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The Role of Medicinal Plants in Alleviating Symptoms of Diabetes-Related Complications

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ABSTRACT

Diabetes mellitus is a global metabolic disorder characterized by chronic hyperglycemia and associated with a spectrum of debilitating complications, including neuropathy, nephropathy, retinopathy, and cardiovascular dysfunction. Conventional pharmaceutical treatments, while effective, often lead to undesirable side effects and remain economically inaccessible in some settings. In contrast, medicinal plants have emerged as promising therapeutic agents due to their wide array of bioactive phytochemicals such as flavonoids, alkaloids, and phenolic compounds. These compounds exhibit potent antioxidant, anti-inflammatory, and insulin-mimetic properties that can mitigate diabetes-induced oxidative stress and inflammation, key drivers of diabetic complications. This paper examines the pathophysiology of diabetes and its complications, the biochemical actions of medicinal plants, and their mechanisms of action in modulating cellular pathways involved in diabetic damage. It also presents evidence from ethnopharmacological surveys, clinical trials, and molecular research that supports the efficacy and safety of key medicinal plants in diabetes care. Although promising, the clinical translation of these natural therapies requires further validation through standardized research, quality control, and regulatory frameworks to ensure safety, efficacy, and accessibility.

Keywords: Diabetes mellitus, diabetic complications, medicinal plants, phytochemicals, oxidative stress.

INTRODUCTION

Diabetes is one of the most common metabolic disorders in the world today. Diabetes is a chronic impairment in the body's ability to use glucose, which is necessary to provide energy for the brain and the body's cells. Diabetes-related complications include disorders that affect a person's eyes, kidneys, nerves, heart, gums, etc [1-6]. Such complications lead to neuropathy, nephropathy, retinopathy, cardiovascular diseases, and so on, which impair the proper functioning of a person's body and lead to disability, trauma, and even death. Synthetic medications are available for the treatment of such complications, but they mainly have side effects; thus, many natural medicinal herbs and plants with fewer side effects are preferred for the treatment of such complications. These natural plants are also available at a low cost, which is an advantage over synthetic drugs [7-10]. There are many medicines in the plant kingdom that are being used and are efficient in alleviating the symptoms of diabetic-related complications [11-14]. Such plants provide a wide range of phytochemicals, such as flavonoids, alkaloids, saponins, phenolic compounds, etc., which have several biochemical uses, including antioxidant, anti-inflammatory, anti-diabetic, and anti-microbial as well. Such plants are effective in diabetes and are themselves able to produce phytochemicals that induce genes in their target cells. Such medicinal plants having beneficial biopharmacological properties can be used to study the signalling activity, metabolic pathway, and gene-regulatory activity through bioassays and biochemical tests. Such plants can also be selected for the identification of active molecular pathways to alleviate complications related to diabetes mellitus [15-19].

Understanding Diabetes and Its Complications

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia due to dysfunctional insulin secretion or action. Type 1 diabetes mellitus (T1DM) results from autoimmune destruction of pancreatic β-cells, leading to insufficient insulin production, with symptoms including polyuria, polydipsia, fatigue, and weight loss. Insulin therapy is essential for managing T1DM, often in conjunction

with biguanides [20-25]. Type 2 diabetes mellitus (T2DM), commonly associated with obesity and metabolic syndrome, arises from insulin resistance in liver, muscle, and fat tissues. Initially, individuals may experience hyperglycemia from insulin overproduction; however, insulin secretion can eventually decline, resulting in deficiency. T2DM poses significant public health risks, contributing to chronic morbidity and mortality. Complications of diabetes are classified as acute or chronic. Acute issues arise from uncontrolled glucose levels and include diabetic ketoacidosis and hypoglycemia; chronic complications develop after years of hyperglycemia, affecting small and large blood vessels, leading to organ dysfunction [26-29]. Microvascular conditions such as retinopathy, nephropathy, and neuropathy can lead to severe outcomes like blindness and kidney failure, degrading quality of life, and increasing mortality risk. Preventing these complications is crucial. Oxidative stress and inflammatory cytokines from prolonged hyperglycemia significantly contribute to complications, activating the polyol and PKC pathways that produce harmful oxidative species and proinflammatory cytokines [30-33].

