insulin resistance by a high-fat diet, obesity models and genetically diabetic animals have provided additional evidence for reduction in blood glucose levels, improvement in glucose tolerance and insulin resistance, protection of β -cells of pancreas and positive effect on

dyslipidemia, lipids accumulation in the liver, oxidative stress and inflammation⁴⁵. Human trials have tested certain herbs and phytochemicals for their ability to affect fasting and postprandial glucose, HbA1c, insulin resistance, lipid profile, body weight and metabolic biomarkers; several interventions have been promising for the management of diabetes and its metabolic complications. Data on certain medicinal plants and phytochemicals, such as *Momordica charantia*, *Trigonella foenum-graecum*, *Gymnema sylvestre*, *Curcuma longa*, *Panax ginseng*, *Berberis* species, curcumin, berberine, resveratrol, quercetin, catechins show various and multitarget mechanisms (Table 2).

While promising pre-clinical data have been reported, some critical issues still exist between pre-clinical and clinical studies, especially related to dosing, pharmacokinetics, bioavailability, standardization, efficacy, and safety concerns. It is thus essential to conduct large-scale randomized clinical trials using well-characterized and standardized formulations of herbs, along with pharmacokinetics, mechanisms of action, and safety studies over a long period of time⁴⁶.

Table 2: Preclinical and Clinical Evidence of Herbal Interventions in Diabetes and Metabolic Disorders

Evidence category	Models/subjects commonly used	Major parameters evaluated	Major findings/effects	Key molecular mechanisms	Major limitations	Ref.
In-vitro evidence	Enzyme assays; pancreatic β -cells; skeletal muscle cells; adipocytes; hepatocytes	α -Amylase/ α -glucosidase activity, glucose uptake, insulin secretion, oxidative stress, inflammatory markers, lipid accumulation	Inhibition of carbohydrate digestion; enhanced glucose uptake; protection of β -cells; reduced oxidative stress and inflammation; improved lipid metabolism	α -Amylase/ α -glucosidase, GLUT4, AMPK, PI3K/Akt, Nrf2, NF- κ B, NLRP3	High concentrations may be required; limited representation of whole-body metabolism; poor prediction of absorption and pharmacokinetics	[47]
Animal studies	Streptozotocin/alloxan-induced diabetic models; high-fat-diet-induced insulin resistance; genetically diabetic and obese models	Blood glucose, glucose tolerance, insulin, HbA1c, lipid profile, oxidative stress, inflammatory biomarkers, histopathology	Reduced hyperglycemia; improved insulin sensitivity; preservation of β -cell function; improved dyslipidemia; reduced hepatic lipid accumulation and inflammation	AMPK, PI3K/Akt, GLUT4, PPARs, Nrf2, NF- κ B, SREBP-1c, ACC, CPT-1	Species differences; variable doses and treatment duration; differences from human disease; uncertain human-equivalent exposure	[48]
Clinical trials and human studies	Patients with type 2 diabetes, prediabetes, obesity, metabolic syndrome, and related disorders	Fasting glucose, postprandial glucose, HbA1c, insulin resistance, lipid profile, body weight, inflammatory and oxidative biomarkers	Selected herbal interventions may improve glycemic control, insulin sensitivity, lipid profile, and selected metabolic biomarkers	AMPK, PI3K/Akt, GLUT4, PPARs, antioxidant and anti-inflammatory pathways, gut-metabolic signaling	Small sample sizes; short follow-up; heterogeneous populations; variable preparations and doses; inconsistent clinical outcomes	[49]
Selected medicinal plants and phytochemicals	<i>Momordica charantia</i> , <i>Trigonella foenum-graecum</i> , <i>Gymnema sylvestre</i> , <i>Curcuma longa</i> , <i>Panax ginseng</i> , <i>Berberis</i> spp.; curcumin, berberine, resveratrol, quercetin, catechins, etc.	Glycemic parameters, insulin sensitivity, lipid metabolism, oxidative stress, inflammation, molecular biomarkers	Potential multitarget effects involving glucose regulation, lipid metabolism, antioxidant defense, inflammation, and gut microbiota	AMPK, PI3K/Akt, GLUT4, PPARs, Nrf2/ARE, NF- κ B, SREBP-1c, gut microbiota/SCFA signaling	Differences in phytochemical composition; poor standardization; variable bioavailability; limited high-quality clinical evidence for several agents	[50]
Comparative efficacy and safety	Herbal preparations compared with placebo, standard therapy, or combination therapy	HbA1c, fasting glucose, insulin resistance, lipid profile, body weight, adverse events, herb-drug interactions	Some herbal interventions show promising complementary effects; potential multitarget activity may benefit multiple metabolic abnormalities	Multiple interconnected metabolic, inflammatory, antioxidant, and gut-signaling pathways	Natural origin does not ensure safety; herb-drug interactions, contamination, adulteration, hepatotoxicity/nephrotoxicity, and batch-to-batch variability	[51]

