

An Overview on Plant Derived Phenolic Compounds and Their Role in Treatment and Management of Diabetes

Himangshu Deka, Ananta Choudhury*, Biplab Kumar Dey

Faculty of Pharmaceutical Science, Assam Down Town University, Guwahati, Assam, India

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*Corresponding Author

Ananta Choudhury
Faculty of Pharmaceutical Science,
Assam Down Town University, Guwahati
781026, Assam, India
Tel: +91-977-001-9143
E-mail: anantachoudhury@gmail.com

Objectives: In recent decades, the trend for treating diabetes mellitus (DM) has shifted toward alternative medicines that are obtained from plant sources. Existing literature suggests that phenolic compounds derived from plants possess promising health-promoting properties. This study aimed to discuss the role of plant-derived phenolic compounds in the effective treatment and management of diabetes.

Methods: Information about plant secondary metabolites, phenolic compounds, and their role in the treatment and management of diabetes was collected from different databases, such as Pubmed, ScienceDirect, Scopus, and Google Scholar. Keywords like secondary metabolites, phenolic compounds, simple phenol, flavonoids, lignans, stilbenes, and diabetes were searched. Research and review articles with relevant information were included in the study.

Results: Anti-diabetic studies of the four major classes of phenolic compounds were included in this review. The plant-derived phenolic compounds were reported to have potent anti-diabetic activities. However, each class of phenolic compounds was found to behave differently according to various mechanisms.

Conclusion: The obtained results suggest that phenolic compounds derived from natural sources display promising anti-diabetic activities. Based on the available information, it can be concluded that phenolic compounds obtained from various natural sources play key roles in the treatment and management of diabetes.

Keywords: diabetes mellitus, secondary metabolites, phenolic acids, flavonoids, stilbenes

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic illness characterized by an increase in blood glucose, also known as hyperglycemia, and is currently an epidemic affecting millions of individuals worldwide. According to a 2017 report from the International Diabetes Federation, 451 million people worldwide have diabetes, and that number is expected to climb to 693 million by 2045 [1, 2]. Diabetes mellitus is classified mainly into 2 common classes: type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). T1DM is insulin-dependent diabetes that occurs due to damaged pancreatic beta cells, which results in insufficient insulin production in the body. T2DM is non-insulin dependent and is associated with insulin resistance by the liver and other peripheral tissues [3, 4]. The rising incidence

of diabetes around the world is a reason for concern, both in terms of morbidity and rising healthcare costs [5]. The literature states that the synthetic drugs that have been employed for the treatment and management of diabetes have many side effects. Some common side effects include hypoglycemia, gastrointestinal disturbance, and an increase in bad cholesterol. Some patients also report thrombocytopenia, lactic acidosis, leucopenia, macular edema, and liver failure [6]. Therefore, the DM epidemic creates a need for effective alternative treatments that can contribute to the management of chronic diseases like diabetes [7].

Most of the therapeutically active plant-derived phytoconstituents are reported as secondary metabolites, which are generated from the plant's primary metabolic pathways. Albrecht Kossel, Nobel Laureate in Physiology or Medicine in

1910, was the first to identify and define the idea of secondary metabolites. Secondary metabolites have been used by different communities as a principal component of traditional medicine against various diseases and ailments. These secondary metabolites protect the plants from various microbial attacks and have potent medicinal properties. Based on their chemical structures, secondary metabolites are categorized into several classes, such as phenolics, alkaloids, saponins, terpenes, lipids, and carbohydrates [8]. Among these compounds, the phenolic group attracts considerable interest as the most promising secondary metabolites for the treatment of several diseases, including diabetes. These phenolic compounds are mainly produced by plants through numerous metabolic pathways, such as the shikimate and acetate pathways [9]. Besides playing a major role in plant defense mechanisms, phenolic compounds have several functions, such as facilitated pollination and coloring for camouflage [10]. Plant-derived phenolic compounds have been the

subject of study for many decades, as these compounds are reported to have numerous health benefits. For example, quercetin has an anti-inflammatory action, naringenin has insecticidal effects, and silybin has been reported as an anti-hepatotoxic [11, 12]. Based on their structures, phenolic compounds are broadly classified as simple phenolics/phenolic acids, flavonoids, stilbenes, and lignans. Compounds that have only one phenolic ring are identified as simple phenols, whereas compounds with more than one phenolic ring are considered polyphenols. Considering the information above, the present study has been designed to give an overview of phenolic compounds and their roles in the treatment and management of diabetes mellitus.