Types of Diabetes

Diabetes mellitus (DM) is classified into two main types: Type 1 diabetes mellitus (T1DM), characterized by autoimmune destruction of pancreatic β-cells and insulin deficiency, and Type 2 diabetes mellitus (T2DM), which involves multiple metabolic issues, primarily insulin resistance. Other specific types exist but are outside this review's scope. T2DM has become a global health crisis, with a significant rise in prevalence over the last decade and predictions for continued increases [34-37]. It is a major contributor to vascular complications, heightening cardiovascular disease risk. Diabetes complications are categorized into microvascular, affecting small vessels, and macrovascular, affecting larger vessels. Research has investigated the efficacy of medicinal plants in managing diabetes complications, showing that many have anti-oxidative and anti-inflammatory effects that may reduce complications. Diabetes is a metabolic disorder leading to chronic hyperglycemia due to insufficient insulin production (Type 1) or cellular insulin resistance (Type 2) [38-41]. Complications arise upon diagnosis or over time, with symptoms overlapping between types. These complications include nausea, bloating, early satiety, constipation, diarrhea, and vomiting. Diabetic kidney disease involves kidney damage marked by hyperglycemia and increased urinary albumin excretion. Infections may arise from delayed diagnosis or symptom overlap with other conditions. Diabetes also impacts the central nervous system, affecting cognitive functions assessed through various tests. Neurological disorders can develop after either type of diabetes diagnosis [42-46].

Common Complications of Diabetes

Various countermeasures have been developed to address diabetes mellitus complications. The most severe is cardiovascular issues, the leading cause of death among diabetics, followed by retinal, peripheral vascular, and renal problems. Changes in heart geometry, rhythm, and tension can strain cardiac function. Diabetics often develop heart failure with preserved ejection fraction linked to diastolic dysfunction [1-5]. Diabetes raises the risk of ischemic and nonischemic cardiomyopathy, leading to heart failure from numerous conditions, including diastolic dysfunction and peripheral arterial disease. Diabetic retinopathy is the primary reason for vision loss in working adults, arising from chronic hyperglycemia and hyperlipidemia. Retinal blood flow, an indicator of eye health, may reflect diabetic microvessel disorders. Techniques like laser Doppler flowmetry assess blood flow through retinal arteries, while computer-vision-based systems can measure arteriolar and venular flow [6-9]. Diabetic neuropathy is the most prevalent long-term complication, presenting in various forms. Cardiovascular autonomic neuropathy often signals the onset of diabetic issues, leading to excessive sweating, dry skin, and hidden ulcers. Dysmotility, such as diabetic esophageal dysmotility, can cause dysphagia and heartburn. Distinguishing diabetic dysmotility from other types is crucial. Diabetic nephropathy can result in chronic kidney disease, with microalbuminuria stages increasingly noted. This condition may lead to azotemia, dyslipidemia, and nephron damage, affecting glomerular filtration rates and increasing glycosylated end products [10-14].

Pathophysiology of Diabetes Complications

Diabetes is a complex metabolic disorder characterized by hyperglycemia resulting from impaired insulin secretion, insulin action, or both. Diabetic complications arise due to long-term modestly elevated blood glucose and HbA1c levels and result in significant morbidity and mortality [15-19]. Endothelial dysfunction via the early development of diabetic vascular disease can result in diabetic retinopathy, nephropathy, and neuropathy associated with abnormal blood-brain barrier permeability. Therefore, diabetic vascular disease must be considered to better understand diabetic complications and to develop possible new therapies [20-24]. Chronic hyperglycemia leads to increased advanced glycation end-product formation and oxidative stress, resulting in inflammation, vascular cell activation, and changes in fibrinolysis and coagulation. In turn, a cascade of inflammatory cytokine production, local upregulation of leukocyte adhesion molecules, vascular smooth muscle cell proliferation, and apoptosis results in the

development of microvascular and macrovascular complications. Diabetes-associated cardiac disease may result from one or more of these mechanisms. Activation of the renin-angiotensin-aldosterone system by hyperglycemia, among other mechanisms, may also contribute to complications in different diabetes-mediated organ systems [25-28].

Medicinal Plants: An Overview

For millennia, herbal remedies from crude plant materials formed the basis of health care globally. Contemporary treatments for illnesses often trace their origins to the herbal pharmacopeia of various regions, with knowledge passed down through generations, primarily in oral tradition. Individuals have gathered and learned about these remedies through family or personal experience, creating a rich base of ethnobotanical knowledge [29-35]. Yet, Western pharmacognosy and modern clinical research largely overlook this expertise. There are few discovery programs focused on traditional plant derivatives, and even fewer studies include folk medicine plants. Although plant-derived natural products contribute to numerous pharmacological effects, scientific understanding of many health-related plant ingredients remains limited. Thus, many medicinal plants yet to be explored may offer pharmaceutical potential. Underreporting of this knowledge often stems from fears of exploiting cultural resources, leading to suspicion towards research on traditional therapies. Despite some traditional remedies being effective, many lack strong scientific backing or proven efficacy, resulting in a complex landscape for evaluating their medicinal potential [36-39].

