

The Complexity of Diabetes Mellitus: Pathophysiology, Prevalence, and Innovative Management Strategies

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Abstract

In recent years, the global use of nutraceuticals, nutritional supplements, and natural therapies for therapeutic purposes has grown significantly. Traditional synthetic drugs often fall short in addressing the therapeutic needs of managing diabetes. In contrast, herbal medicines offer a promising alternative with fewer side effects. Nutraceuticals include a wide range of biological interventions such as amino acids, fatty acids, botanicals, antioxidants, vitamins, and minerals designed to enhance overall well-being, manage symptoms, and prevent diseases. These agents offer diverse therapeutic benefits and show potential in disease management, prevention, and health promotion. Numerous nutraceuticals in clinical practice address the root causes of diabetes mellitus, metabolic syndrome, and their related complications, thereby positively influencing various biochemical and clinical outcomes. Hypoglycemic agents are commonly used in traditional medicine systems to mitigate the risk of diabetes mellitus. In this review, we highlight the risk factors and regional approaches to utilizing nutraceuticals for diabetes management.

Keywords: *Biological Therapies, Diabetes, Dietary Supplements, Herbal remedies, Nutraceuticals.*

Introduction

Diabetes Mellitus is a complex condition involving insulin resistance, impaired insulin signaling, β -cell dysfunctions, inflammation, and disrupted glucose and lipid metabolism, leading to increased oxidative stress. Affecting 2.8% of the global population in 2000, its prevalence is expected to rise to 4.4% by 2030, driven by aging and obesity trends [1, 2]. The metabolic imbalances in diabetes result in chronic pathological conditions such as micro- and macrovascular complications, neuropathy, retinopathy, and nephropathy, which lower the quality of life and increase mortality [3, 4].

Diabetes is characterized by elevated blood sugar due to impaired insulin secretion or reduced tissue responsiveness, and it includes type 1, type 2, gestational diabetes, and forms related to other causes like pancreatic disorders or medications [5]. Persistent high blood sugar and metabolic changes can damage multiple organs, causing complications like cardiomyopathy, retinopathy, nephropathy, neuropathy, and foot ulcers [5, 6].

Based on the current understanding of type 2 diabetes, which involves insulin resistance, both pharmacological and non-pharmacological interventions aim to maintain

glycemic control and prevent complications. Individuals with insulin resistance face heightened risks of severe cardio-metabolic and infection-related complications, including those from COVID-19, impacting societal and economic spheres. Precision nutrition and the use of functional foods and bioactive constituents are emerging as promising strategies for targeted diabetes prevention and management [7]. Nutraceuticals are foods with medical and health benefits, including disease prevention and treatment. They include natural foods with functional or medicinal properties, and bioactive phytochemicals that support health and disease prevention. Traditional medicinal plants are widely used for their effectiveness, minimal side effects, and cost-efficiency in managing diabetes [8, 9]. In this review highlighted the role of nutraceuticals with established hypoglycemic potential, including plant-based agents like cinnamon and coenzyme Q10, for diabetes management. Advances in precision medicine and nutrition aim to enhance treatment, prolong lifespans, and improve quality of life for those with diabetes [10].

Diabetes Mellitus

Diabetes mellitus is a complex metabolic condition influenced by genetic, lifestyle, and environmental factors. The emergence of diabetes is linked to various risk factors, which may vary depending on the type of diabetes

Type 1 Diabetes: Type 1 diabetes risk is heightened by a family history of the condition, although genetics alone are not determinative [11]. The disease commonly begins with an autoimmune reaction, where the immune system erroneously attacks and destroys the insulin-producing beta cells in the pancreas [12]. Additionally, some viral infections, especially enteroviruses, can increase the risk of developing type 1 diabetes [13].