MATERIALS AND METHODS

In this review, articles on the role of phenolic compounds in the treatment and management of diabetes were incorpo-

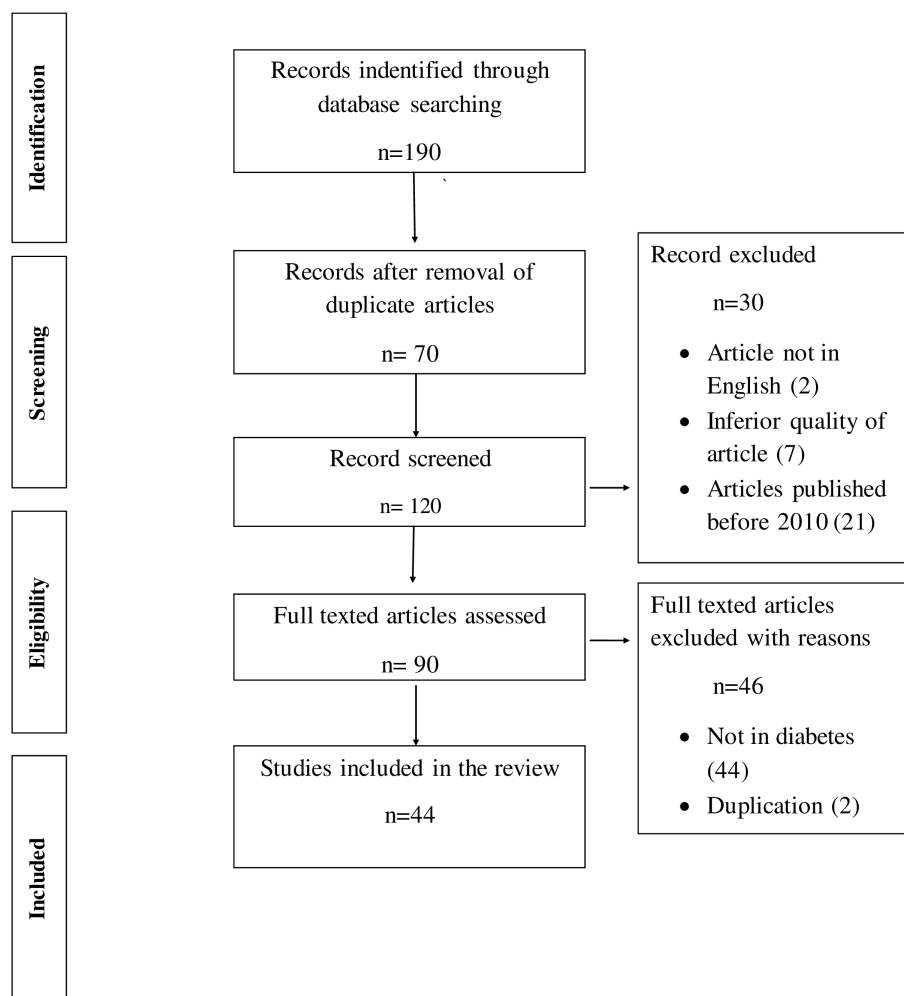


Figure 1. Flow chart of the study selection process.

rated. A literature search was conducted to identify the relevant articles associated with plant secondary metabolites, phenolic compounds, and the anti-diabetic activity of the phenolic compounds through several search engines, such as Pubmed, ScienceDirect, Scopus, and Google Scholar. The keywords used for the search were secondary metabolites, phenolic compounds, simple phenol, flavonoids, lignans, stilbenes, and diabetes. Most of the review articles related to phenolic compounds and their ability to act as diabetes treatments from 2010 onwards were included. All duplicate articles, abstracts, articles with poor correlation with the study's objective, and articles written in a language other than English were excluded. The overview of the method is presented in Fig. 1.

RESULTS

1. Phenolic acids

Phenolic acids (Pas) are aromatic carboxylic acids. They are one of the most common bioactive compounds that occur in various plants, and they possess a minimum of one carboxylic acid group in the phenol ring [13]. Phenolic acids are further subdivided into hydroxyl benzoic acid, which contains seven carbon atoms, and hydroxyl cinnamic acid, which contains nine carbon atoms. Some examples of phenolic acids are caffeic, ferulic, *p*-coumaric, and sinapic acids. Their roles in the management of diabetes are discussed below [14].

