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(Review Article)

A review on phenolic compounds and their role in treatment and management of diabetes, including vanilic acid

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Abstract

In recent years, there has been a noticeable shift in the approach to treating diabetes mellitus (DM), with a growing interest in alternative medicines sourced from plants. Current literature indicates that phenolic compounds extracted from plants exhibit significant health benefits. This study aims to explore the contribution of plant-derived phenolic compounds in the effective treatment and management of diabetes. Data regarding plant secondary metabolites, phenolic compounds, and their implications for diabetes treatment and management. The review includes anti-diabetic research on the four primary classes of phenolic compounds. It was found that plant-derived phenolic compounds exhibit strong anti-diabetic properties. However, each class of phenolic compounds demonstrated distinct behaviors through various mechanisms. The findings suggest that phenolic compounds from natural sources show promising anti-diabetic effects. Therefore, it can be concluded that phenolic compounds derived from diverse natural sources are crucial in the treatment and management of diabetes. Vanillic acid is a naturally occurring phenolic compound with a variety of health benefits. It is found in many fruits, vegetables, and plant extracts, and it is also produced as a metabolic byproduct. Vanillic acid has antioxidant, anti-inflammatory, and antimicrobial properties. It is also used as a flavoring agent in food products and in various industries. The study aims to review on Phenolic Compounds and Their Role in Treatment and Management of Diabetes, including vanilic acid

Keywords: Phenolic compounds; Diabetes mellitus; Vanillic acid; Treatment

1. Introduction

Diabetes mellitus (DM) is a metabolic disorder with multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action or both. The World Health Organization recognizes three main forms of diabetes, which have different causes and population distribution: type 1, type 2, and gestational DM. Type 1 DM is usually due to an autoimmune disorder caused by auto-aggressive T lymphocytes that infiltrate the pancreas and destroy insulin-producing β-cells, leading to hypoinsulinemia and thus hyperglycemic condition. Type 2 DM is characterized by altered lipid, glucose metabolism, impaired insulin secretion, and increased insulin resistance (or resistance to insulin-mediated glucose disposal) (ADA, 2009). A progressive decrease of β-cell function leads to glucose intolerance, which is followed by type 2 DM. Gestational diabetes forms from glucose intolerance diagnosed during pregnancy. Gestational diabetes requires treatment to optimize maternal blood glucose levels to lessen the risk of complications to the infant's health. Chronic hyperglycemia imposes damage (glucosetoxicity) on a number of cell types and is strongly correlated with a myriad of DM-related complications. Tissues most vulnerable to the effects of prolonged elevated plasma glucose levels include pancreatic β-cells and vascular endothelial cells. The ensuing β-cell dysfunction promotes decreased insulin synthesis and secretion, further perpetuating the associated hyperglycemia. As for the vascular endothelium, chronic hyperglycemia is strongly correlated with many DM related microvascular complications, including retinopathy, nephropathy, and neuropathy.

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Diabetic complications are also reported to be associated with significant economic burden. The average cost of health care for patients with diabetes was 4.3 times higher than for patients without diabetes. Each year, 3.2 million people around the world die from complications associated with diabetes. Type 2 diabetes, which accounts for 90% of all diabetes, has become one of the major causes of premature illness and death, mainly through the increased risk of cardiovascular disease, which is responsible for up to 80% of these deaths. The majority among the 382 million people with diabetes are aged between 40 and 59, and 80% of them live in low-income and middle-income countries. All types of diabetes, but in particular type 2, are on the increase, and the number of people with diabetes is expected to increase by another 55% by 2035 (IDF, 2015). Population based surveys of 75 communities in 32 countries show that diabetes is rare in communities of developing countries where a traditional lifestyle has been preserved. Consequently, diabetes is rapidly emerging as a global healthcare problem that threatens to reach pandemic levels by 2035. According to the World Health Organization, Southeast Asia and the Western Pacific regions are at the forefront of the current diabetes epidemic, with India and China facing the greatest challenges. In these countries, the incidence and prevalence of diabetes among children are also increasing at an alarming rate, with potentially devastating consequences.