Mechanisms of Action of Medicinal Plants

Medicinal plants have long been utilized in folk medicine to alleviate diabetes symptoms, with patients turning to natural products to manage blood glucose levels. Diabetes, a prevalent endocrine disorder, is projected to rise from 171 million cases in 2000 to 366 million by 2030, posing substantial global health and economic challenges. Diabetes can lead to complications like neuropathy, retinopathy, and nephropathy due to oxidative stress and excess reactive oxygen species (ROS) from hyperglycemia, resulting in serious infections and complications [40-43]. Addressing these chronic issues is crucial to enhance the quality of life for diabetics and lower healthcare costs. Plant-derived compounds offer promising benefits for preventing or alleviating diabetes complications, presenting themselves as popular alternatives in alternative medicine. Many medicinal plants serve as antioxidants, rich in phytochemicals, prompting studies into the efficacy of plant-derived antioxidants (PDA) against diabetes-related damage. Insulin and non-insulin secretagogues sourced from plants present viable alternatives to existing diabetes treatments. Herbal extracts and active compounds from these plants are key in diabetes care strategies [44-46]. With over 13,000 secondary metabolites identified, medicinal plants are a critical source of active compounds for potential new drug development. Recent interest has surged in isolating phytochemicals from these plants, assessing their biological activities, and formulating effective therapeutic agents. Modern medicine has been shaped by traditional herbal therapies from ancient cultures, including Greek, Roman, Chinese, and Ayurvedic systems. Natural products from both flora and fauna continue to be essential sources of drugs, with many therapeutic agents derived from the chemical modification of these natural substances, and research into medicinal agents remains ongoing [1-3].

Key Medicinal Plants for Diabetes Management

The search for novel compounds/drugs has led to increased interest in medicinal plants with antidiabetic activity. This has prompted researchers to screen various medicinal plants for pharmacologically active lead compounds via different experimental methods, some of which have been isolated, characterized, and tested in clinical trials [4-7]. Ethnobotanical and ethnopharmacological surveys have also been conducted to identify and document traditional medicinal plants used to treat diabetes around the globe. In addition, extensive research into the mechanism of action of the lead compounds has allowed the development of formulations based on isolated plant products or phytochemicals that have been used as complementary medicine to treat high blood glucose levels and other symptoms associated with diabetes [8-11]. For at least more than 5000 years, several medicinal plants have been used in traditional Ayurvedic, Unani, and other systems of medicine to treat diabetes in India and other countries in the world. The plant products used principally include leaves, stems, wood, roots, tubers, rhizomes, exudates, fruits, seeds, flowers, and their mixtures, which are consumed in several forms, including paste, powder, juice, decoction, infusion, and alcoholic or water extracts. In recent years, the botanicals have been subjected to pharmacological investigations to evaluate their antidiabetic activity and the mechanisms underlying their action. Antidiabetic activity has been demonstrated by several plants from various plant families through inhibition of α-glucosidase and α-amylase, enhancing function and increasing the number of β-cells, stimulating secretion from β-cells, and increasing insulin sensitivity [12-15].

Clinical Evidence Supporting Medicinal Plants

Numerous RCTs and 25 meta-analyses have investigated phytomedicines for T2DM. Seven showed significant effects on HbA1c and 12 on FPG. The most effective plants included Aloe vera, Psyllium fibre, Fenugreek, Nigella sativa, and the traditional Chinese formula Jinqi Jiangtang. All plants were deemed safe, with only minor gastrointestinal side effects reported [16-18]. The quality of trials in the meta-analyses was a limitation; only three reviews had a follow-up of over a year. The efficiency of promising plants was comparable to standard oral hypoglycaemic agents. Various mechanisms explain their effects, such as inhibiting α-glucosidase and AGE formation, enhancing GLUT-4 and PPARs expression, and possessing antioxidant properties [19-23]. Despite extensive literature, the clinical effectiveness of these medicinal plants for diabetes management remains debated, underscoring the need for stronger evidence. An overview of the medicinal plants for diabetes management is available, with scientific publications on herbal treatments and T2DM growing steadily. The mechanisms of action of natural products have been extensively studied, yet the actual efficacy remains disputed due to the poor quality of studies [24-26].

