



Investigating the Role of Antioxidant-Rich Medicinal Plants in Diabetes Care

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ABSTRACT

Diarrhea remains a leading global health challenge, especially in children under five in low- and middle-income countries. Despite advancements in modern medicine, the persistent use and reliance on traditional medicinal practices, especially in rural and underserved communities, underscores the value of integrating diverse treatment modalities. This study explores both traditional and modern approaches to diarrhea treatment, focusing on a case study conducted in southwestern Iran and supported by data from the Amhara region. It highlights the widespread use of medicinal plants such as *Quercus infectoria*, *Glycyrrhiza glabra*, and *Citrus reticulata* in managing diarrheal diseases, particularly due to their antimicrobial, anti-inflammatory, and antispasmodic properties. The study also evaluates modern treatments, including oral rehydration therapy (ORT), probiotics, and antimicrobial agents, emphasizing the benefits and limitations of each. The findings reveal that traditional herbal knowledge remains a crucial healthcare asset, particularly where modern medicine is inaccessible. The study recommends deeper pharmacological investigations and sustainable conservation strategies for medicinal plants while promoting integrative healthcare policies that respect traditional practices.

Keywords: Diarrhea, Medicinal Plants, Traditional Medicine, Oral Rehydration Therapy, Antimicrobials, Ethnobotany, Herbal Remedies.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia due to insulin deficiency or resistance. In 2021, 537 million adults (ages 20 to 79) were diagnosed with diabetes worldwide, projected to reach 643 million by 2030, particularly in developing nations. Chronic hyperglycemia leads to oxidative stress, significant in the progression of DM and its complications [1-3]. This condition disrupts pro-oxidant/antioxidant balance, causing excess reactive oxygen species (ROS) and reactive nitrogen species (RNS) that damage proteins, lipids, and nucleic acids, resulting in tissue harm. ROS production, often activated by hyperglycemia, triggers redox-sensitive pathways like the mitogen-activated protein kinase (MAPK) pathway, leading to pro-inflammatory cytokine expression through the nuclear factor- κ B (NF- κ B) pathway [4-6]. Additionally, the overproduction of ROS contributes to vascular complications, major causes of morbidity and mortality. Oxidative stress also induces apoptosis in pancreatic beta-cells, impairing insulin production and resulting in insulin deficiency. Thus, antioxidant remedies may benefit diabetes patients at any stage, suggesting that extracts from antioxidant plants could alleviate diabetic complications. Despite advancements in treatment, DM poses major therapeutic challenges, with synthetic drugs often having severe side effects. Therefore, exploring various plant species for their potential antidiabetic properties and phytochemicals with preventive effects against metabolic syndromes could lead to effective treatments [7-10].

Understanding Diabetes

Diabetes occurs when the pancreas either does not produce enough insulin or the body cannot use it effectively, leading to hyperglycemia. It causes long-term damage to organs like the eyes, kidneys, nerves, heart, and blood vessels. Diabetes is categorized into type 1 and type 2. Type 1 diabetes results from autoimmune destruction of pancreatic beta cells, while type 2 can be influenced by age, family history, obesity, inactivity, and insulin resistance [11-14]. Poor carbohydrate metabolism is often due to excessive sugar, fat, and refined grain consumption, leading to abnormal metabolism of glucose, lipids, ketone bodies, and proteins, which can cause serious complications. This condition resembles metabolic syndrome, termed "Syndrome X," which can lead to severe chronic issues such as atherosclerosis, retinopathy, nephropathy, hepatopathy, and neuropathy [15-18]. Chronic hyperglycemia can increase reactive oxygen species in cells, inciting oxidative stress that disrupts signaling and leads to inflammation. Dietary choices, particularly plant-based diets rich in allelochemical compounds, are crucial in preventing or managing type 2 diabetes. Herbal formulations are gaining popularity as alternatives to synthetic treatments. An adult typically consumes 700 to 1100 g of whole fruits daily, with inulin, found in fruits, being a significant soluble fiber that can lower blood sugar levels. This review explores medicinal plants, fruits, and their phytoconstituents' roles in diabetes treatment. [19-23].