Type 2 Diabetes: Several factors contribute to the onset of type 2 diabetes. Obesity, particularly excess abdominal fat, is a primary

predisposing factor[14]. A sedentary lifestyle and insufficient physical activity increase susceptibility. An unhealthy diet rich in sugary and processed foods, and low in fiber and whole grains, further raises the risk. A family history of type 2 diabetes heightens the likelihood, as does belonging to certain ethnic groups such as African Americans, Hispanic Americans, Native Americans, and Asian Americans. Women with gestational diabetes during pregnancy face a higher risk later in life, and those with polycystic ovary syndrome are also at increased risk [15]. Additionally, hypertension and metabolic syndrome comprising obesity, high blood pressure, abnormal lipid levels, and high blood sugar substantially elevate the risk of developing type 2 diabetes [16, 17].

Gestational Diabetes: Several factors contribute to the likelihood of developing gestational diabetes. Obesity or being overweight before pregnancy increases the risk, as does advancing age, particularly for women over 25, especially those over 30. A family history of diabetes and belonging to specific ethnic groups predisposed to type 2 diabetes also elevate the possibility of gestational diabetes. Women who have previously experienced gestational diabetes in one pregnancy are more prone to it in subsequent pregnancies. Lifestyle modifications, such as maintaining a healthy weight, staying physically active, and adopting a balanced diet, can significantly reduce the risk of diabetes [18]. Regular medical check-ups and screenings are essential for early detection and effective management of diabetes risk factors [19].

Role of Nutraceuticals in Diabetes

In European medical law, nutraceuticals are classified as medicinal due to their ability to modify physiological functions and treat diseases [20,21]. They cover diverse therapeutic areas, including diabetes management, within three main sectors:

herbal/natural products, dietary supplements, and functional foods. Nutraceuticals provide advantages such as natural dietary supplementation, health enhancement, and potential disease management with minimal side effects, promoting accessibility and affordability. Research and development efforts are robust, focusing on standardizing nutraceutical compounds and conducting rigorous clinical studies to validate health claims, crucial for consumers and industry advancement [22].

Nutraceuticals are integral to managing diabetes by addressing specific needs and contributing to overall health. They target nutritional deficiencies common in diabetic individuals, supporting general well-being. Additionally, nutraceuticals like probiotics and prebiotics promote a healthy gut microbiome, potentially enhancing metabolic function and insulin sensitivity [23]. The main compounds such as cinnamon, berberine, and bitter melon aid in regulating blood sugar levels by improving insulin sensitivity and glucose metabolism [24]. Moreover, antioxidants found in nutraceuticals such as vitamins C and E, α -lipoic acid, and coenzyme Q10 help reduce oxidative stress and inflammation, which are significant contributors to diabetes complications [25]. Omega-3 fatty acids from sources like fish oil and flaxseed oil found in nutraceuticals can also play a crucial role in managing lipid levels, thereby reducing cardiovascular risks associated with diabetes [26]. Overall, nutraceuticals offer a holistic approach to diabetes management, emphasizing both therapeutic benefits and overall health improvements.

Nutraceuticals play crucial roles in managing various diabetes-related health challenges. They are beneficial for kidney health, with alpha-lipoic acid and coenzyme Q10 showing promise in protecting against diabetes-related kidney damage [27]. In addressing neuropathy, specific vitamins, and alpha-lipoic acid can alleviate symptoms and

support nerve health in diabetic individuals [28]. Nutraceuticals like garlic, coenzyme Q10, and certain amino acids contribute to cardiovascular health by regulating blood pressure and reducing the risk of cardiovascular diseases prevalent among diabetics [29]. Additionally, dietary fiber-rich nutraceuticals such as psyllium husk and glucomannan aid in weight management and promote satiety, essential for overall diabetes management [30]. While nutraceuticals can complement diabetes care, they should not substitute medications or a balanced diet. These supplements may help reduce inflammation and potentially lower the risk of developing diabetes preventively. Regular monitoring of blood sugar levels and other health markers is crucial to evaluating these supplements' effectiveness and safety, thereby enhancing the quality of life for individuals managing diabetes.

