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REVIEW

Bioactive Compounds in Blueberry Fruit and Their Antidiabetic Activity

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Abstract

Purpose of Review This review aims to explore the anti-diabetic properties of blueberries, focusing on their bioactive components and the mechanisms underlying their effects. Specifically, it examines how blueberries, through their rich content of polyphenols like anthocyanins, phenolic acids and vitamins, contribute to the amelioration of diabetes mellitus.

Recent Findings Recent research has highlighted the significant role of blueberries in improving glucose metabolism, reducing oxidative stress and inflammation and protecting against diabetes-associated complications such as retinopathy. Various studies have elucidated the impact of blueberry bioactive compounds on various metabolic and signalling pathways involved in diabetes progression.

Summary Blueberries, known for their abundance of bioactive compounds, particularly anthocyanins, offer promising anti-diabetic effects. This review provides a comprehensive analysis of recent findings, emphasizing the therapeutic potential of blueberries in diabetes management.

Keywords Blueberry · Diabetes mellitus · Polyphenol composition · Mechanism

Introduction

Diabetes mellitus (DM) is a persistent metabolic dysfunction marked by elevated blood glucose levels and frequently associated with comorbidities like hypertension, cardiovascular ailments and obesity, thereby posing an escalating worldwide health challenge. The ailment comprises diverse clinical classifications: Type 1 diabetes (T1DM) is typified by insulin deficiency resulting from auto-immune mediated pancreatic β-cell damage, whereas Type 2 diabetes (T2DM) stems from metabolic dysfunction leading to diminished insulin secretion from β-cells along with cellular resistance to insulin, causing a decline in cellular glucose absorption [1]. T2DM is more prevalent than T1D and accounts for over 90% of all DM cases [2]. The cases of DM and its associated complications have notably risen in recent decades, partly attributed to lifestyle changes. At present, diabetes has no known cure, but its impacts can be mitigated through medication and dietary adjustments.

Apart from conventional insulin therapy and medications, dietary factors also exert a notable influence on the pathophysiology and early management of diabetes.

Oxidative stress, plays a crucial role in the onset of DM, affecting both insulin secretion and sensitivity. Fruits, abundant in dietary antioxidants like polyphenols, alkaloids and bioactive polysaccharides, offer beneficial effects on glucose regulation. An inverse relationship is found between the progression of diabetes and intake of antioxidants rich fruits [3, 4].

Bioactive compounds like phenols, flavonoids and carotenoids found in fruits are gaining more interest due to their potential health advantages. Consuming fruit-rich diets may

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contribute to slowing down aging processes and lowering the risks associated with various cancers, cardiovascular diseases, diabetes and other chronic conditions. These bioactive components, beyond meeting basic nutritional requirements, have the potential to positively impact the health of both humans and animals. Among various fruits, blueberry (*Vaccinium* spp.), known as a "super fruit," is rich in a plethora of bioactive compounds beneficial to human health, such as phenolic acids, flavonoids (including flavonols and anthocyanins), and proanthocyanidins [5]. Anthocyanin flavonoids, constituting up to 60% of total polyphenolics in ripe blueberries, are believed to contribute significantly to their health advantages as they provide protection against oxidative stress and various chronic diseases such as cardiovascular disorders, neurodegenerative diseases, and certain cancers [6, 7]. These compounds, including malvidins and delphinidins, are associated with improving insulin sensitivity [2, 8]. *Vaccinium corymbosum*, *Vaccinium poasanum*, *Vaccinium ahei*, *Vaccinium myrtillus* and *Vaccinium angustifolium*, are some common species of blueberry. Between 2010 and 2019, global blueberry production surged from 439,000 metric tons to nearly 1.0 million metric tons, more than doubling in that period. The leading fresh blueberry producers and exporters include Peru, Chile, Mexico, the United States, South Africa, Poland, and Canada [9].

Various studies have reported the antidiabetic activity of blueberry fruit, juice, extracts and also isolated bioactive compounds. Blueberries confer protective effects in diabetic individuals through several mechanisms, including the suppression of pro-inflammatory cytokines in peripheral blood, reinforcement of the antioxidant defense system, upregulation of genes encoding glucose transporters to enhance cellular glucose uptake, and other pathways [10, 11]. Furthermore, anti-oxidant and anti-inflammatory activities of blueberries also provide various health beneficial effects particularly in metabolic conditions such as T2DM [12, 13].

