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The Role of Medicinal Plants in Strengthening Immune Response in Diabetic Patients

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder that impairs the immune system, making patients more susceptible to infections and related complications. Conventional treatments for diabetes often involve synthetic drugs, which may cause adverse effects and do not fully address immune dysfunction. Medicinal plants offer a promising complementary strategy due to their immunomodulatory, anti-inflammatory, and antioxidant properties. This paper explores the potential of selected medicinal plants, such as *Zataria multiflora* (Thyme), *Camellia sinensis* (Green Tea), and *Echinacea purpurea*, in enhancing immune responses in diabetic patients. The mechanisms of action are examined through phytochemical pathways and cellular immune signaling. Clinical and preclinical studies indicate that these plants improve both innate and adaptive immunity, reduce inflammation, and mitigate oxidative stress. Despite promising outcomes, challenges in standardization, dosage, and safety remain. Further clinical trials and regulatory measures are essential to integrate herbal therapies into mainstream diabetic care effectively.

Keywords: Medicinal plants, Diabetes mellitus, Immune response, Phytochemicals, Herbal medicine, Antioxidants.

INTRODUCTION

Diabetes is a global epidemic impacting all countries, regardless of economic status. The rising number of diabetes patients and related complications present significant challenges to health care systems and national economies [1-4]. Complications such as blindness, limb amputation, renal failure, and cardiovascular disease add to the complexity of managing diabetes. The increasing prevalence and severity of diabetes contribute to its position among the top ten highest disease burdens worldwide, causing immense suffering, chronic disability, and premature death, particularly in the working-age population [4-7]. By 2030, projections estimate that over 300 million people will be living with diabetes, doubling current figures. The past two decades have seen a 70% rise in diabetes prevalence across various nations, with diabetic patients experiencing a life expectancy that is 6 to 10 years shorter than non-diabetics [7-9]. Diabetes results from insufficient insulin action, leading to elevated blood sugar levels that harm blood vessels and nerves, resulting in significant damage to organs like the eyes, kidneys, and heart. Efficient blood sugar management is essential, and current medications address both blood sugar levels and complications [10-13]. Many modern drugs are evolutions of well-established medicines, with some derived from herbal sources. Herbal remedies maintain strong popularity in many cultures, offering benefits such as broad acceptability, minimal side effects, and a synergistic effect when combined with other treatments. Numerous studies have focused on herbal preparations for diabetes, particularly since the 1990s, although few systematic reviews have reported on their side effects [14-18].

Overview of Diabetes

Diabetes mellitus (DM) is a chronic disorder characterized by high blood glucose levels (hyperglycemia) due to insulin hormone deficiency or insulin resistance. It is a chronic disorder of the path of blood

glucose regulation [19-22]. Diabetes mellitus (DM) is characterized by a disorder of carbohydrate, fat, and protein metabolism, resulting from an absolute or relative deficiency of insulin. Pancreatic β-cells distinctively secrete insulin during the post-meal phase to lower blood glucose levels. Dysregulation of both blood glucose and insulin levels leads to hyperglycemia or impaired glucose tolerance, associated with elevated risk of cardiovascular, renal, or hematological diseases. Uncontrolled diabetes leads to serious health complications [23-26]. Approximately 415 million people are diabetic; about 204 (49%) million of them are undiagnosed. The burden is markedly greater in lower middle-income countries. Infants all over the world have type 1 diabetes (T1D) and in many countries the incidence of T1D is increasing alarmingly. Obesity is endemic and the diabetes map has been dubbed as a map of obesity in most countries. Uncontrolled diabetes will remain a major public health crisis in the next decades unless new approaches in prevention and management are discovered [27-30]. Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia due to insulin deficiency, insulin resistance, or both. Insulin resistance is the impaired biological response of target tissues to insulin, which is compensated by a greater secretion of insulin (more from β-cells) [31-32]. This eventually leads to β-cell dysfunction with progressive decline in insulin secretion. In type 1 diabetes (T1D), autoimmune destruction of pancreatic β-cells leads to ketosis-prone insulin deficiency, while in type 2 diabetes (T2D) with inherited obesity (more adiposity), insulin resistance is the main pathophysiology. The current medications of diabetes mellitus focus on controlling and lowering blood glucose levels to a normal level. However, most modern drugs have many side effects causing serious medical problems during treatment. Therefore, traditional medicines have been used for a long time and play an important role as alternative medicines [33-36].