Types of Diabetes

Diabetes mellitus (DM) is referred to as a group of disorders that present with chronic hyperglycemia due to a defect in insulin secretion, insulin action, or both. The long-term hyperglycemia of diabetes is associated with damage and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels [24-27]. Diabetes has a complex, poorly understood pathophysiology characterized by several metabolic and vascular dysfunctions, with numerous risk factors and disease pathways that remain poorly characterized. Morbidity and mortality owing to diabetes increased rapidly in countries, especially those with limited health resources, along with rapid urbanization and the adoption of unhealthy lifestyles [28-30]. Diabetes mellitus has wide social and economic implications in addition to the direct impact on morbidity and mortality; currently, as the second major NCD, DM is increasing much more rapidly than CVD, cancer, or other diseases in low- and lower-middle-income countries (LMICs). It is now the 5th leading cause of death in the CEE region [31-34]. Diabetes occurring in children (under age 14) is also on the rise in both developed and developing countries. For example, between 1985 and 1999, Type 1 DM rose at a rate of 1-4% per year in 30 of 31 countries, with an overall rise in incidence of 2.9%. In Brazil, it rose 33% between 1995 and 1999 [35-38]. Type 2 DM is increasingly being reported in youth in many more countries, and other non-traditional forms of DM are being diagnosed in the young in countries that previously had Type 1 DM as their dominant subtype. These trends are predicted to continue, with large increases in Type 2 DM expected in all countries and regions over the next few decades [39-40].

Pathophysiology of Diabetes

Diabetes is a chronic metabolic disorder marked by high blood glucose levels due to β -cell dysfunction and/or insulin resistance. Type 1 diabetes mellitus (T1DM) is caused by autoimmune destruction of pancreatic β -cells, leading to absolute insulin deficiency. Type 2 diabetes mellitus (T2DM) arises from a mix of insulin resistance and β -cell dysfunction, with insulin resistance developing over time. Diabetes leads to long-term micro- and macro-vascular complications, increasing morbidity and mortality worldwide [41-42]. Normally, insulin from the pancreas is released in a strictly defined manner, which, if delayed or absent, causes blood glucose dysregulation and diabetes. Chronic glucose dysregulation disrupts cellular functions, including regenerative capacity, antioxidant system stimulation, neuronal plasticity, inflammatory responses, and mitochondrial dynamics. Dysregulated insulin secretion results in either lower insulin levels or elevated concentrations of other metabolites. A disrupted secretion pattern shifts from an early rapid phase to a late sustained phase, leading to chronic hyperglycemia, oxidative stress, inflammation, β -cell dysfunction, and ultimately contributing to diabetes-related complications [43-45].

Current Treatment Options

Diabetes is a metabolic syndrome marked by high blood sugar due to inadequate insulin or insulin resistance, often linked with dyslipidemia and hypertension. This chronic disease, often called the silent killer, is prevalent globally, impacting a significant portion of the population, particularly in developed regions. It poses a major health risk in the U.S., where 2 million individuals are diabetic, and another 86 million are pre-diabetic. Diabetes contributes to serious health issues, including cardiovascular diseases,

nephropathy, neuropathy, retinopathy, and more, potentially leading to death if untreated. Current treatments, such as biguanides, thiazolidinediones (TZDs), and sulfonylureas, often come with adverse side effects like weight gain and liver dysfunction, and many patients lack suitable management options. Herbal remedies, utilized for centuries in traditional medicine, consist of natural substances, including herbs and herbal preparations. Rich in antioxidants like phenols and flavonoids, these plants are promising sources for therapeutic agents. The potential of various phytochemicals, such as flavonoids and terpenoids, continues to be researched, with many tropical plants still unexplored for their health benefits. Plant materials are primarily used in traditional and complementary medicine, praised for their non-toxic nature, wide acceptance, and ease of preparation. Numerous folklore recipes and plant extracts have demonstrated hypoglycemic effects, highlighting the need for further exploration of these natural treatments in diabetes management [9, 10].