Numerous reviews have detailed the antidiabetic properties of blueberries. This short review encompasses the latest research studies on the antidiabetic activity of blueberries, offering updated insights on the anti-diabetic mechanism and comprehensive analysis not previously covered in earlier reviews.

Bioactive Compounds in Blueberries

Blueberries are a rich source of bioactive compounds as depicted in Fig. 1. Blueberries mainly consist of 9.7% carbohydrates, 0.4% fat, 0.6% proteins, 84% water and approximately 192 KJ of energy has been estimated in 100 g serving of fresh fruit. They also provide 3-3.5% of dietary fiber. Phytochemicals present in fruits are the key complexes that have multitude role in nutrition and health. They are known to exhibit several biological activities which may provide a suitable platform for the betterment of human health endowed with lesser toxicity. The polyphenol content in blueberries ranges from 48 to 304 milligrams per 100 g of fresh fruit weight. Approximately 60% of the total polyphenolic content in ripe blueberries consists of anthocyanin flavonoids, which include delphinidin, malvidin, cyanidin, peonidin and petunidin [14]. Average anthocyanins, total phenolic and flavonoid content were 81.88 mg cyanidin-3-*O*-glucoside, 165.48 mg catechin equivalent and 709.92 mg gallic acid equivalent in 100 g of fresh fruit from seventeen hybrids of 'Simultan' and 'Duke' cultivars of *Vaccinium corymbosum* blueberry cv [15]. Different genotypes of highbush blueberries show variations in total phenolic and anthocyanin content, ranging from 1.41 to 2.24 mg of gallic acid equivalent per gram of frozen berries and 0.789 to 2.375 mg per gram of berries (frozen weight), respectively [16]. Besides anthocyanins, blueberries contain other beneficial compounds like flavonols, flavanols, and phenolic acids. Quercetin, kaempferol and myricetin are the common flavonols in blueberries [17]. Phenolic and flavonols content in blueberries varies depending on the variety and other conditions such as geographical

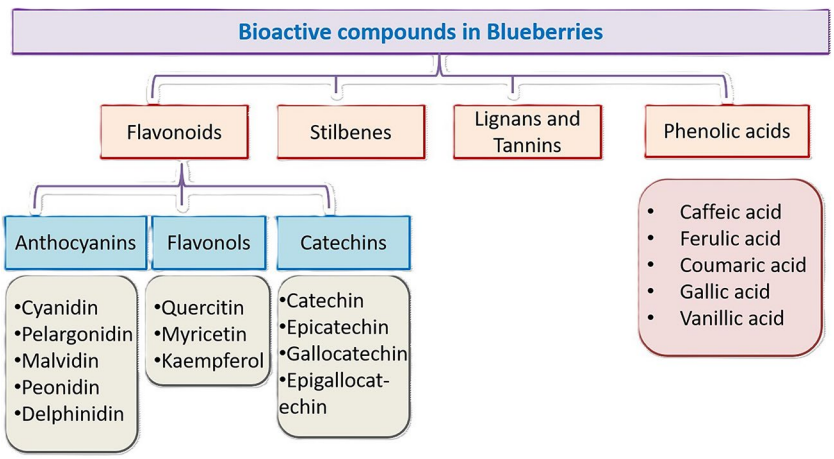

Fig. 1 Major bioactive compounds in blueberry fruit

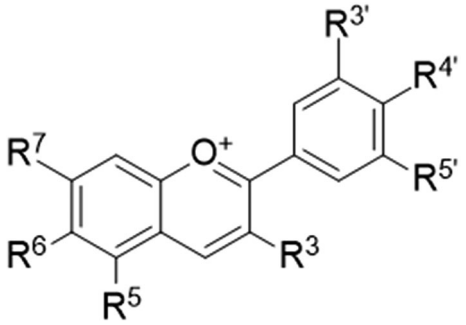

Fig. 2 Basic structure of Anthocyanidins

origin and environmental factors. The composition of bioactive components of different types of berries is comprehensively reviewed by Golovinskaia and Wang [18]. Phenolic content in 100 gram of fresh blueberry fruit ranged from 261.9 to 585.3, 181.1–390.5, 154.7–398.0, 314.0–382.0 and 212.7–460.4 mg in different studies. Furthermore, flavonols in 100 gram of fresh blueberry fruit ranged from 15 to 17, 17.2–32.7, 17–19 and 19.4–23.8 mg [18].