Regional Strategies for Nutraceutical Utilization

Nutraceuticals play a pivotal role in regional healthcare strategies worldwide, tailored to meet specific health needs, cultural preferences, and dietary traditions [31, 32]. In the Asia-Pacific region, there is a focus on traditional herbal remedies like ginseng and green tea, alongside incorporating ingredients such as seaweed and medicinal mushrooms into daily diets for their health benefits, including potential applications in managing conditions like diabetes. The Mediterranean region promotes the renowned Mediterranean diet rich in olive oil, nuts, and fish, which naturally provides nutraceuticals like omega-3 fatty acids and polyphenols. North America emphasizes fortified foods and supplements like vitamin D and omega-3 fatty acids for cardiovascular and bone health. At the same time, Latin America highlights superfoods like quinoa and chia seeds, integrating herbal remedies and natural antioxidants into local diets.

In Africa, indigenous plants such as moringa and baobab are explored for their nutritional

and medicinal properties, complementing traditional dietary practices. The middle east promotes dried fruits and spices like turmeric for their health benefits, and Europe champions fermented dairy products and regional superfoods like berries and dark chocolate. Oceania emphasizes native ingredients like Manuka honey and seaweed for their unique health-promoting properties. These regional approaches underscore the importance of evidence-based practices and the role of healthcare professionals in integrating nutraceuticals into local healthcare systems,

especially in managing chronic conditions such as diabetes.

Management of Diabetes with Nutraceuticals

Nutraceuticals encompass a variety of biological therapies designed to enhance well-being, prevent diseases, and manage symptoms, categorized into nutrients like vitamins, minerals, amino acids, and fatty acids; herbs derived from herbs or botanicals; and dietary supplements serving specific purposes such as sports nutrition and weight management (Figure 1).

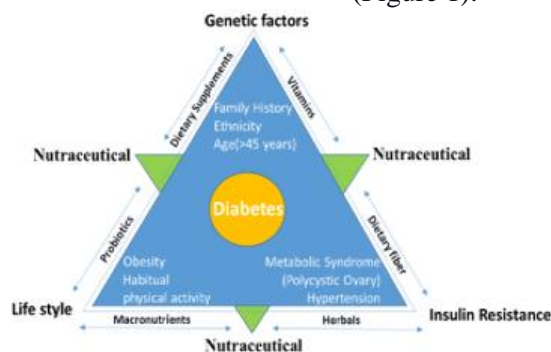


Figure 1. Regional Utilization of Nutraceuticals for Diabetes Management

In managing diabetes, nutraceuticals play crucial roles across dietary components: monitoring carbohydrate intake is vital for blood sugar control, while dietary fiber from fruits, vegetables, and whole grains improves glycemic control and overall health. Balanced protein consumption supports muscle mass and overall health, and reducing saturated fats while opting for healthier fats like monounsaturated and polyunsaturated varieties is key for managing diabetes and related conditions [33]. Micronutrients such as vitamins and minerals contribute to overall health and aid in diabetes management, and omega-3 fatty acids from fish and supplements help lower triglycerides and support cardiovascular health. Certain dietary supplements like cinnamon, berberine, and bitter melon show promise in enhancing insulin sensitivity and glucose metabolism. Personalizing dietary choices and nutraceutical use under healthcare professional guidance is

essential in diabetes care, complementing other treatments and a balanced diet. Regular monitoring of blood sugar levels and health markers ensures the efficacy and safety of nutraceutical supplementation, contributing to improved health outcomes for individuals managing diabetes.

Micronutrients and Minerals in Diabetes Management

Chromium: Chromium, specifically in the Cr^{+3} form, is an essential trace element critical for glucose metabolism. Its role includes enhancing insulin efficiency by increasing insulin receptors, improving insulin binding to these receptors, and activating the insulin receptor. Chromium supplements are most beneficial for individuals with deficiencies, as ageing often leads to decreased chromium levels, potentially increasing the risk of Type II diabetes among the elderly. Dosages ranging from 100 to 500 mcg/day have shown the

ability to reduce blood glucose, insulin, and cholesterol levels [34].

Magnesium: Epidemiological studies have shown a link between magnesium-rich diets and a reduced risk of diabetes. There's a significant inverse relationship between magnesium intake and fasting insulin levels, indicating improved insulin sensitivity. Limited clinical data and animal studies support magnesium's role in sustaining adipocyte insulin sensitivity. Adequate magnesium intake is vital for overall health, with potential benefits in diabetes management [35, 36].