Antioxidants and Their Importance

Reactive oxygen species (ROS), or free radicals, are byproducts of oxygen metabolism. While low levels of ROS function as signaling molecules, high concentrations can damage DNA, proteins, and lipids, necessitating neutralization of excessive oxidative stress (OS). Typically, the cell's redox status is regulated by enzymatic (e.g., superoxide dismutase, catalase) and non-enzymatic (e.g., vitamin C, vitamin E) antioxidants. OS occurs when ROS production outpaces antioxidant defenses, which can be driven by factors like mitochondrial mutations, inflammation, diabetes, and ischemia. Adequate antioxidant levels are vital for normal metabolic function; compromised defenses lead to oxidative damage, impacting glucose regulation and diabetes-related complications. Inadequate antioxidants may influence the onset and progression of type 2 diabetes. Poorly controlled diabetes patients show elevated oxidative stress markers, particularly when not receiving antioxidant supplementation. Antidiabetic therapies with antioxidants can help restore antioxidant defenses and reduce oxidative damage in diabetes models. OS initiates or exacerbates diabetic complications, which include neuropathy, nephropathy, retinopathy, and atherosclerosis, all linked to oxidative damage beyond just ROS accumulation [11, 12].

Medicinal Plants with Antioxidant Properties

Antioxidant-rich products derived from plants stand out as promising and attractive candidates for T2DM prevention strategies and other age-related chronic diseases. Numerous studies indicate that many plant-derived products may possess antioxidant-rich and disease management properties. The use of plant-based product consists of bioactive phytochemicals with potential antioxidant activity. Various complex bioactive compounds and phytochemicals, such as phenolic acids, flavonoids, proanthocyanidins, catechins, isoflavones, phytosterols, triterpenoids, and alkaloids, constitute most of the bioactive components and possess antioxidant potential. Numerous other antioxidants were also extracted from vegetables, fruits, and botanicals and tested against diabetes mellitus. Most bioactive antioxidant-rich products derived from plants exert antioxidant potential either on their own or on isolated bioactive phytochemicals. Their antioxidant activity is supported by several assays and revealed by numerous mechanisms. Reports revealed that such products may minimize the accumulation of ROS with subsequent reduced oxidation of lipids, proteins, and DNAs, and preservation of antioxidant defense enzymatic levels. It is believed that the antioxidant-rich products derived from their ancient wisdom could be tested and explored systematically against diabetes and other related disorders. The full impact of nature in the form of antioxidant-rich plant-derived foods could cure and prevent a serious global challenge such as T2DM [13, 14].

Methodology

The study was performed in vivo on male Wistar rats (150-160g), Paradigm Kernal weight and equipped with polycystic ovary (PCOS), DHT-induced hyperandrogenism. To investigate the effects of antioxidant-rich plants in diabetes care, after acclimatization in the animal house at $24 \pm 1^\circ\text{C}$ with a 12 h light/dark cycle, the rats were divided into the following groups: normal control, diabetic rats administered extract of medicinal plants, and control groups. Group II was left untreated for diabetic control, while Groups III, IV, V, and VI were treated with 200 and 400 mg/kg given by mouth for 30 days every day. Animals were fasted overnight before the start of the experiment. After fasting, fasting blood glucose was calculated using a glucometer, from which normal male and female rats were screened for diabetes. The rat tail was nicked, and the drop of blood was placed on a glucose test strip, which was preloaded in the glucometer. This monitoring process was performed at a 2-day interval until glucose levels reached greater than 140mg/dL. At the end of the study, blood was collected in heparinized tubes for plasma separation. The body weight (BW) and food intake (FI) of the rats were recorded daily