Flavonoids

Blueberries are considered as potential source of flavonoids. Among various flavonoids, anthocyanins are the most abundant flavonoid found in blueberries. These water-soluble pigments are the driving force behind the vivid purple, red and blue colors seen in several vegetables and fruits. They constitute a significant portion of total phenolic compounds and represent the primary subclass of flavonoids [6]. Anthocyanins, which are glucosides of anthocyanidins, are flavonoid derivatives synthesized through the phenylpropanoid pathway. Depending on the variety and geographical origin, anthocyanin content in 100 gram of fresh blueberry fruit ranges from 93.1 to 235.4, 94.5–301.0, 143.5–822.7, 308.9–464.3 and 35.5–129.9 mg [18]. However, not all of the anthocyanin content is bioavailable. While anthocyanins are absorbed in the stomach and small intestine, a significant portion is metabolized and excreted before it can exert its effects. These compounds are absorbed primarily in the stomach and small intestine, with some entering the bloodstream directly from the stomach, causing a rapid but temporary increase in serum levels. Once absorbed, anthocyanins undergo extensive metabolism in the liver and intestines, transforming into various metabolites that also contribute to their biological effects. Despite their potential benefits, the bioavailability of anthocyanins is generally low due to factors such as poor stability in the digestive tract, rapid metabolism, and excretion. Factors like the food matrix, anthocyanin structure, and gut microbiota can influence their absorption and efficacy. Despite these challenges, the bioactive metabolites of anthocyanins can still provide

Table 1 Functional groups variation in different anthocyanidins at R3' and R5'

Anthocyanidin	R3'	R5'
Malvidin	OCH3	OCH3
Peonidin	OCH3	H
Petunidin	OCH3	OH
Pelargonidin	H	H
Delphinidin	OH	OH
Cyanidin	OH	H

notable health benefits [18]. The basic structure of anthocyanidins is shown in Fig. 2. They are distributed across various plant tissues, such as stems, leaves, roots, fruits and flowers. There are six major anthocyanidins (delphinidin, cyanidin, peonidin, pelargonidin, malvidin and petunidin) that exist in both aglycone and glycoside forms as depicted in Table 1. Various research findings suggest that delphinidin and malvidin are the primary compounds found in blueberries and could account for approximately 75% of the total anthocyanin content. The percentage of malvidin, cyanidin, delphinidin, petunidin and peonidin varies from 22 to 33%, 6–14%, 27–40%, 19–26% and 1–5% respectively [19]. Flavonoids exhibit potential applications in production of food color and nutraceutical components [20].

Recent studies suggest that the anthocyanins present in blueberries contribute to lowering the risk of several chronic diseases such as CVD, diabetes, neurological disorders and many more [6]. An investigation by a group of researchers has revealed flavonoid's antidiabetic effect with improved carbohydrate metabolism, insulin regulation, glucose absorption and fatty acid deposition [21, 22]. A study performed on 200,000 people living in US, lead to the conclusion that higher intake of blueberries slows down diabetes progression indicating close association between flavonoids intake and T2D [23]. Dietary polyphenols mainly anthocyanins (cyanidin-3-glucoside) exhibit remarkable antioxidant potential and impart protection against diabetes. Cyanidin-3-glucoside treated diabetic rats demonstrated lower blood glucose, cholesterol and triglyceride levels [24].

Quercetin, one of the predominant flavonol constitutes 24 mg/kg of fresh fruit of blueberry. A group of researchers reported chloronapthoquinone (O-substituted derivatives) and monochloropivaloyl quercetin as promising therapeutics in treatment of diabetes. Quercetin exhibits potential as a pharmacological agent for diabetes treatment by enhancing insulin sensitivity, promoting glycogen synthesis and mitigating cellular oxidative damage. In vivo investigations have demonstrated that quercetin alleviates oxidative damage and enhances β-cell function, thereby facilitating sufficient insulin secretion [25].

