REVIEW ARTICLE

Herbal Immunotherapeutics in Diabetes: A Comprehensive Review on Plants Explored for Simultaneous Antidiabetic and Immunomodulating Effects

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ABSTRACT

This extensive review explores the intricate relationship between immunomodulation and diabetes mellitus (DM), emphasizing herbal interventions and formulations showcasing dual efficacy. Immunomodulation, characterized by interventions altering the host's immune response, holds significant promise for addressing the complex pathophysiology of DM. An array of herbs reveals diverse mechanisms, ranging from down-regulating inflammatory markers to influencing glucose metabolism. In the domain of immunomodulation, herbs demonstrate the ability to modulate immune responses, suppressing pro-inflammatory cascades and regulating immune cell functions. Concurrently, formulations like HemoHIM and polyherbal formulations provide insights into their potential by lowering specific immune cells, presenting a dual-action paradigm for managing DM. The antidiabetic effects of these herbal interventions are elucidated, shedding light on their roles in mitigating insulin resistance, inadequate insulin secretion, and immune-mediated destruction of insulin-producing cells. For instance, *Gymnema sylvestre* and *Phyllanthus emblica* exhibit antidiabetic effects by inhibiting α-glucosidase and regulating IL-17 expressions. HemoHIM and polyherbal formulation showcase efficacy in streptozotocin (STZ)-induced diabetic models, accentuating their potential in diabetes management. The synergy between immunomodulation and antidiabetic effects underscores a holistic approach to DM management. Mechanisms span the modulation of immune system components to the regulation of glucose homeostasis, contributing to the comprehensive nature of these interventions. Future research in this field involves a deeper exploration of the specific molecular pathways these herbs engage. Rigorous clinical trials are imperative for validating efficacy and safety, facilitating the seamless integration of herbal interventions into mainstream diabetes management. This work signifies a dynamic and evolving field, offering the prospect of personalized and effective therapeutic strategies in DM management through the integration of herbal interventions.

Keywords: Immunomodulation, Diabetes, Herbal drugs, Alloxan, STZ, Anti-inflammatory.

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INTRODUCTION

Immunomodulatory approaches involve interventions aiming to modulate and regulate the host's immune response rather than directly targeting the disease.[1] These approaches encompass a spectrum of strategies, including the use of immunostimulators and immunosuppressives, as highlighted.[2] The versatility of immunomodulatory approaches lies in their ability to alter the immune system's response through various mechanisms, disrupting the pro-inflammatory cascade. This involves actions such as antioxidative effects, modulation of bacterial flora, utilization of monoclonal antibodies, cytokines, and related extracellular immune mediators, along with alterations in cell signaling.[3]

Immunomodulation is a broad therapeutic concept that finds application in diverse clinical scenarios. In conditions of immunodeficiency, addressing the underlying cause, such as malnutrition or human immunodeficiency virus (HIV), takes precedence. While specific immune defects are challenging to correct, allogeneic stem cell transplantation may be considered to establish a new immune system. Vaccination emerges as a powerful immunomodulatory technique for preventing infections, with evolving tools like cytokines, viral vectors, and "naked DNA" offering new avenues for response manipulation. In fighting infections, the objective is often to shift the immune response toward a Th1-type phenotype. In cancer treatment, efforts focus on making cancer cells the preferred targets of

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the patient's immune system. Various approaches are explored, including cytokines, anti-CTL-4, tumor-specific antibodies, and cellular therapies using tumor-infiltrating lymphocytes and stem cell transplantation.[4] Conversely, in cases of allergy, autoimmunity, and organ transplantation, the goal is to attenuate the immune response. Desensitization proves effective for selected allergies. However, in autoimmunity and transplantation, broad immunosuppressive drugs become essential. These drugs, targeting different aspects of the immune response, are employed individually or in combination. This arsenal includes agents interfering with antigen presentation, T-cell activation, and T-cell proliferation. Corticosteroids play a crucial role with their multifaceted impact on the immune response and significant anti-inflammatory properties.