ADVANCED DELIVERY SYSTEMS FOR HERBAL BIOACTIVES

Nanoparticles and lipid-based nanocarriers

Delivery system based on nanoparticles has gained tremendous interest for augmenting the efficacy of

aqueously insoluble, poorly permeable, rapidly degradable and low bioavailability herbal bioactives. Nanoparticles not only increase the surface area of phytochemicals but also increase their dissolution, protect bioactives from chemical and enzymatic degradation, and enable sustained or controlled release of drugs. Lipid-based nanoparticles such

as solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), and lipid-drug conjugates are especially effective for lipophilic phytoconstituents like curcumin, resveratrol, quercetin, and polyphenols⁵². The lipid-based nanocarriers improve stability in the gastrointestinal tract, lymphatic transport, and reduce first-pass effect. Moreover, due to their nanoscale size, lipid-based nanoparticles also aid in cellular uptake and increased distribution. This way, the pharmacokinetics of phytochemicals could be improved by lipid-based nanoparticles, leading to enhanced effects of herbs on glucose metabolism, insulin resistance, oxidative stress, inflammation, and lipid profile.

Phytosomes and nano-phytosomes

Phytosomes are drug delivery systems made of phospholipids, where the bioactive components of the herbs make molecular complexes with the phospholipids, typically phosphatidylcholine. The complexation makes the interaction of the phytochemicals with the biological membranes more effective and enhances their absorption and systemic availability. Phytosomes are most effective for the transport of polar or low-absorption herbal substances whose efficacy is affected by poor gastrointestinal absorption⁵³⁻⁵⁴. Nano-phytosomes are smaller complexes that increase the surface area and, therefore, increase the possibility of improved dissolution and dispersion, as well as the interaction with membranes and cell uptake. Several studies have used phytosomes to improve the delivery of various bioactive components with antioxidative, anti-inflammatory, antidiabetic, and metabolic properties.

Liposomes and nanoemulsions

Liposomes are drug delivery vesicles that are made up of phospholipid bilayer which encloses water-soluble as well as lipophilic drugs. The protective capacity of liposomes to preserve herbs from being decomposed and their interaction with cell membrane make them suitable for the delivery of poorly bioavailable phytoconstituents. Nanoemulsion is a dispersion of submicron oil-in-water or water-in-oil emulsions that contain either surfactant or emulsifier and is well suited for poorly water-soluble as well as lipophilic components of herbs⁵⁵. Droplet size reduction leads to an increased surface area for dissolving and digestion that can improve the intestinal uptake. Besides, these systems can help in improving the chemical stability as well as dispersion of the phytoconstituents.

Polymeric and inorganic nanocarriers

Polymer-based nanocarriers are flexible systems for the controlled and sustained release of natural plant-derived compounds. Natural and synthetic polymers may be utilized in the preparation of nanoparticles, nanocapsules, polymeric micelles, and other carriers that would offer protection to phytochemicals against early degradation and control the release of these bioactives at certain biological targets. There has been considerable research on biodegradable polymers like chitosan, alginate, PLGA, and others for oral and targeted delivery purposes⁵⁶⁻⁵⁷. Surface modification of polymeric carriers with appropriate ligands may also be performed to enhance cellular internalization and tissue-targeting ability of the carriers. Inorganic nanocarriers such as selected biocompatible silicas, gold, iron oxide, and other nanomaterials also offer more opportunities for controlled

delivery and imaging, as well as surface functionalization. The long-term safety, biodegradability, and toxicity of inorganic nanomaterials need careful evaluation before translating them to clinical use⁵⁸.

Strategies for improving solubility, stability, absorption, and bioavailability

One of the primary goals of such advanced delivery systems is the improvement of unfavorable physicochemical and pharmacokinetic properties of herbal bioactives. The use of nanocarrier systems can enhance the water solubility of herbal bioactives by decreasing particle size and increasing their surface area or by incorporating poorly water-soluble compounds into suitable lipids or polymers. Such encapsulation provides protection against the oxidative, hydrolytic, photolytic, and metabolic degradation of phytochemicals, thus leading to their increased chemical and physical stability. Additionally, increased interaction with gastrointestinal membranes, enhanced mucus penetration, and modulation of epithelial transport can facilitate gastrointestinal absorption. In some cases, lipophilic systems can enhance lymphatic absorption and decrease first-pass effect⁵⁹. Controlled and sustained release delivery can provide prolonged maintenance of therapeutic levels and decreased variability of the systemic levels of herbal compounds. There are many other techniques that can be used, such as surface modifications, mucoadhesive systems, permeability enhancement, and responsive release systems.