1) Chlorogenic acid (CGA)

CGA is a group of phenolic secondary metabolites generated by various plant species. It is one of the most ubiquitous phenolic acids typically seen in human diets. Coffee is one of the richest sources of CGA, though it is also found in various vegetables and fruits [15]. CGAs obtained from various plant sources were reported to have favorable anti-diabetic effects. Many researchers have discussed the possible mechanism for its anti-diabetic activity. A recent investigation conducted by Ong et al. [16] on Leprdb/db mice explored the pathways through which CGA exerts anti-diabetic effects. Their study suggested that CGA stimulated glucose uptake by the skeletal muscle cells through the activation of the 5' adenosine monophosphate-activated protein kinase (AMPK) pathway. The authors also found that 2 weeks of treatment with CGA showed inhibitory effects on glucose production in hepatic cells, which resulted in reduced plasma blood glucose levels, improved insulin sensi-

tivity, and glucose tolerance [16]. In the oral glucose tolerance test, CGA was found to help reduce the plasma glucose peak. Similarly, CGA also produce inhibitory effects on α -amylase and α -glucosidase in a dose-dependent manner [17-19]. These studies show the potential use of CGA as a preferred compound for lowering the risk of T2DM.

2) Ellagic acid (EA)

EA is a polyphenolic compound mostly found in fruits and nuts. Several *in-vitro* and *in vivo* studies established that the administration of EA can induce significant anti-diabetic effects. Amin and Arbid [20] demonstrated that a combination treatment with repaglinide (0.5 mg/kg) and EA (10 mg/kg) for 2 weeks improved insulin signaling, lipid profiles, and glucose balance in insulin-resistant type 2 diabetic albino rats. In another study, EA treatment in female rats for 28 days at a dose of 50 mg/kg/day reduced blood glucose levels and further activated the insulin signaling pathways in the liver, which was indicated by the increased phosphorylated Akt levels [21]. EA was also found to improve insulin release from glucose-induced isolated mouse islet cells. Based on the oral glucose tolerance test performed by Fatima et al. [22] on type 2 diabetic rats treated with EA, it was found that a dose of 25 mg/kg showed no significant changes; however, doses of 50 mg/kg and 100 mg/kg improved glucose tolerance.

3) Caffeic acid (CA)

CA is a dietary hydroxycinnamic acid that is derived mostly from the secondary metabolism of plants, such as olives, coffee beans, fruits, potatoes, carrots, and propolis. Like the other phenolic acids, CA participates in defending plants against herbivores, pests, and microbial growth, and protects the leaves from UV radiation [23]. CA is also reported to have numerous pharmacological effects, including anti-diabetic activity. CA (12.5 μ M) was found to improve glucose metabolism by inhibiting gluconeogenesis and enhancing glycogenesis in tumor necrosis factor α (TNF α)- treated insulin-resistant mouse hepatocytes [24]. In another study, the administration of CA (50 mg/kg) in alloxan-induced type 1 diabetic mice also caused a reduction in fasting blood glucose levels [25].

4) Gallic acid (GA)

Gallic acid (GA) is another common phenolic acid that is found in various fruits and medicinal plants. It contains a number of health-promoting properties and shows promis-