In solid organ transplantation, immunosuppressive agents are necessary to prevent rejection, and if rejection occurs, a new organ may be required. While offering therapeutic benefits, stem cell transplantation also carries the risk of graft vs host disease, akin to rejection. When this disease proves unresponsive to steroids, treatment options become limited, impacting prognosis significantly. This integrated approach underscores the intricate balance of immune modulation across diverse medical scenarios, each necessitating tailored strategies for effective therapeutic outcomes.

Diabetes

Diabetes mellitus, characterized as a metabolic disorder, is marked by an inherent or acquired inability to efficiently transport sugar from the bloodstream into cells. The fundamental issue in diabetes stems from inadequate insulin secretion or reduced responsiveness of tissues to insulin. Type 2 diabetes, the predominant form, often commences asymptomatically, complicating early detection and leading to extended undiagnosed periods.[5] This chronic metabolic disease is typified by elevated blood glucose levels, posing a gradual threat to the heart, blood vessels, eyes, kidneys, and nerves over time. Type 2 diabetes, commonly diagnosed in adults, manifests when the body develops resistance to insulin or fails to produce an adequate amount. The global prevalence of type 2 diabetes has surged significantly in the past three decades across countries of varying income levels. Simultaneously, type 1 diabetes, formerly juvenile or insulin-dependent diabetes, involves a chronic condition where the pancreas produces minimal or no insulin independently.

For those managing diabetes, access to affordable treatment, notably insulin, becomes paramount for survival. A collective global effort has been set forth to curb the escalating trends in diabetes and obesity by the year 2025. The worldwide impact of diabetes is stark, with approximately 422 million individuals affected, predominantly residing in low- and middle-income countries. The toll is compounded by 1.5 million annual deaths directly attributed to diabetes.[6] Over the last few decades, both the number of cases and the prevalence of diabetes have experienced steady and concerning increases. This underscores the urgent need for comprehensive strategies to address the escalating global burden of diabetes and its associated health implications.

Immunomodulation in Diabetes

The relationship between diabetes and the immune system is multifaceted, with insights into the inflammatory nature of type 2 diabetes (T2DM) and the T cell-mediated autoimmune genesis of type 1 diabetes (T1D).[7-10] T2DM, characterized by an inflammatory host response, is further substantiated by studies linking inflammation markers, such as C-reactive protein, fibrinogen, interleukin-6, and tumor necrosis factor-α (TNF-α), with the disease. This inflammatory backdrop underscores the intricate pathogenesis of T2DM.

In contrast, T1D stems from the selective destruction of insulin-producing β-cells, primarily mediated by T cells targeting β-cell autoantigens. The involvement of both CD4+ and CD8+ T cells, particularly the predominant role of CD8+ T-cells in insulitis and beta-cell killing, accentuates the complexity of T1D pathogenesis.[11] Immunomodulatory approaches emerge as pivotal players in addressing diabetes-induced cardiovascular and renal diseases. Multi-potent stromal cells (MSCs), with their extensive immunomodulatory capabilities, contribute to altering adaptive and innate immunity through differentiation into various cell lineages.[12,13] Chronic low-grade inflammation, significant in obesity and T2DM, further contributes to the pathogenesis of diabetic cardiomyopathy (DCM).[14]

Advancements in immunomodulatory approaches for diabetes-related cardiorenal diseases highlight improvements in clinical applications, leading to more effective treatments. Recognizing the limitations of single-agent treatments, future approaches aim at refining dosing, timing, and understanding species-specific differences, emphasizing combined therapy to enhance efficacy.[15] While various treatments like immunotherapy, chemotherapy, radiation, and hormonal therapy exist, they often pose substantial shortcomings, such as severe toxicities and drug resistance. This recognition of limitations propels the demand for plant-based natural products with therapeutic efficacy, offering potential solutions for diseases ranging from the common cold to cancer and diabetes.[16] It's crucial to acknowledge these alternatives in the therapeutic landscape. In the evolving field of immunomodulation, particularly in diabetes, the emphasis on immunotherapy as a cornerstone in disease treatment is pronounced. The exploitation of the immune system to recognize and eliminate cancer-specific antigens has become a favorable approach, although challenges such as counteractive immunomodulation in cancer persist. This understanding opens avenues for novel and more effective therapeutic strategies at the intersection of immunomodulation and diabetes management, reflecting the dynamic nature of these intertwined fields.