Immune Response in Diabetic Patients

Immune response is a natural defense mechanism protecting against infectious organisms, mediated mainly by leukocytes and effector molecules like antibodies. An herbal formulation, KM108, is derived from Saussurea lappa, Terminalia chebula, and Zingiber officinale. Saussurea lappa, or Aloo Bukhara, grows mainly in northern Pakistan; Zingiber officinale, or Adrak, is prevalent in India, Pakistan, and China; and Terminalia chebula, or Haritaki, is found across South Asia's forests. The cytotoxicity and immuno-stimulation of KM1608 were assessed through cell viability and nitric oxide assays, indicating that its compounds may have anticancer potential by regulating immune signaling and apoptosis. KM1608 extract also boosts the expression of various immune cytokines. Immune responses are classified into innate and adaptive immunity. Innate immunity acts immediately against infectious agents using physical barriers, chemical barriers, and effector cells like macrophages and neutrophils. Adaptive immunity takes days to develop after pathogen detection and results in immunological memory, enabling faster responses to subsequent encounters. This response is mainly driven by T or B lymphocytes and antigen-specific receptors. The immune response involves activation of effector cells, proliferation, and clonal expansion, with regulation by multiple isoforms, transcription factors, and epigenetic modifications. However, immune dysfunction, such as malnutrition or aging, can impair responses, and certain pathogens can suppress immunity in chronic disease cases [37-39].

Medicinal Plants: An Overview

Medicinal plants are used for health benefits due to their active chemical constituents, which promote desired medicinal effects. Aside from these active elements, they contain "inactive" constituents that, while not providing medicinal benefits directly, play important roles in regulating the active constituents and their effectiveness in the body. This feature contributes to the safety and sustained activity of medicinal plants, highlighting the need for research in phytochemistry and pharmacology to discover "lead" molecules for drug development. Traditionally, medicinal plants are recognized for treating ailments and producing diverse phytomedicines. They are essential in pre-modern medicine, nutrition, and cosmetics, enhancing health care globally. Medicinal plants, herbs, and spices offer a wealth of bioactive compounds, with many modern drugs derived from them. Recent research has emphasized basic pharmacology, with bioactive compounds being isolated through batch extraction and examined using various analytical techniques, including the emerging 2D-NMR method. Screening often targets acute toxicity or specific bioassays but can be cumbersome and yield uncertain efficacy results. Furthermore, there is a lack of straightforward techniques that offer a comprehensive overview of extracts from a health or pharmaceutical perspective [8].

Mechanisms of Action of Medicinal Plants

Medicinal plants and derivatives play a significant role in traditional medicine. Phytochemicals have pharmacological properties that modulate cellular processes, with specific bioassays designed for different

targets. Various phytochemicals are isolated from medicinal plants and examined for antidiabetic and immune-boosting properties. Promising results emphasize traditional antidiabetic plants' effectiveness in managing diabetes mellitus, while other plants are screened for immunomodulatory benefits for future applications. The traditional medicinal use of plants and bioassays for in vitro or in vivo validation are discussed, highlighting plant-based lead compounds, novel phytochemicals, and the future of drug discovery in diabetes management. The glycemic index of food and its position in the stomach are crucial for insulin secretion, with insulin receptors activating the phospholipase-C signaling pathway. This process stimulates phospholipase-C, which cleaves phosphatidylinositol-4,5-bisphosphate, releasing diacylglycerol and inositol trisphosphate, leading to calcium release and the activation of calmodulin. This results in the activation of calmodulin-dependent protein kinases affecting hormone-sensitive lipase and perilipin, promoting lipolysis and free fatty acid release. Oral antidiabetic agents act as insulin secretagogues but pose side effects. Glinides, being cheaper than sulfonylureas, yield less blood glucose variability and are effective pre-meal, though can cause hypoglycemic events. Dietary patterns significantly influence postprandial glucose responses. While metformin is a potent antidiabetic agent, it has a slow onset and variable effectiveness across populations. Some pharmacological agents manage both conditions, albeit with a risk of adverse effects when combined. Natural products remain a vital source for drug discovery, although the limited pharmacological activity restricts the clinical use of some plant-based therapies like curcumin for diabetes and agmatine for neurovascular disorders [20].