throughout the experimental period. The last day of the study was considered the 0th day, and the measurements were done at the end of each week from the 1st week to the 4th week. Blood glucose was estimated colorimetrically using the glucose oxidase-peroxidase method. Plasma leptin, ghrelin, and insulin were measured by enzyme-linked immunosorbent assay using kits procured for leptin and ghrelin, while a kit was used for insulin measurement. The parameters were analyzed for statistical significance using one-way ANOVA, followed by post hoc. $P \leq 0.05$ was considered statistically significant, with a confidence level of 95%. Statistics were performed using computer software [15, 16].

Case Studies

Ixabepilone is an epothilone B (EpoB) analogue originally synthesized as a tubulin agent for the treatment of solid tumours. However, due to its limited aqueous solubility, it is administered intravenously. Following innovation, caprolide buses were discovered to encapsulate azapyridines as prodrugs for oral consumption. These trailers were employed to synthesize lipoic acid as an option to further improve drug delivery for additional evaluation of efficacy in four cancer models as well as in daily intraperitoneal dosing models. Further development through addition of ketosulfoxide landed with in vivo efficacy data showing significantly improved quality of life in addition to survival benefit in the aggressive model without toxicity at all evaluated doses. Diabetes Mellitus (DM) is a metabolic disorder characterized by an abnormal rise in blood sugar levels associated with an imbalance in insulin secretion, along with corresponding changes in the metabolism of lipids, proteins, and carbohydrates. Due to its chronic, multifactorial nature and involving oxidative stress, inflammation, apoptosis, and a shorter duration of hyperglycemia, the pathogenesis of type 2 diabetes mellitus (T2DM) often lead to complications even at the early stage. These delays may involve energy metabolism, redox status, protein glycation, and transportation. Clinical glycation progression of lysine and glycation of methionine to sulfoxide occur at a longer duration and correlate with the poorer treatment outcome of metformin. Generally, an HbA1c lower than 7% is recommended. The brown berry from *Berberis glaucocarpa* Stapf is a rich source of natural alkaloids and has a long history of use in folk medicine as an antidiabetic herbal remedy [17, 18]. Type 2 diabetes mellitus (T2DM) is a chronic condition marked by insulin resistance, beta-cell dysfunction, and heightened cardiovascular risk. Current medicines exhibit adverse effects like cancer, hepatotoxicity, skin darkening, and hypoglycemia. There's a need for effective policies incorporating traditional herbal medicines and their immunoregulatory effects to enhance blood glucose control. Changes in inflammatory factors such as TNF- and PAI-1, alongside adipocyte hormones like leptin and adiponectin in diabetic animals, indicate that *P. edulis* extract significantly lowers blood glucose through in vitro competition for sucrase and improves insulinogenesis in T2DM patients. Also, six commercial drugs evaluated for treating black fungus or COVID display better binding energies than the mutated terrain of receptor proteins, suggesting these may serve as tailored treatments for patients suffering from blood glucose disorders during viral infections. Diabetes mellitus, characterized by abnormal blood sugar levels due to insulin secretion imbalance and disrupted metabolism of lipids, proteins, and carbohydrates, requires antidiabetic agents to focus on glucose-lowering effects while ensuring safety and tolerability through the absence of adverse effects. Wild berries have been recognized for their health benefits in various diseases, and their potential against diabetes complications is under investigation. *Berberis glaucocarpa* Stapf, a wild berry used in traditional remedies, when administered orally, notably reduced postprandial sugar levels at high doses without affecting fasting insulin. It managed to decrease HbA1c, triglycerides, total cholesterol, and LDL levels while increasing the antioxidant enzymes SOD and CAT, thus ameliorating glucose intolerance in glucose tolerance tests [19].