In the current platform of diabetes research, the exploration of herbal remedies with dual immunomodulatory and antidiabetic properties is of paramount importance. As the prevalence of diabetes continues to rise globally, there is an urgent need for novel and comprehensive therapeutic strategies that not only target glucose regulation but also address the immune dysregulation associated with diabetes. The synthesis

of herbal interventions capable of modulating both the immune system and glucose metabolism represents an innovative approach in the field. The potential for holistic and synergistic effects arises by enlisting herbs with dual properties, providing a more integrated solution to the complex interplay between immune responses and diabetes pathogenesis.

Hence, this review is particularly critical, as it aims to consolidate and analyze the existing literature on herbal plants with both immunomodulatory and antidiabetic activities. This synthesis not only contributes to the scientific understanding of these botanical agents but also holds promise for the development of novel therapeutics that can address the multifaceted challenges posed by diabetes. In light of the increasing global burden of diabetes and the growing body of evidence supporting the efficacy of herbal interventions, a comprehensive review becomes a timely and essential endeavor in advancing therapeutic options for individuals managing diabetes and its associated immune aspects.

Herbal Immunomodulatory Agents with Antidiabetic Potential

While effective, current immunomodulatory and antidiabetic treatments may come with a spectrum of side effects. Immunomodulatory medications, such as corticosteroids and immune suppressants, are known for their immunosuppressive

Table 1: Herbs investigated for immunomodulatory activity in diabetic models

Plant name	*Part and extract*	*Immunomodulation*	*Antidiabetic activity*	*References*
Tribulus terrestris	Methanol and ethanol extracts of roots	Down-regulation of inflammatory markers	α-glucosidase inhibition in HepG2 cell lines	17
Boerhavia erecta L.	Hydroalcoholic extract of root and stem	Inhibition of TNF-α and nitric oxide (NO) in RAW cell lines	Inhibition of glycosylation of Hb, glucose reuptake	18
Plumeria acuminate	Hydroalcoholic extract of leaves			
Alpinia galanga	Hydroalcoholic extract of rhizomes			
Picrorhiza kurroa	Hydroalcoholic extract of whole plant			
Trapa natans	Hydroalcoholic extract of fruits			
Badri cow	Cow urine	Increase of delayed hypersensitivity, hemagglutination	Alloxan-induced diabetic mice	19
Securinega virosa	Methanol extract of leaves	Increase in IL-10 and regulation of TNF-α		20
Pedicularis longiflora	Ethanol extract of aerial parts	Lowering of leukocytes and NF-κB		20
Allium carolinianum	Ethanol extract of whole plant			
Murraya koenigii	Water and methanol extract of leafs	Lowering of apoptosis in the pancreas		21
Phyllanthus emblica	Ethyl acetate extract of fruits	regulating IL-17 expressions, decreased CD4+ and CD8+	non-obese diabetes (NOD) mice and cyclophosphamide-induced DM	22
Garcinia kola	Aqueous extract of nuts	decreasing the frequency of helper (TH) and cytotoxic (TC) T cells	low-dose streptozotocin-induced mice	23
Crocus sativus	Aqueous extract of saffron	Lowered expression of cytokines	streptozotocin-induced mice	24
Gymnema sylvestre	Methanol extract of leaves	Generation of NO in macrophages and lymphocyte proliferation, stimulation of myeloid and lymphoid fucntions	STZ induced rats	25
Elleteria cardamomum	Methanol extract of fruits	Lowered INF, IL-5 and IL-17		26
Zingiber officinale	Methanol extract of rhizome			
Cinnamomum verum	Methanol extract of bark			
Curcuma longa	Ethanol extract of rhizome	Lowered levels of IgE, nitric oxide, and cytokine levels	STZ-induced *Staphylococcus*-infected rats	27
Allium sativum	Crude drug	Increase in granulocytes, lowering of lymphocytes and monocytes	Alloxan-induced diabetic rats	28
Nigella sativa				
Trigonella foenumgracum	Oil of seeds	Lowering of lymphocytes and inflammation in B-cells		28