2. Role of phenolic compounds in diabetes

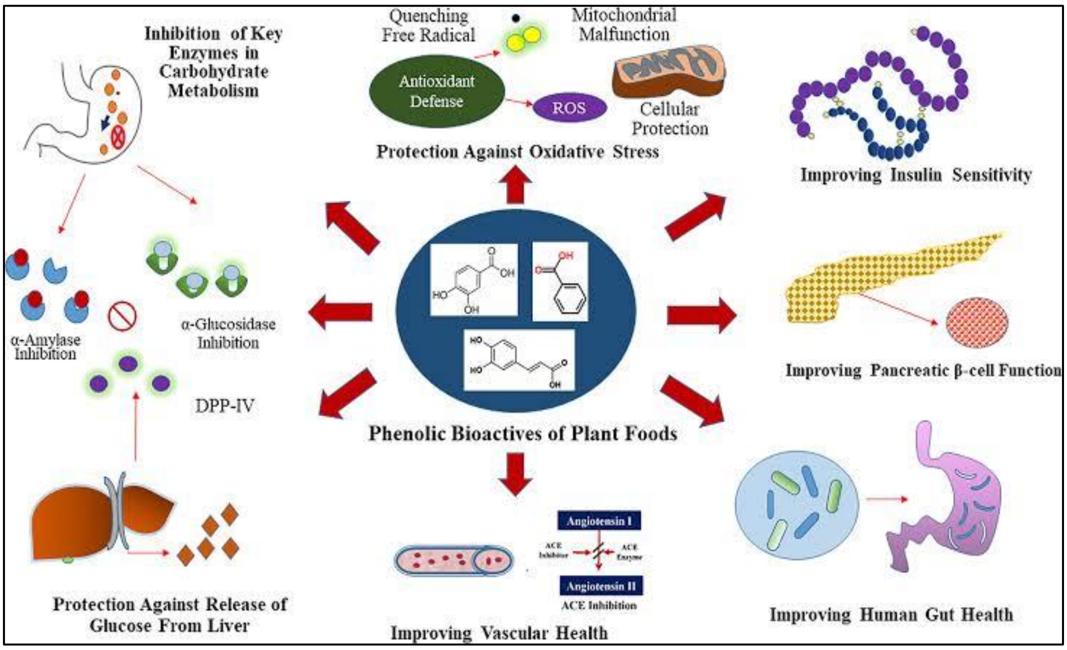

Figure 1 Role of Phenolic compounds in diabetes

In addition to antioxidant properties, phenolic bioactives of diverse plant foods have therapeutic functional activities such as improving insulin sensitivity, reducing hepatic glucose output, inhibiting activity of key carbohydrate digestive enzymes, and modulating absorption of glucose in the bloodstream, thereby subsequently improving post-prandial glycemic control [1].

3. Diabetes

Diabetes is a group of metabolic disorders characterized by high blood sugar levels, which can lead to a variety of complications if left untreated or poorly managed [2].

3.1. Types of Diabetes

- Type 1 Diabetes: An autoimmune disease in which the body's immune system attacks and destroys the insulin-producing beta cells in the pancreas.
- Type 2 Diabetes: A metabolic disorder characterized by insulin resistance and impaired insulin secretion.
- Gestational Diabetes: A type of diabetes that develops during pregnancy, usually in the second or third trimester.
- LADA (Latent Autoimmune Diabetes in Adults): A form of type 1 diabetes that develops in adults.
- MODY (Maturity-Onset Diabetes of the Young): A rare form of diabetes caused by genetic mutations.

3.1.1. Causes and Risk Factors

- Genetics: Family history and genetic predisposition.
- Obesity: Excess body fat, particularly around the abdominal area.
- Physical Inactivity: Sedentary lifestyle.
- Age: Risk increases with age.
- Ethnicity: Certain ethnic groups, such as African Americans, Hispanics/Latinos, and American Indians, are at higher risk.

3.1.2. Symptoms

- Increased Thirst and Hunger: High blood sugar levels can cause feelings of thirst.
- Frequent Urination: High blood sugar levels can cause the kidneys to produce more urine.
- Fatigue: High blood sugar levels can cause fatigue and weakness.
- Blurred Vision: High blood sugar levels can cause blurred vision.