Vanadium: Research suggests that vanadium operates similarly to insulin by facilitating glucose transport into cells, making it advantageous for Type I and Type II diabetes. Vanadium supplementation has demonstrated the ability to lower fasting blood glucose levels, Hemoglobin A1c levels, and cholesterol levels. Dosages from 45 to 150 mg/day show promise in improving fasting glucose levels. Comprehensive toxicity assessments confirm the safety of these dosages for most individuals, with only mild gastrointestinal discomfort reported in some cases [37].

Vitamins in Diabetes Management

Biotin: Biotin, a vital B vitamin, is crucial in metabolism and growth. It stimulates liver glucokinase activity, enhances insulin production, and improves glucose uptake in muscle cells. Rich sources of biotin include organ meats, soy, egg yolks, whole grains, and yeast. There's evidence that many individuals in the United States may not meet their recommended biotin intake, making a daily dosage of 9 mg advisable for those managing diabetes [37].

Vitamin E: Vitamin E acts as an important fat-soluble antioxidant. Low vitamin E levels are linked to a higher risk of diabetes, and individuals with diabetes may require higher antioxidant levels to counteract free radical production from hyperglycemia. Dosages up to 400 IU are generally considered safe, but doses

exceeding 800 IU could potentially impact blood clotting, although studies have not shown significant increases in Prothrombin time[38].

Calcium/Vitamin D: High calcium intake has been identified as a protective factor against diabetes in some studies. Women with the highest calcium intake demonstrated a 30% lower risk of diabetes over a 6-year follow-up period. Maintaining a healthy calcium/vitamin D status might help preserve insulin sensitivity and contribute to diabetes prevention. No follow-up studies have explored the consequences of vitamin D intake or sunlight exposure on diabetes risk [39, 40].

Vitamin C: Recent research suggests potential benefits of Vitamin C supplementation for individuals with Type II diabetes. Higher Vitamin C dosages (approximately 1000 mg daily) may regulate blood sugar levels, enhance antioxidant status, and possibly prevent or mitigate cataracts and nerve disorders commonly observed in people with diabetes. These doses might also inhibit protein glycosylation, a process believed to contribute to diabetes-related complications [41].

α -Lipoic Acid: α -Lipoic acid, a naturally occurring antioxidant, distinguishes itself with its robust ROS (Reactive Oxygen Species) scavenging capabilities. Its unique ability to function as a ROS scavenger even in its oxidized state makes it effective in neutralizing various radicals. It operates synergistically with dihydrolipoic acid, forming a redox couple that offers additional antioxidant benefits, including chelation of transition metals and regeneration of other antioxidants like glutathione, Vitamin C, and Vitamin E [33, 42].

Research has demonstrated α -Lipoic acid's capacity to protect the retina from ischemia-reperfusion injuries, particularly relevant to diabetic retinopathy. Furthermore, it enhances insulin sensitivity by approximately 18–20% in individuals with type 2 diabetes mellitus. Clinical trials targeting diabetic neuropathy have reported positive outcomes, including

notable improvements in acute symptoms and disease progression [33, 43].

Coenzyme Q10 (CoQ10): Coenzyme Q10 (CoQ10) holds significant importance, especially as many medications used in diabetes management and its complications can deplete CoQ10 levels. This nutrient shows promise as a nutritional intervention for addressing insulin resistance, particularly in individuals with hypertension. In an eight-week, randomized, double-blind trial involving hypertensive patients, the effects of a water-soluble form of CoQ10 (60 mg taken twice daily) were compared to a vitamin B complex. The results indicated that CoQ10 at this dosage level contributed to reductions in glucose and fasting insulin levels, suggesting potential improvements in insulin resistance [44, 45].

Omega-3 Fatty Acids: Fatty acids are essential for the composition of cell membranes, facilitating glucose entry into cells for energy production. Since the human body cannot synthesize omega-3 fatty acids, it relies on dietary sources. Excellent dietary sources include fatty fish like salmon, mackerel, sardines, herring, and tuna, as well as flaxseed, evening primrose, borage, walnuts, and wheat germ.