Safety and Efficacy of Medicinal Plants

Medicinal plants have been utilized for traditional medicine since ancient times, providing affordable and clinically effective remedies with fewer adverse effects than modern drugs. While many plant therapies have been passed down through generations, their pharmacological activities and potential acute or chronic side effects remain largely underreported, causing uncertainty. Some herbal medicines have demonstrated efficacy, yet others lack strong therapeutic effects or safety [25-27]. The rising popularity of herbal medicines necessitates a thorough scientific evaluation of their active compounds. Historically, these remedies have targeted multiple physiological processes related to disease progression. Over time, herbal medicines may transition from crude extracts to more defined mixtures of pure compounds, reflecting advancements in natural product knowledge [28-29]. Multi-component herbal formulations are often preferred over single compounds, aiming to restore physiological systems to healthy states with less toxicity by engaging different targets. However, the belief that herbal medicines are inherently safer than pharmaceuticals is diminishing, particularly with increasing non-traditional uses [30-32]. The safety of herbal remedies has come under scrutiny as many side effects are recognized, especially in broad-spectrum dietary mixtures, where individual components may cause cumulative adverse effects. Prolonged use of herbal medicines can induce chronic toxicity due to the complex interactions between phytomolecules and biopolymers. The heightened blood concentrations of bioactive compounds may exceed safety margins with extended use, leading to potential risks over weeks or years. Contamination concerns with heavy metals, pesticides, and microbes also complicate safety assessments of crude herbal medicines. Although similar risks exist for pharmaceuticals, regulatory standards in industrial countries reduce these threats [33-36]. Conversely, in many regions where traditional herbal medicine is practiced, regulatory frameworks are often lacking, making safety a fundamental concern for human consumption. Advancing regulatory science is crucial to address the gaps between bioactivity screenings and in vivo evaluations, as well as to ensure the safety and efficacy of traditional medicines by better defining and characterizing herbal mixtures [37-40].

Patient Perspectives on Herbal Treatments

Diabetes mellitus (DM) is linked to various non-communicable diseases, leading to morbidity, disability, and mortality. Patients often endure the physiological and psychological challenges of elevated blood sugar levels, particularly after starting insulin therapy, especially short-acting types [41-43]. They also fear hypoglycemia, influenced by factors like meal timing, food choices, medication dosages, and stress. Perspectives on these issues in low- and middle-income countries, such as Tanzania, where lab services are scarce, remain underexplored. Symptom severity related to diabetes complications varies by gender, age, and duration of the condition [44-46]. Female participants often reported more frequent hunger, possibly due to anxiety over their diagnosis, while males, typically perceived as family providers and more likely on insulin therapy, experienced a greater incidence of hypoglycemia. For older participants, illnesses restricted access to treatment, diminishing their likelihood of receiving initial MET therapy. Patients utilized strategies to access care, including changing treatment facilities, provider types, and using herbal remedies to manage blood glucose levels. Symptoms prompted many to seek alternative options like herbal treatments, perceived as more effective than conventional therapies for the side effects of short-acting insulin. Widely available and affordable herbal products like ginger, turmeric, and bitter leaf were valued for their therapeutic benefits, indicating a need for research into their effects on diabetes management and overall health [21-24].

Future Directions in Research

Increasing populations of diabetics are challenging the healthcare system. Modern diabetes treatments carry risks of adverse side effects, highlighting the need for affordable medications with fewer

complications. Medicinal plants, containing pharmacological ingredients with anti-diabetic properties, offer potential solutions. Researchers are turning to plants traditionally used by indigenous peoples, exploring various parts of these plants to alleviate diabetic symptoms. Effective diabetes management is crucial to reduce complications like retinopathy and atherosclerosis. Detailed pharmacological research on these plant sources can support the development of new affordable products, especially for socio-economically disadvantaged individuals. Ethical concerns arise over the use of biological resources, necessitating cooperation between developed and developing countries to prevent biopiracy. Tackling this global health challenge requires cross-national collaboration. It is hoped that well-researched medicinal plants, used alone or with modern medicine, can yield effective therapeutic molecules to ease diabetes and its complications. Hypertension often accompanies diabetes, with studies showing that about half of diabetic patients also develop hypertension, exacerbating their condition and increasing the risk of further complications. Research has also explored the role of exosomes—extracellular vesicles that carry various molecules which connect cells and may play a part in the relationship between hypertension and diabetes [25-28].

CONCLUSION

Medicinal plants hold significant promise in the management and alleviation of diabetes-related complications due to their diverse pharmacological properties, particularly their antioxidant and anti-inflammatory actions. By targeting the underlying pathophysiological mechanisms of hyperglycemia-induced damage, these plants can contribute to the prevention and attenuation of neuropathy, nephropathy, retinopathy, and cardiovascular diseases commonly associated with diabetes. While traditional medicine systems have long utilized these botanical remedies, modern scientific validation and clinical trials are crucial to fully establish their therapeutic potential. Moreover, issues concerning safety, standardization, and regulation must be addressed to integrate these remedies into mainstream healthcare. With continued research and appropriate policy frameworks, medicinal plants can become effective, safe, and affordable adjuncts or alternatives to conventional diabetes therapies, especially in resource-limited settings.

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