3.2. Therapeutic approaches in diabetes

3.2.1. Statin Therapy: A New Perspective

Statins are defined as inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A and inhibit the crucial process of LDL cholesterol in liver, thereby decreasing its level in the blood besides increasing healthy blood vessel lining [3]. Since the long term effect of diabetes includes the high risk of cardiovascular diseases, statins (HMG-CoA reductase inhibitor) are a main line of therapy in reducing cardiovascular risk in the patients suffering from type 2 diabetes [4]. The lipid lowering agents popularly known as statins, cause inhibition of HMG-CoA reductase specifically and reversibly [5] The enzyme catalyzes the conversion of HMG-CoA to mevalonic acid, the rate-limiting step in the formation of cholesterol. These compounds are highly effective in reducing cholesterol levels as compared to dietary supplements [6].

Statin therapy reduces low density lipoprotein (LDL) cholesterol to a significant level thereby greatly decreasing the chances of developing a coronary artery disease [7] .National Institute for Health and Clinical Excellence (NICE) and Scottish Intercollegiate Guidelines Network (SIGN) diabetes guidelines showed lipid lowering therapy as primary prevention (when used regularly) for patients with type 2 diabetes, aged over 40 (Grade A recommendation), as well as consideration for patients aged over 40 with type 1 diabetes (Grade B recommendation)[8].

3.2.2. Stem Cell Technology: A Novel Therapeutic Approach:

The interest to find a possible therapeutic for diabetes has eventually explored various new scientific areas of research, with the stem cell technology being one of them, It is known that both type 1 and type 2 diabetes results from the β cell deficiency of the pancreatic cells, resulting in insufficient insulin secretion. The strategies should aim at either removing the defects in pancreatic β cell or enhancing the sensitivity of the body cells to the action of insulin. β cell replacement strategies offer a novel source while current strategies aiming at islet cells and pancreas transplantation are limited due to shortage of donor organs [9].

In contrast to type 1 diabetes, which is caused by autoimmune destruction of pancreatic β cells, type 2 diabetes results from irregularities in β cells function together with insulin resistance in peripheral organs [10]. Mesenchymal stem cell (MSC) therapy has emerged as a promising therapy in the treatment of type 1 diabetes due to its immunosuppressive nature.

3.2.3. Gene Therapy in Diabetes

The in vivo gene therapy is the method of choice as a therapeutic strategy because it is simpler and the vector containing the desired gene is directly inserted into the patient, but the development of safe (not toxic to host) and effective vectors remains as a challenging task for gene therapist. Presently, the strategies for in vivo therapy involve three methods: genetic transfer of glucose lowering genes which are noninsulin in nature. Presently, the strategies for in vivo therapy include genetic transfer of glucose lowering genes which are non-insulin in nature and application of blood sugar lowering genes: an enhancer of glucose utilization by liver or skeletal muscles and an inhibitor of glucose production by the liver [11]. For example, glucokinase as a transgene is found to have glucose lowering effect in the liver [12]. It was a possibility that the gene Gck enhances glucose utilization by the body [13]. The genetic transfer of glucokinase had been used as an adjuvant therapy in the treatment of diabetes[14].

3.2.4. Medical Nutrition Therapy

Medical nutrition therapy in prevention and management of diabetes puts forth numerous advances in clinical research, aiming to use nutrition therapy for the treatment of disorders and illnesses. American Diabetes Association in 1994 coined the term "medical nutrition therapy" constituting 2 phases, namely, adjudging the nutritional requirement of a person and treatment through counselling and nutrition therapy, respectively [15]. The objectives of nutritional therapy in diabetes is to regulate optimal level of lipids in blood, ideal body weight, and blood glucose level in normal range[16]. Nutrition therapy as a therapy for diabetes depends on certain factors such as patient's age-based nutritive requirements and food preferences as well as other medical conditions together with an exercise regime and recommended nutritional requirement depending upon the patient's abilities and health conditions [17].

4. Natural Products and Diabetes

The bioactive constituents found in many plant species are isolated for direct use as drugs lead compounds, or pharmacological agents. These traditional approaches might offer a natural key to unlock diabetic complications [18]. The chemical structures of a Phyto molecule play a critical role in its antidiabetic activity. Several plant species being a major source of terpenoids, flavonoids, phenolics, coumarins, and other bioactive constituents have shown reduction in blood glucose levels.