Table 1. Some example of phenolic compounds and their anti-diabetic mechanism

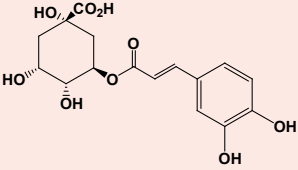
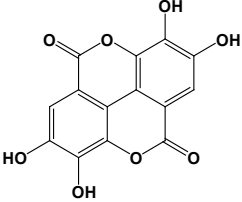
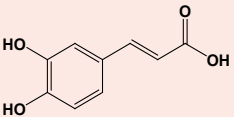
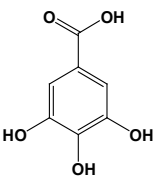
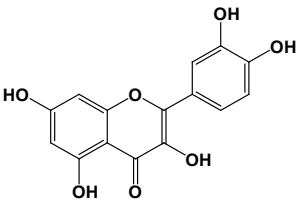
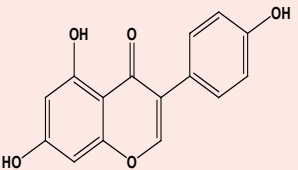
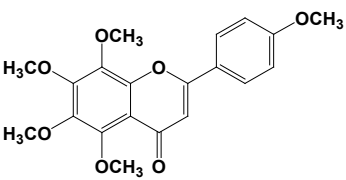
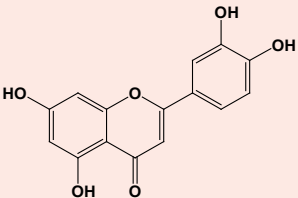
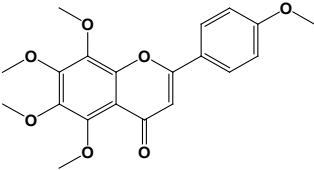
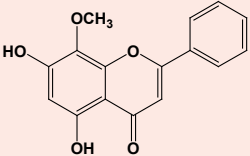
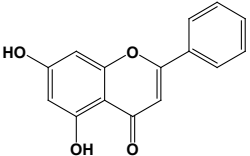
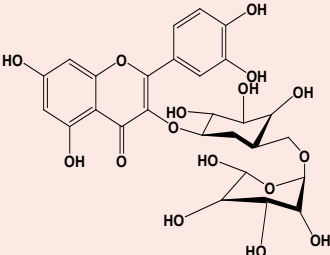
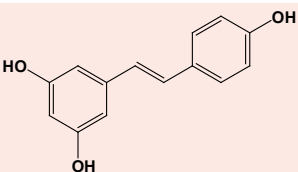
Class of phenolics	Sources	Structure	Mechanism	References
Phenolic acids				
Chlorogenic acid	Coffee, tea		Activate AMPK, Inhibit α -glucosidase, \uparrow Glucose uptake	[16]
Ellagic acid	Pomegranates, grapes		\uparrow Insulin signaling \uparrow Glucose transporter	[20]
Caffeic acid	Coffee, tea		\uparrow Glucokinase activity, \downarrow Glucose-6-phosphatase	[40]
Gallic acid	Pomegranates, oak bark		\uparrow Glucose absorption \uparrow Phosphatidylinositol-3 kinase, Akt/protein kinase B	[27]
Flavonoids				
Quercetin	Fennel, tea		\uparrow Glycogen synthase	[41]
Genistein	Soy food		\uparrow cAMP signalling \uparrow PKA activation	[31, 32]
Kaempferol	Spinach, dill		\downarrow Apoptosis, \downarrow caspase-3	[33]
Luteolin	Celery, boccoli		\uparrow NF- κ B pathway	[34]

Table 1. Continued

Class of phenolics	Sources	Structure	Mechanism	References
Tangeretin	Peel		Activate AMPK pathway	[35]
Wogonin	<i>Scutellaria radix</i>		Anti-adipogenic effect	[36]
Chrysin	Propolis, honey		↑PPAR α & MAPK pathways ↓TNF- α	[37]
Rutin	Grapes, lemons		Inhibit α -glucosidase & α -amylase ↑Hexokinase activity ↓Decrease G6Pase, PEPCK, glycogen phosphorylase	[38]
Stilbens				
Resveratrol	Grapes, berries		Activation of AMPK, SIRT1, inhibition of (PTP) 1B	[39]

↑ indicating increase or improvement, ↓ indicating decrease or reduction.

ing effectiveness against gastrointestinal, cognitive, metabolic, and cardiovascular diseases [26]. GA was studied for its hypoglycemic effects on glucose absorption in an insulin-resistant cell culture model, which improved the glucose absorption capacity by 19.2% at a concentration of 6.25 g/mL in insulin-resistant FL83B mouse hepatocytes. In diabetic rats fed a high fructose diet, GA treatment for 4 weeks at a dose of 10-30 mg/kg increased the expression of hepatic insulin signaling proteins like phosphatidylinositol-3 kinase, Akt/protein kinase B, insulin receptor substrate 1, and glucose transporter 2 [27]. The complementary effects of GA has been studied by Oboh et al. [28], who observed that the combined administration of GA at a dose of 50 mg/kg with metformin and acarbose significantly elevated the α -amylase and α -glucosidase inhibitory activity of

the two drugs in streptozotocin-induced diabetic rats.