Table 2: Formulation with immunomodulatory activity in diabetic models

Formulation	*Herbs used*	*Immunomodulation*	*Antidiabetic activity*	*References*
HemoHIM	*Angelica gigas, Cnidium officinale, Paeonia japonica*	Lowering of CD4T and CD8T cells in spleen and pancreas	STZ induced rats	29
Polyherbal formulation	*Sesbania grandiflora* seeds, *Salacca zalacca* leaves and *Acalypha indica* roots	Lowering of CD4+a dn CD8+		30
Kefir	*Fermented milk with lactic acid bacteria*	Activation of macrophages, increased cytokines	STZ induced type1 diabetes	31
Kal-1	*Polyherbal decoction*	Lowered inflammatory cytokines	C57BL/6J mice model	32

properties, leaving individuals susceptible to infections. These treatments can also lead to adverse effects like weight gain, osteoporosis, and mood swings. Antidiabetic medications, including insulin and oral hypoglycemic agents, may cause hypoglycemia, weight gain, and gastrointestinal disturbances. Additionally, some individuals may experience allergic reactions or skin issues with certain antidiabetic drugs.

In contrast, herbal alternatives offer a promising avenue with potentially fewer side effects. Many herbal remedies, such as bitter melon, fenugreek, and ginseng, have demonstrated antidiabetic properties with minimal adverse effects. These natural compounds often work synergistically with the body, promoting overall well-being. For instance, bitter melon has shown hypoglycemic effects without the risk of hypoglycemia associated with some pharmaceutical antidiabetic agents. The holistic approach of incorporating herbs alongside conventional treatments may provide a comprehensive strategy with reduced side effects, promoting the overall health and well-being of individuals managing immunomodulation and diabetes.

The vast repository of herbal plants, exceeding 400 in number, has been extensively studied and demonstrated to harbor significant antidiabetic activities. This wealth of botanical resources highlights their potential significance in treating and managing diabetes.

Tribulus terrestris root extracts exhibited down-regulation of inflammatory markers and demonstrated α-glucosidase inhibition. *Boerhavia erecta L*, specifically its root and stem extracts, showcased inhibition of tumor necrosis factor-alpha (TNF-α) and nitric oxide, affecting glycosylation and glucose reuptake processes. *Gymnema sylvestre* leaf extracts displayed a multifaceted impact, including nitric oxide generation in macrophages, lymphocyte proliferation, and stimulation of myeloid and lymphoid functions in models induced with streptozotocin (STZ). *Pedicularis longiflora* aerial parts demonstrated a reduction in leukocytes and NF-κB in alloxan-induced diabetic mice. *Murraya koenigii* leaves contributed to lowering apoptosis in the pancreas of alloxan-induced diabetic mice. *Phyllanthus emblica*, ethyl acetate extracts from its fruits, played a role in regulating IL-17 expressions and decreasing CD4+ and CD8+ in non-obese diabetes (NOD) mice. Table 1 further explores the effects of *Securinega virosa*, *Garcinia kola*, Badri Cow, *Crocus sativus*, and various other herbs, presenting a comprehensive overview of their potential in the realms of both immunomodulation and antidiabetic activities. These findings collectively contribute to expanding our understanding of herbal interventions and their diverse impacts on immune responses and diabetes-related issues.

Table 2 presents various formulations designed to harness both immunomodulatory and antidiabetic properties. One such formulation is HemoHIM, incorporating *Angelica gigas, Cnidium officinale*, and *Paeonia japonica*. In studies, HemoHIM demonstrated efficacy in lowering CD4T and CD8T cells in the spleen and pancreas, particularly in streptozotocin (STZ)-induced diabetic models.[29] Another notable polyherbal formulation comprises *Sesbania grandiflora* seeds, *Salacca zalacca* leaves, and *Acalypha indica* roots. This formulation exhibited the ability to lower CD4+ and CD8+ cells, indicating potential immunomodulatory effects in STZ-induced diabetic models.[30]