Table 1 Summary of the effects elicited by plant foods and phenolic acid in the control of Diabetes Mellitus

Phenolic acids	**Plants/dietary source**	**Mechanism of action**	**Experiment model**
Gallic acid	*Cyamopsistetragonoloba, Terminalia bellerica Roxb, tea, mango, strawberries, rhubarb, and soy*	Improves β-cell regeneration, insulin secretion, and lipid profile and could be used as a drug to bring about insulin secretagogue and hypolipidemic effect Regeneration β-cells of the islets of Langerhan's, thereby stimulating the release of insulin and alleviating the oxidative stress through its antioxidant nature Upregulation of peroxisome proliferator-activated receptor (PPAR)γ expression and Akt activation	Streptozotocin (STZ) induced diabetic rats and Diet-induced obesity mice
Protocatechuic acid	*Oryza sativa L, onion, bran, and grain brown rice*	Protocatechuic acid normalizes hyperglycemia, reverses dyslipidemia generally associated with diabetes. It was also revealed that repressing chronic inflammation response is a possible mechanism contributing to the antidiabetic properties. In Gluconeogenic enzymes increased whereas the glycolytic enzyme glucokinase decreased in liver along with glycogen content Protocatechuic acid improves high-density lipoprotein C and low-density lipoprotein (LDL)-C levels in diabetic rats. It also increases glutathione peroxidase, superoxide dismutase, and catalase and decreases lipid peroxidation level in tissues of diabetic rats	STZ-induced Balb/cA mice and STZ-induced diabetic rats
Ellagic acid	*Myriophyllum spicatum/ blackberries, cranberries, pecans, pomegranates, raspberries, strawberries, walnuts, wolfberries, and grapes*	Stimulates the insulin signaling pathway in human adipocytes increasing GLUT4 translocation and glucose uptake Reducing oxidative stress and improving histopathology in brain Preventing lipid deposition and decreasing vascular smooth muscle cell proliferation Suppressing oxidative stress and inflammation Ellagic acid was most efficient in increasing sexual function in diabetic rats The reactions of immunohistochemistry for fibroblast growth	Human visceral adipocytes, STZ-induced diabetic rats High-carbohydrate, HFD-induced diabetic rats

		factor-2 and alkaline phosphatase presented stronger expression, predominantly in ellagic acid-treated diabetic rats Ellagic acid attenuation of inflammatory processes via inhibition of NF-κB pathway	
Syringic acid	*Alpinia calcarata Roscoe/Acai oil, wine, citrus fruits*	Syringic acid potential to secrete insulin from existing islet β-cells Syringic acid exhibited significantly lower HbA1c and fasting plasma insulin levels and also improved glucose homeostasis in liver Lower blood concentrations	Alloxan-induced diabetic rats
Salicylic acid	*Grapes, kiwi fruits, guavas, apricots, green pepper, olives, and mushrooms*	Inhibition of thromboxane A2 synthesis as measured with S-TxB2 concentrations and increased platelet reactivity	Diabetic Goto Kakizaki rats Type 2 diabetic patients
Ferulic acid	Grain bran, whole-grain foods, citrus fruits, banana, coffee, orange juice, eggplant, bamboo shoots, beetroot, cabbage, spinach, and broccoli	Decreased blood glucose levels and glucose-6-phosphatase and phosphoenol pyruvate carboxykinase activities and higher glycogen and insulin Reduced oxidative stress and inflammation pathway	HFD- induced mice and HFD /low dose STZ-induced T2D Rats
Rosmarinic acid	Rosemary, sage, lemon balm, and thyme	Activation of Nrf-2 and inhibition of NF-κB, mitogen-activated protein kinase expression	HFD/STZ-induced diabetic rats

4.1. Vanillic Acid

Vanillic acid is a common monohydroxybenzoic acid found in many plants and presents antioxidant, anti-inflammatory, anti-allergy, and anti-diabetes activities. Bai etal demonstrated that treating asthmatic rats with vanillic acid reduced the BALF's macrophages, lymphocytes, eosinophils, and neutrophils levels and reduced the IL-4, IL-5,IL-13, IgE, TNF-a, and increased IFN-Y levels in serum[19].It also reduced ROS and MDA and increased the superoxide dismutase (SOD),CAT, and GSH levels in the lung tissue. This study illustrated that vanillic acid improves allergic asthma by modulating inflammation and oxidative stress.