2. Flavonoids

Flavonoids are the most prevalent and well-studied class of polyphenols. Flavonoids are available in 4,000 different varieties and are mostly found in medicinal plants, fruits, vegetables, nuts, seeds, stems, flowers, and tea [29]. Flavonoids have two phenolic rings (A and B rings) joined together by three carbon atoms to produce a pyran ring (the heterocyclic C ring containing oxygen) with a C6-C3-C6 skeletal structure. Flavonoids are separated into six subclasses based on the degree of oxidation of the core heterocycle. These subclasses include flavanones, isoflavones, flavonols, flavones, flavan-3-ols, and anthocyanidins

[30]. Flavonoids, such as quercetin, naringin, hesperidin, epigallocatechin gallate, baptigenin, myricetin, and anthocyanins, possess powerful anti-diabetic activities. The reported mechanisms are shown in Table 1 [16, 20, 27, 31-41].

1) Quercetin

Quercetin dihydrate (C₁₅H₁₀O₇) is a flavonoid found primarily in fennel, tea leaves, almonds, and lovage [42]. In the literature, various mechanisms have been reported that are responsible for the anti-diabetic activity of quercetin. In one of the studies, quercetin (25-50 M) extracted from berries had a similar anti-diabetic activity to the synthetic drug by inducing an insulin-independent AMPK pathway that slowed adenosine diphosphate oxygen consumption by stimulating glucose transporter type 4 (GLUT 4) translocation and expression in isolated mitochondria [42]. Other studies suggest that quercetin and its derivatives stimulate glucose uptake in muscle cells by activating AMPK. Quercetin inhibits glucokinase activity in streptozotocin-induced diabetic rats and decreases hyperglycemia by stimulating GLUT 4, hepatic gluconeogenesis, and glycogenolysis. In addition, it increases glucose uptake in the liver [43].

2) Rutin

Rutin, also known as quercetin-3-O-rutinoside, sophorin, and glycosylated quercetin, is found in high amounts in fruits, such as grapes, lemons, and buckwheat. Rutin's ability to inhibit glucose absorption from the small intestine is responsible for its anti-diabetic properties. Rutin exerts its anti-diabetic activity through improved glucose uptake by tissues due to the suppression of tissue gluconeogenesis, activation of insulin production from beta-cells, and protection of the islets of Langerhans from degenerative alterations. Rutin also inhibits the production of reactive oxygen species, precursors of advanced glycation end products, sorbitol, and pro-inflammatory cytokines [44]. Notable decreases in glycated hemoglobin (HbA1c) and fasting blood glucose were seen in streptozotocin (STZ)-induced rats after oral or intraperitoneal administration of rutin at a dose of 50 or 100 mg/kg. Rutin also induces significant increases in insulin levels and carbohydrate metabolic enzyme activity [45].

3) Kaempferol

Kaempferol, also called 3,4,5,7-tetrahydroxyflavone, is a non-toxic flavonol which is mostly found in various medicinal herbs, edible fruits, and vegetables, such as onions, broccoli, tea, and spinach. Kaempferol is reported to have several health benefits,

which include neuroprotective, antihypertensive, antimicrobial, antioxidant, anti-inflammatory, and anti-carcinogenic effects [46]. Many studies have been performed to evaluate the anti-diabetic activity of Kaempferol. In one report, STZ-induced diabetic mice treated with Kaempferol for 12 weeks showed a significant reduction in blood glucose levels in both the fasting and non-fasting groups [47]. Another study reported that in high-fat, insulin-resistant rats, oral administration of kaempferol (50 mg/kg) substantially reduced fasting blood glucose levels and improve impaired glucose tolerance and insulin sensitivity. Improved pyruvate tolerance and lower hepatic glucose production were linked to these positive outcomes. As a result, kaempferol administration enhanced Akt and hexokinase activity while decreasing pyruvate carboxylase activity in the livers of obese mice. In obese mice, kaempferol also enhanced systemic insulin sensitivity without affecting weight gain or food intake [48].