Combination and targeted delivery approaches

The use of combination and targeted delivery methods is another cutting-edge approach aimed at optimizing the therapeutic potential of phytochemical bioactives in complicated metabolic diseases. The combination delivery strategy can include either multiple phytochemicals with various mechanisms of action or a mixture of herb-derived bioactives with antidiabetic medicines. These drugs will produce additive or synergistic effects in relation to their activity in regulating glucose metabolism, insulin resistance, inflammation, oxidative stress, and lipids imbalance⁶⁰. Encapsulation in one nanocarrier may increase the stability of multiple therapeutic compounds and their simultaneous delivery. Meanwhile, targeted delivery can be performed by decorating the surface of nanocarriers with ligands, peptides, antibodies, carbohydrates, and other targeting molecules that specifically interact with the cell receptors. This approach may result in the selective delivery of a drug to such metabolically important organs as the liver, pancreas, skeletal muscles, adipose tissue, and intestine. Therefore, the efficiency of therapy may be increased while the nonspecific delivery will be decreased, and the doses needed to administer the drug will be reduced⁶⁰⁻⁶¹.

Future Perspectives And Emerging Trends

Precision medicine, nanotechnology, artificial intelligence, microbiome research, and systems biology may drive the future of herbal-based interventions for the management of diabetes and other metabolic disorders. Individualized herbal treatments may allow one to choose appropriate phytochemicals based on an individual's genetic, metabolic, inflammatory and microbiome status, thus enhancing efficacy of treatment while reducing variability of response. Pharmacological network, molecular docking,

metabolomics, proteomics, and artificial intelligence (AI) may help discover novel targets, synergistic effects, modes of action and herb-drug interactions among various phytochemicals⁶². Because of the complex nature of diabetes and metabolic disorders, which are characterized by numerous interacting mechanisms, including insulin resistance, oxidative stress, chronic inflammation, mitochondrial dysfunction and dysregulation of lipid metabolism, the future treatments may be focused on multi-targeting and combination therapies as opposed to mono-molecular targets. Such advanced drug delivery systems as phytosomes, nano-phytosomes, liposomes, nanoemulsions, solid lipid nanoparticles and polymeric nanoparticles may resolve the problem of poor solubility, stability, rapid metabolism and low bioavailability of numerous herbal compounds⁶³⁻⁶⁴. Future developments in the area of targeted and responsive nanocarriers may allow enhanced delivery of phytochemicals to metabolically active tissues such as liver, pancreas, skeletal muscle, adipose tissue, and intestine. The gut microbiome is yet another novel therapeutic target as there can be significant modulation by herbal bioactive compounds of the microbial diversity, short chain fatty acid synthesis, integrity of the intestinal barrier, bile acid metabolism, and gut hormones like GLP-1. The combination therapy involving standard herbal formulations along with conventional antidiabetic or hypolipidemic medications can be useful, but this would need careful evaluation of pharmacokinetic and pharmacodynamic interactions. In addition, the standardization of phytochemicals, botanical identification, quality control, and advanced analytics would be necessary to ensure reproducibility and batch consistency. In future clinical studies, emphasis needs to be placed on well-designed, large-scale and long term randomized controlled trials involving standardized formulations and clinically relevant dosing with simultaneous pharmacokinetic, efficacy and safety evaluations. Lastly, harmonization of regulations, Good Manufacturing Practices, scalable manufacturing processes, and post marketing surveillance would be crucial to translating novel herbal bioactives to clinically proven therapies for diabetes and metabolic disorders⁶⁴⁻⁶⁵.

CONCLUSION

The use of herbal drugs and bioactive compounds derived from plants has great potential as complementary therapies for the treatment of diabetes and metabolic diseases. Various phytochemicals such as flavonoids, phenolics, alkaloids, terpenoids, and saponins have been shown to have positive impacts on different levels of therapy such as improving insulin sensitivity, regulating glucose and lipid metabolism, inhibition of carbohydrate digestive enzymes, and reduction of oxidative stress and chronic inflammation. Nevertheless, their wider application in therapy is restricted due to inconsistencies in the composition of phytochemicals, extraction methods, bioavailability, dosages, standardization, and quality controls. Safety issues, interaction between herb and drugs, contamination, and limited clinical trials are some issues that require further research. The use of advanced drug delivery systems such as phytosomes, liposomes, nanoparticles, and other types of nano-carriers can improve the stability, solubility, and bioavailability of phytochemicals. For future research, emphasis should be placed on standardization, mechanism validation, and

pharmacological and clinical assessment of the herbal preparations. The inclusion of metabolomics, systems biology, pharmacogenomics, and artificial intelligence may help achieve personalized herbal therapies guided by biomarkers. Effective regulations and manufacturing processes will be necessary for clinical application of the herbal products. In all, evidence-based herbal medicines have potential benefits in managing the increasing problem of diabetes and other metabolic diseases.

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