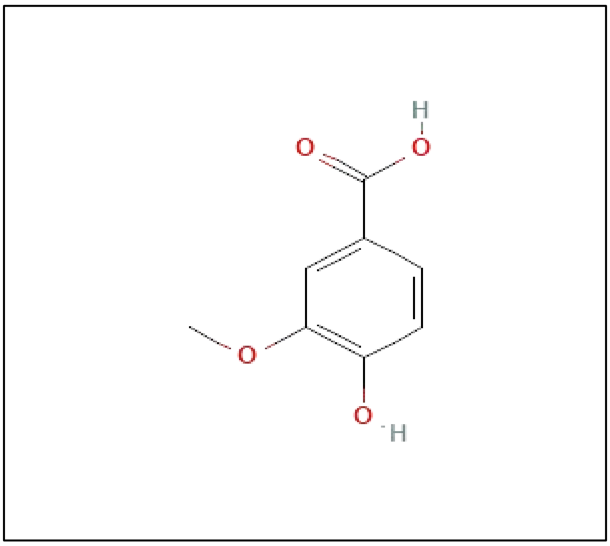

Figure 2 Structure of vaniliic acid

4.1.1. Background

Vanillic acid is a phenolic compound, found in various dietary sources and medicinal plants. Apart from its extraction from these biological sources, it is also synthesized chemically. It is used as flavouring_agent in various food products[20]. It possesses anticancer, antiobesity, antidiabetic antibacterial, anti-inflammatory, and antioxidant effects. Despite possessing good therapeutic potential and safety profile, it has not been well explored as nutraceutical or, therapeutic moiety [21].

4.2. Scope and Approach

Literature search was conducted to systematically review the various mechanistic pathways through which yanillic acid showed multiple therapeutic effects. Along with these pathways, other applications of vanillic acid and its derivatives are highlighted. Some of the patents that have been filed hitherto, for the production and uses of vanillic acid are also entailed in the manuscript.

5. Key Findings

Vanillic acid exerts diverse bioactivity against cancer, diabetes, obesity, neurodegenerative cardiovascular, and hepatic diseases by inhibition of the associated molecular pathways. Its derivatives also possess the therapeutic potential to treat autoimmune diseases as well as fungal and bacterial infections [22]. Owing to these benefits, vanillic acid has great potential to be used as a nutraceutical and provides scope for therapeutic uses beyond its traditional use as a flavouring agent. However, its oral bioavailability is limited due to its rapid elimination (metabolism) from the plasma this, in turn, impedes its successful delivery through conventional formulations. Hence, efforts are required to develop nanoformulations of vanillic acid to overcome the associated challenges [23].

Anti diabetic Activity of vanillic Acid

- Inhibition of α-Amylase and α-Glucosidase
  - These enzymes break down carbohydrates into glucose.
  - Vanillic acid inhibits their activity, reducing postprandial glucose spikes [24].
- Enhancement of Insulin Secretion
  - Studies on pancreatic β-cells indicate that vanillic acid may stimulate insulin release.
  - It also protects β-cells from oxidative stress [25].
- Antioxidant and Anti-inflammatory Properties
  - Diabetes is linked to oxidative stress and inflammation.
  - Vanillic acid scavenges free radicals and reduces inflammation, protecting pancreatic function [26].
- Inhibition of Protein Glycation
  - Glycation leads to the formation of advanced glycation end-products (AGEs), which worsen diabetic complications.
  - Vanillic acid reduces glycation, potentially preventing complications like neuropathy and nephropathy [27].
- Activation of AMPK Pathway
  - AMPK (AMP-activated protein kinase) improves glucose uptake and metabolism.
  - Vanillic acid may activate AMPK, enhancing glucose utilization [28].

6. Conclusion

This review covers phenolic compounds with anti-diabetic potential. These phenolic compounds may influence glucose metabolism by several mechanisms, such as inhibition of the carbohydrate digestion and glucose absorption in the intestine, stimulation of the insulin secretion from the pancreatic β-cells, modulation of glucose release and output from liver, and activation of insulin receptor and glucose uptake in insulin-sensitive tissues. Vanillic acid shows the positive effect in different in biological parameters like decrease in level of glucose Antioxidant enzymes, Oxidative stress and Treatment of Obesity.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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