4) Genistein

One of the major soy isoflavones, genistein (4', 5, 7-trihydroxyisoflavone), has intrigued researchers in recent decades after several epidemiological studies suggested that eating a soy-rich diet may be an important factor contributing to the lower incidence of breast and prostate cancer in Asian countries [49]. It is the most abundant isoflavone, followed by daidzein, which differs from genistein only by having a hydroxyl group at C5. Some recent evidence indicates the potential for using genistein as a preventative and therapeutic treatment for patients with diabetes. Gilbert and Liu [50] studied the anti-diabetic benefit of genistein on alloxan-induced Sprague-Dawley rats aged 7-8 weeks. The rats were orally gavaged with 8, 18, or 30 mg/kg body weight (BW) of genistein daily for 4 weeks. The authors reported that a 30 mg dose of genistein was the most successful in mitigating alloxan's effects, with lower fasting blood glucose, higher serum insulin, and increased islet mass after 4 weeks. Dietary genistein intake lowered hyperglycemia and improved glucose tolerance, blood insulin levels, and islet cell proliferation, survival, and mass in STZ-induced diabetic mice. These findings suggest that genistein may have a natural anti-diabetic moiety that works by activating the cyclic adenosine 3', 5'-monophosphate (cAMP)/protein kinase (PKA)-dependent extracellular signal-regulated kinases 1 and 2 (ERK1/2) signaling pathway [33].

5) Chrysin

Chrysin (5,7-dihydroxyflavone) is a flavonoid found mainly

in the aerial parts of *Oroxylum*, chamomile, and members of the *Passiflora* genus, as well as in propolis and honey. Chrysin possesses promising anti-diabetic, anti-inflammatory, and antioxidant qualities, and its aromatase suppressive action makes it a popular dietary supplement for bodybuilders [51]. A recent study showed that chrysin exhibits anti-hyperglycemic activity similar to insulin, which has been linked to improved glucose metabolism and glucose uptake after intestinal glucose absorption. It is also reported to act on insulin sensitization caused by chrysin-induced peroxisome proliferator activated receptor (PPAR) activation and 11 β -hydroxysteroid dehydrogenase type 1 (11-HSD1) inhibition [52]. Phytosomes containing chrysin (100 mg/kg) improved glucose uptake in the muscle, as evidenced by the increased expression of hexokinase 2, GLUT 4, and PPAR ($p = 0.05$) [53].

3. Stilbenes

Stilbenes have a 1,2-diphenylethylene nucleus and consist of two phenolic rings connected by a two-carbon methylene bridge. Stilbene production is initiated by the enzyme stilbene synthase, which is found in small amounts in plants [54]. Resveratrol (RSV) is a non-flavonoid polyphenolic compound belonging to the stilbenoid class. It is the most important stilbene due to its well-known bioactivity. It is usually found at different

concentrations in grapes, berries, soy, and dark chocolate. RSV has been reported to improve the status of diabetes mellitus through a diverse mechanism, which includes a reduction in blood glucose concentration by increasing glucose uptake and proper utilization. It also increases insulin sensitivity and the restoration of abnormal insulin signaling pathways by silencing the transcription of certain genes or inactivating certain proteins. High plasma glucose levels have the potential to damage pancreatic cells, resulting in a considerable decrease in insulin output. RSV has been demonstrated to stimulate an increase in the pancreatic cell population and insulin secretion as a strategy for reducing hyperglycemia. Oyenihni et al. [39] explained the hypoglycemic activity of RSV through various mechanisms, such as the activation of sirtuin 1 (SIRT1) in the muscle and the inhibition of protein tyrosine phosphatase (PTP) 1B expression in the liver.

4. Lignans

Lignans are a type of secondary metabolite formed when two or more phenylpropanoid units are oxidatively dimerized. They have a wide structural variety despite their similar biosynthetic molecules. This class of phytochemicals has also been shown to have a wide range of biological functions. Various vegetables, fruits, legumes, whole grain cereals, and oilseeds contain dietary