Omega-3 essential fatty acids (omega-3 EFAs) have shown potential in improving insulin resistance based on animal models. However, human studies have produced varying results regarding insulin metabolism, ranging from improvements to no significant changes and, in some cases, a decline in glycemic control. A recommended daily intake of flaxseed oil is 1-2 tablespoons or 1/4 cup of freshly ground flaxseed [46].

L-carnitine (β -hydroxy- γ -trimethylaminobutyrate) is a naturally occurring compound with vitamin-like properties throughout mammalian plasma and tissues, primarily in skeletal and cardiac muscles. The body obtains L-carnitine from dietary sources such as meat and dairy products

and through biosynthesis from lysine and methionine [33, 47].

Extensive research on L-carnitine supplementation has revealed its potential to enhance insulin sensitivity and reduce lipid levels. L-carnitine plays essential intracellular and metabolic roles, including facilitating the transport of fatty acids across the inner mitochondrial membrane for β -oxidation, detoxifying potentially harmful metabolites, regulating the mitochondrial acyl-CoA/CoA ratio, and stabilizing cell membranes [33].

Moreover, L-carnitine aids in the removal of short- and medium-chain fatty acids that may accumulate in mitochondria due to typical or irregular metabolic processes. It also influences the oxidative metabolism of glucose in various tissues. In an experimental model involving insulin-resistant rats fed a fructose-rich diet, L-carnitine demonstrated potential in improving insulin function, particularly in insulin-sensitive tissues susceptible to insulin resistance and oxidative damage [48, 49].

Claims of Herbs' Anti-diabetic Properties

Diabetes mellitus presents a growing global health challenge, with India experiencing a significant rise in this metabolic disorder. Diabetes profoundly affects lipid and carbohydrate metabolism, exerting physical and psychological effects. As our understanding of diabetes heterogeneity advances, the demand for more effective treatments becomes increasingly urgent. Traditional herbal remedies and nutraceuticals have emerged as safe alternatives to conventional hypoglycemic agents. This is especially significant as synthetic drugs for Non-insulin-dependent diabetes mellitus (NIDDM) and insulin for Insulin-dependent diabetes mellitus (IDDM) often exhibit limited effectiveness and an increased risk of drug tolerance, necessitating frequent dose adjustments or medication changes [50]. The abundance of essential phytonutrients,

nutraceuticals, and Ayurvedic herbs may serve as "potentiators" for these medications, offering valuable support in enhancing the quality of life for individuals managing diabetes.

There is a notable emphasis on exploring the connections between dietary nutrients and their potential in preventing diseases. Numerous herbs, some with ancient origins, have been found to play pivotal roles in disease prevention [51]. In addition to the essential macronutrients and micronutrients like proteins, fats, carbohydrates, vitamins, and minerals crucial for standard metabolic functions, a plant-based diet includes a diverse range of non-nutritive phytoconstituents that can significantly promote health [51, 52]. These phytoconstituents encompass many potential health benefits and are often embraced as supplementary or alternative approaches to conventional medicine [51]. However, it is crucial to emphasize that while nutraceuticals can offer a spectrum of health advantages, they should not be considered a replacement for a well-rounded diet and a healthy lifestyle. Furthermore, ensuring the quality and safety of nutraceutical products by selecting reputable brands and products is paramount to guarantee their effectiveness and safety.

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In conclusion, it is vital to recognize that nutraceuticals are dietary supplements infused with inherent nutritional value. The management of diabetes with nutraceuticals discussed in this review has displayed substantial clinical and pharmacological effectiveness. Herbal remedies exhibit remarkable potency while carrying fewer side effects than synthetic anti-diabetic drugs. Patients are increasingly drawn to natural products with anti-diabetic properties. Hypoglycemic herbs are effective because they stimulate insulin secretion at a molecular level, increase glucose uptake by adipose and muscle tissues, prevent glucose absorption in the intestines, and regulate glucose production by hepatocytes. Nutraceuticals are increasingly recognized for their role in clinical practice. Nevertheless, it is crucial to emphasize that significant nutraceutical and clinical considerations persist, warranting further investigation.

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Conflicts of Interest

The authors declare no conflicts of interest.

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