Kefir, a formulation based on fermented milk with lactic acid bacteria, demonstrated immunomodulatory effects by activating macrophages and increasing cytokine levels. These observations were made in STZ-induced type 1 diabetes models.[31] Additionally, the polyherbal decoction Kal-1 exhibited a reduction in inflammatory cytokines, showcasing its immunomodulatory properties. This effect was observed in a C57BL/6J mice model, suggesting the formulation's potential therapeutic value.[32] In summary, these formulations represent promising approaches in the realm of both immune system modulation and diabetes management. Each formulation, be it HemoHIM, the polyherbal mixture, Kefir, or Kal-1, presents a unique combination of ingredients, providing valuable insights into potential therapeutic applications for addressing immune responses and diabetes-related issues.

DISCUSSION

It is evident that there is a substantial body of research focusing on the intersection of immunomodulation and antidiabetic activities, particularly in the context of herbal formulations. Numerous herbs and polyherbal formulations have been explored for their potential to modulate the immune system while concurrently exhibiting antidiabetic effects. The immune-modulatory approaches often involve the regulation of immune responses, including the down-regulation of inflammatory markers, modulation of T-cell activity, and enhancement of macrophage function. Simultaneously, the antidiabetic activities range from inhibiting key enzymes involved in glucose metabolism to protecting pancreatic cells from apoptosis.

The synergy between immunomodulation and antidiabetic effects is crucial in addressing conditions like diabetes, which

have inflammatory components intertwined with metabolic dysregulation. This dual approach has the potential to not only manage diabetes but also mitigate associated complications, especially in the cardiovascular and renal domains. Herbs like *T. terrestris* and *G. sylvestre* demonstrate the ability to down-regulate inflammatory markers, generate nitric oxide, and modulate immune cell functions. These actions contribute to suppressing pro-inflammatory cascades and regulating immune responses in conditions like diabetes.

In the context of diabetes mellitus, characterized by impaired glucose metabolism, the herbs and formulations exhibit diverse methods of action. They target key aspects of diabetes, including insulin resistance, inadequate insulin secretion, and immune-mediated destruction of insulin-producing cells. For example, *G. sylvestre* and *P. emblica* showcase antidiabetic effects by inhibiting α-glucosidase and regulating IL-17 expressions. The formulations HemoHIM and poly herbal formulations also demonstrate efficacy in STZ-induced diabetic models, lowering specific immune cells and indicating potential in diabetes management. Polyherbal formulations, such as Hemo HIM, Kefir, and Kal-1, showcase the versatility of combining various herbs to achieve comprehensive health benefits. These formulations act on multiple fronts, simultaneously influencing immune responses and glucose homeostasis. In summary, the research highlights the promising role of herbs and herbal formulations in providing a holistic approach to address both immunomodulation and antidiabetic activities. Understanding these intricate relationships contributes to the ongoing exploration of natural remedies for better diabetes management and overall health.

CONCLUSION

The exploration of herbs and formulations for their dual roles in immunomodulation and diabetes mellitus presents a promising avenue for holistic health management. The mechanisms deployed by these interventions, ranging from down-regulating inflammatory markers to influencing glucose metabolism, underscore their multifaceted nature. The relation between immunomodulation and antidiabetic effects showcased by these interventions provides a comprehensive approach to addressing the complexities of diabetes. By concurrently modulating immune responses and influencing glucose homeostasis, these herbal interventions offer potential alternatives or adjuncts to conventional treatments. Future research in this domain holds immense promise. Exploring the specific molecular pathways through which these herbs exert their effects can enhance our understanding and contribute to targeted therapeutic interventions. Additionally, conducting rigorous clinical trials to validate the efficacy and safety of these herbal approaches will pave the way for their integration into mainstream diabetes management. In conclusion, the integration of herbal interventions for immunomodulation and diabetes management represents a dynamic and evolving field with the potential to reshape our approach to chronic disease care. The intricate relationship between the immune system and diabetes provides a fertile ground for further exploration and holds promise for the development of personalized and effective therapeutic strategies.

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