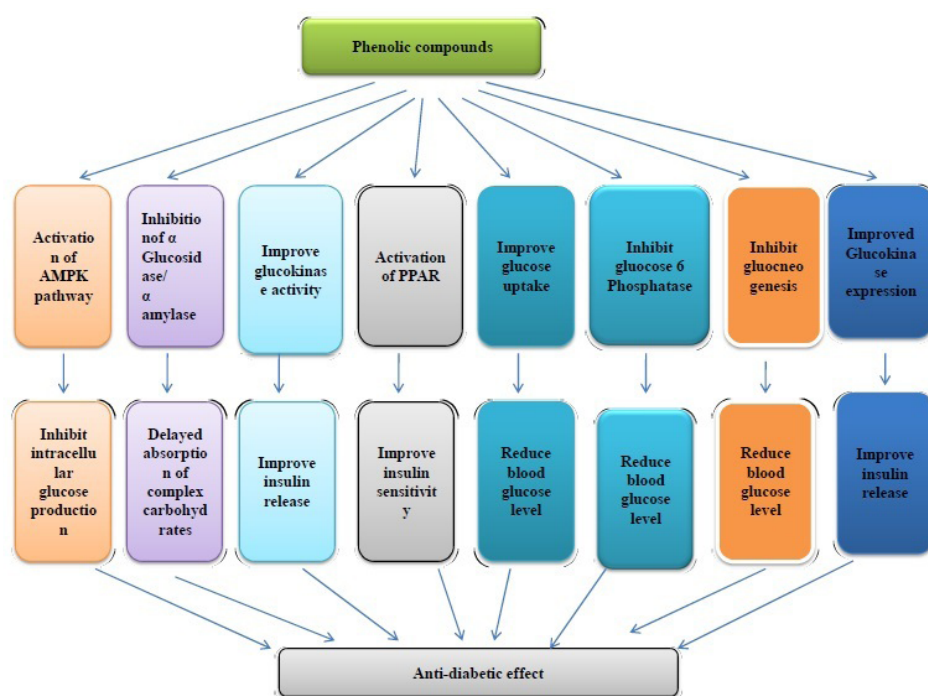


Figure 2. Anti-diabetic mechanisms of phenolic compounds.

lignans. Sesame and flax seeds are the richest sources of lignans among edible plant components [55]. In STZ-induced diabetic rats, the anti-diabetic effects of lignans and polyphenols found in flaxseed extract were explored. Flaxseed supplementation resulted in positive improvements in body weight, food and water consumption, glycosylated hemoglobin, and blood glucose levels in diabetic rats. Furthermore, considerably good findings were observed with biochemical markers, such as lower plasma cholesterol, LDL cholesterol, triglycerides, plasma creatinine, urea, and uric acid levels, highlighting the traditional use of this seed in medicine [56].

DISCUSSION

High levels of antioxidant compounds and a diet abundant in fruits and vegetables could potentially reduce the risk of diabetes and the associated increased risk of microvascular and macrovascular complications. Studies have suggested that phenolic phytochemicals obtained from various sources, including plants, vegetables, and fruits, show potential therapeutic benefits for the treatment and management of diabetes mellitus. Many researchers have reported that plant-derived phenolic phytochemicals are capable of exerting antioxidant activities that potentially reduce the risk of different types of diabetes and the associated microvascular and macrovascular complications [11]. The bioactive phenolic phytochemicals have the ability to modulate metabolic and signaling pathways at various cellular levels, including gene expressions, epigenetic regulation, protein expressions, and enzyme activities. Furthermore, phenolic acids have proven their ability to reduce glucose levels and exert other effective anti-diabetic activities. According to the literature, phenolics may protect against hyperglycemia-induced chronic illnesses by providing antioxidant protection and inhibiting starch digestion. Flavonoids have shown potential glucose lowering activities in several clinical studies [54]. Further, stilbenes and lignans have been reported to significantly improve glycemic control in type 2 diabetic patients through diverse mechanisms. The various mechanisms of phenolic compounds against diabetes are summarized in Fig. 2. Well-controlled long-term clinical studies will help to determine the efficacy, optimal dose, and safety of these bioactive phenolic compounds in the presence of other dietary components and medicines.

CONCLUSION

Phytochemicals obtained from various plant sources are considered proven and time-tested sources of medicine. In this present work, an effort has been made to summarize the role of polyphenolic compounds in the management of diabetes based on various experimental studies performed during the recent decade. Based on the available information, it may be concluded that phenolic compounds obtained from various natural sources showed promising anti-diabetic activities. The plant-derived phenolic compounds produce anti-diabetic effects through various mechanisms, such as AMPK pathway activation, α glucosidase/ α amylase inhibition, glucose uptake and insulin sensitivity improvement, and PPAR activation. Furthermore, these compounds can be utilized as alternative medicines in the treatment and management of other associated diseases. However, more studies are required to confirm the potential benefits of these compounds in humans.

CONFLICT OF INTEREST

There were no conflicts among the interests of the participating authors.

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ORCID

Himangshu Deka, <https://orcid.org/0000-0003-2344-7019>

Ananta Choudhury, <https://orcid.org/0000-0002-6894-1670>

Biplab Kumar Dey, <https://orcid.org/0000-0002-9672-3478>

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