Key Medicinal Plants for Immune Support

1. Thyme (Zataria Multiflora) Thyme is one of the most important medicinal plants of traditional Persian medicine, which has attracted the attention of researchers in recent years due to its wide-ranging healing effects. Thyme extract, being rich in phenolic compounds, carbohydrates, terpenoids, flavonoids, and tannins, stimulates and strengthens the immune system. In diabetic rats treated with thyme extract, the blood level of pro-inflammatory factors of the immune system decreased, and the activity of the anti-inflammatory factor increased. The extract also hydrolyzed and released phenolic compounds, which inhibited the proliferation of cancer cells in cell culture. Thyme extract exerted a strong antioxidant effect against DPPH radical scavenging and a significant cytotoxic effect on L929 cells with an IC50 equal to 436.98 µg/mL. It may be recommended as a therapeutic agent for skin malignancies due to the liberating and anti-cancer properties of marine extracts [11].

2. Green Tea (Camellia Sinensis) Green tea is rich in polyphenols, especially catechins, which boost immunity. In type 1 diabetic patients, green tea increases cellular and humoral responses against infections, especially viral and intracellular infections. The anti-inflammatory properties of catechins modulate the immune response and inflammatory process. In T1D patients, FF extract pollens with a high antioxidant capacity elevate the immune response by affecting some positive factors like CD40, CD80, and nitric oxide. Z. multiflora is an herbal medicine with antiviral and anti-inflammation properties that are impacted by carvacrol with a strong effect on the emulation of the immune system [12].

3. Echinaceae Boiled echinacea has long been used as a preventive strategy for strengthening the immune system against diseases due to the wide range of effects of its active ingredients. This herb can prevent, treat, and alleviate the symptoms of colds, flu, and respiratory and urinary tract infections. Preclinical studies indicated the immunomodulatory activities of echinaceae affecting innate and adaptive immunity activation. The plant has also been shown to improve immune response such as stimulating non-specific immunity, macrophage activation, increasing lymphocyte proliferation, enhancing AB production, and stimulating the activity of weight virus in cell culture [13].

Clinical Evidence and Studies

Over the past decades, many studies have been undertaken to assess the efficacy of medicinal plants in the management of diabetes-related symptoms. The studies have been well summarized in review articles, where the main categories of effects provided by the extracts are illustrated. For example, concerning a total of 281 plant species used for diabetes therapy, the effect categories that emerged were 1) Insulin and Insulin-like effects; 2) Reduction in stone and hyperlipidemic agents; 3) Improvement on energy metabolism; 4) Inhibition of hyperglycemia; 5) Inhibition of downstream effects of glycation; 6) Hypotensive; 7) Antioxidants; 8) Anti-inflammatory; 9) Antimicrobials; 10) Smooth muscle relaxants; and 11) Effects on teeth. Many effects were also grouped under the biological terminology, and the final categories amounted to 23 types of biological effects. From the inventiveness in the search for new medicines, a steep rise in the literature on the effects of extracts or purified molecules resulting from the screening of medicinal plants has been observed. It may be estimated that, on average, around ten studies

agent/year have been published in the last 50 years, with an increase in the intensity of this research in the last 20 years. Individual positive effects have been tested with extracts or molecules on a variety of in vitro targets, cell cultures, and experimental animal models to prove eligibility for further studies in clinical settings. The dual-purpose plant Flavahum obtained from a species native to the western Himalayas, has been promoted for a rural population searching for a phytomedicine for diabetes. The mode of action is indirect, and there is absolute faith in the efficacy of this approach. Repeated studies and articles claiming success in blood sugar reduction have been published. No attempt has yet been made on the reverse, that is, to start from clinical investigation to verify which medicinal plant is effective in humans. The main focus has been on diabetes, and there is an absence of any study on the clinical suitability of potential agents in contrast to the recent advances in bioflavonoid research [14-19].