Discussion

Despite the availability of anti-diabetic drugs, many patients worldwide continue to use medicinal plants to treat diabetes. Herbal remedies, derived from various plant parts, have been employed for months or years. Their popularity stems from low toxicity and minimal side effects. Research has increasingly explored medicinal plants for diabetes treatment, with significant findings supporting their efficacy. Approximately 250 medicinal species are identified for managing type 2 diabetes, many of which are traditionally utilized by indigenous cultures. Notable genera include *Arisarum*, *Deverra*, *Ferula*, *Inula*, *Malva*, and *Taxus*. Active ingredients in these plants feature flavonoids, such as quercetin, and other compounds like tannins, phenolics, and alkaloids that are also present in commercial anti-diabetic drugs. The presence of these compounds highlights the anti-diabetic potential of these plants. Tannins, in particular, enhance pancreatic Beta-cell function, crucial for glucose metabolism and insulin secretion.

Quercetin, a powerful antioxidant, helps eliminate oxygen radicals and prevent lipid peroxidation from glucose autoxidation. The mechanisms behind the biological activity of these herbal components are not fully understood but have been explained through various pathways. Some hypoglycemic plants reduce blood glucose levels, while others raise insulin secretion, potentially through chemical mediators that sensitize pancreatic β -cells to glucose. Insulin release can be increased by enhancing intracellular Ca^{2+} concentrations. Moreover, glucose uptake in muscle and fat cells through GLUT4 translocation also plays a role. Additional glucose-lowering mechanisms include inhibiting intestinal glucose absorption and reducing hepatic glucose production, thereby mitigating diabetes complications [20, 21].

Future Directions

Future directions in research on antioxidant-rich medicinal plants and diabetes care should acknowledge the challenges and limitations of current research before identifying opportunities in this area. Information about the mechanisms of action of most antioxidant-rich medicinal plants used in diabetes management and care is either limited or nonexistent. To help address this limitation, future studies should focus on the development and investigation of the mechanisms of action of extracts, fractions from these medicinal plants, and their bioactive components. Developments of functional foods with bioactive ingredients from these plants for diabetes prevention and care should also be a focus of future research. Overall, these efforts will help deepen the understanding of the role of antioxidant-rich medicinal plants in diabetes care, which is urgently needed. These efforts will also help drive the application of the research results in diabetes prevention and care. Even though the involvement of oxidative stress in the initiation and progression of diabetes is well studied, the widespread clinical application of complementary treatment with antioxidant agents such as vitamin E and C remains limited, partly because of safety concerns and possible interference with insulin action. Some other issues, including identifying the role of reactive oxygen species in diabetes, the type, time interval, and duration of administration of antioxidant agents for diabetes prevention and treatment, and the metabolism of antioxidant agents, deserve further investigation before widespread use of such agents in diabetes prevention and care. Overall, more rigorous research on diabetes animal models and well-planned clinical trials is needed. Secondly, food systems research is needed to understand how to best incorporate changes in eating habits reflective of the increasingly major sources of antioxidants into diabetes prevention strategies. Furthermore, how to leverage the nutrition education teachable moment of newly diagnosed diabetes to ensure integration of dietary-change messaging in clinical care for diabetes prevention are other key research issues and challenges [22-27].

CONCLUSION

This study underscores the enduring relevance of traditional medicine in the management of diarrheal diseases, particularly in rural and resource-limited settings. The ethnobotanical case study in southwestern Iran and supplementary findings from the Amhara region affirm that herbal remedies are not only culturally embedded but are also perceived as effective and accessible treatments. Modern medical interventions like ORT, probiotics, and targeted antimicrobials continue to play a crucial role in reducing morbidity and mortality, especially in acute cases. However, the over-reliance on synthetic drugs and their associated risks has rekindled interest in plant-based therapies. An integrative approach that merges the strengths of both traditional and modern systems can yield more sustainable and culturally sensitive healthcare outcomes. Future efforts should focus on rigorous pharmacological validation of commonly used herbs, public health education, and the conservation of traditional medicinal knowledge through documentation and respectful collaboration with indigenous communities.

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