Safety and Efficacy of Medicinal Plants

A large number of marketing firms promote herbal remedies for diseases like dyslipidaemia, diabetes, and anxiety. Regulatory agencies in India ensure the quality and safety of Ayurvedic and other traditional medicines. Numerous studies have assessed the safety and efficacy of herbal remedies and phytochemicals. Biocompatibility, efficacy, and safety are influenced by biological, psychological, medical, and socio-economic factors. Manufacturers must follow good manufacturing practices while evaluating raw materials and dosage forms for contaminants to ensure quality. Reporting side effects by patients and practitioners can reduce risks associated with herbal remedies. More clinical studies are needed to establish their safety profiles in India. Stringent guidelines should curb misleading advertising, and consumers are urged to verify herbal products through reputable resources. Herbal garden builders should create databases on plant types, uses, and toxicity. Awareness of herbal medicines often comes from friends or relatives, but these recommendations may lack proper knowledge. Supporters should aim to provide genuine help to patients in need [20-26].

Integrating Medicinal Plants into Diabetes Management

In all cultures throughout history, people have used plants for healing and health. The extensive diversity of plants on the earth has led to an equal variety of bioactive compounds that aid in the treatment and prevention of ailments. Over 80% of the world's population relies on plants as a traditional source of medicines. Treatment in both traditional and molecular medicine is designed to fi-ght illness, and both employ biological agents that displace or neutralize harmful organisms. Instead of fighting, immunomodulatory and immunoregulating plants are meant to regulate and strengthen the immune system to better cope with existing symptoms and disease. More effort has been focused on such plants recently. The general speculation is that, as diseases become chronic and multifactorial, traditional agents would be more effective for wider segments of the population and be less affected by changing microbial resistance. Medicinal plants have been used for immunomodulation. Anti-diabetic drugs based on medicinal plants have been researched. Plants are sources of inexpensive, effective proteins or pharmaceuticals with few side effects for the treatment of diabetes. Medicinal plants and their bioactive compounds have been recognized as a source of therapeutic agents for the prevention and treatment of diabetes. Some of the plants have been used in traditional medicine for the treatment of diabetes in various countries. The exploration of the bounding mechanisms for better medicinal plants can increase the concentration or potency of the effective medicinal component for the management of diabetes [29-34].

Future Directions in Research

There is a dire need to increase healthful mechanisms to strengthen immunity against infections and COVID-19 in diabetes patients. Recently, biomolecular phytochemistry has opened up a new therapeutic approach with the exploration and introduction of new anti-COVID-19 compounds/delivery systems. Novel anti-COVID-19 compounds from medicinal plants and endophytes, and/or the use of more effective and biocompatible nanocarriers for drug delivery, are recommended. The effects of these biocompatible compounds/delivery systems should be tested on diabetes and non-diabetic cells by molecular docking, MMP, DLS, and TNBS methods. Their observed results should be validated in in vivo animal models before clinical trials. Most importantly, research should be performed to discover phytocompounds of plant and/or animal origin with the potential to inhibit plant cell expansion, to slow down the timeline of the human population explosion. The optional point is still very important; production and use of engineered mice with a reduced birth rate and transfer of the transgenes to rice or wheat should be intensely researched. Further research on the landscape of inhibitory compounds is needed. The current understanding is limited by the few compounds that have been characterized mechanistically. Most of the inhibitory compounds are expected to have many cellular targets, which complicates their mode of action.

Therefore, obtaining more structure-based inhibitors is an urgent task. Moreover, new biophysical approaches such as FRET-TIRF microscopy and labelled probes should be developed to visualize cell walls and their biogenesis in situ with higher spatial and temporal resolution [35-39].

CONCLUSION

The rising prevalence of diabetes and its associated immune dysfunction underscores the urgent need for safe, effective, and complementary therapeutic strategies. Medicinal plants, rich in bioactive compounds, demonstrate significant potential in modulating immune responses, reducing oxidative stress, and managing hyperglycemia. Evidence from laboratory and animal studies supports the efficacy of plants like *Thyme*, *Green Tea*, and *Echinacea* in enhancing both innate and adaptive immune responses in diabetic contexts. However, translating these findings into clinical practice necessitates rigorous human trials, standardized extract preparations, and stronger pharmacovigilance. While not a substitute for conventional therapy, medicinal plants can serve as valuable adjuncts in personalized diabetes management. Integrating traditional knowledge with modern pharmacological research could pave the way for innovative, holistic approaches to strengthen immune resilience in diabetic patients.

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