Blueberries also contain significant amount of myricetin. HPLC analysis of extracts from eight blueberry species including highbush, half highbush and bilberry revealed the

presence of two flavonols i.e., myricetin and quercetin. The amount of quercetin estimated in frozen fruit was 163.6 µg/g (Bilberry), 102.56 µg/g (half-highbush blueberry) and 86.4 µg/g (highbush blueberry). Likewise, myricetin was 200, 19.8 and 12.9 µg/g in Bilberry, half-highbush and highbush blueberry frozen fruits [26].

Non-flavonoids/Phenolic Acid

Phenolic acids are carboxylic group containing phenol and have two main classes known as hydroxybenzoic acid and hydroxycinnamic acid. In blueberries, the amount of these phenolics varies to a large extent for instance 1.5 mg/kg FW of hydroxybenzoic acid and 135 mg/kg FW of hydroxycinnamic acid has been reported [27]. Maximum phenolic acids are known to exist in conjugation with esters, glycosides, amides and very less in free forms. Several studies have reported the presence of vanillic acid, chlorogenic acid, ferulic acid, caffeic acid, gallic acid and p-coumaric acid and it is worth mentioning that chlorogenic acid was found in high abundance in blueberry [28, 29]. Researchers have represented a highly variable range of chlorogenic acid (34.3 to 113.8 mg/100 g FW) in between highbush and lowbush blueberry varieties that might be responsible for anti-inflammatory activity [30].

Moreover, blueberries are also reported with two forms of tannins i.e., hydrolysable (gallotannins, ellagitannins) & condensed (proanthocyanidins) and stilbenoids. Tannins play a therapeutic role in diabetes, either by slowing down glucose absorption or by regulating the β-cells in the pancreas. This may help prevent the onset of insulin-dependent Type 2 Diabetes [31]. Blueberry extract has also reported presence of procyanidin B1(300 mg/100 g), predominant condensed tannin as compared with other berry fruits like blackberries, raspberries that mainly contain ellagitannin [32].

Carotenoid

These are tetraterpene natural pigments responsible for yellow, orange and red colors. During the ripening process, a fall in carotenoid content has been noticed and minute amounts are present in peel of blueberry. However researchers found that unlike other berry fruits, the overall content of carotenoid is still up to considerable amount in blueberry [32, 33].

Vitamins

Blueberries are rich in ascorbic acid, a pivotal water-soluble vitamin crucial for immunity boosting, also play a protective role in inflammation. A previous study reported that blueberries contain 10 mg of ascorbic acid per 100 g, amounting to one-third of the daily recommended dietary intake. However, this amount may vary in different species for instance 5 to 15 mg/100 g and 16.4 mg/100 g of quercetin has been detected in highbush and lowbush blueberry respectively [34]. ‘Simultan’ and ‘Duke’ cultivars of *Vaccinium corymbosum* blueberry cv. showed an average 14.35 mg ascorbic acid per 100 g of fresh fruit [15].

Mechanisms of Antidiabetic Activity of Blueberries

Blueberries are abundant sources of several bioactive phytochemicals especially the polyphenolic compounds such as anthocyanins. These compounds produce anti-diabetic effect via various mechanisms including amelioration of oxidative stress, regulation of signalling pathways, inhibition of enzymes, amelioration of insulin resistance and many more. Some of the mechanisms are described in the following sub-sections.

Amelioration of Oxidative Stress in Diabetes

Free radical mediated disruption of redox balance of the body have been implicated in the onset and development of various metabolic diseases including chronic inflammation, some types of cancers, cardiovascular disease, diabetes mellitus, neurodegenerative diseases among others [35, 36].

During various metabolic processes, exposure to radiation, chemicals, and smoking, the body produces free radicals, which are chemical species possessing one or more unpaired electrons, including reactive oxygen species (ROS) such as singlet oxygen ($^1O_2$), peroxyl radical ($RO_2\cdot$), superoxide anion ($O_2\cdot$), and reactive nitrogen species (RNS) such as nitrate (NO_3^-), nitric oxide ($NO\cdot$) [37, 38]. Cells utilize various endogenous and or extrinsic antioxidants (compounds that can neutralize or slow down generation of free radicals) to defend the adverse effects of free radicals [39, 40]. Failure of the antioxidant systems create pro-oxidative conditions, called as oxidative stress [36].

Numerous studies highlight the crucial involvement of oxidative stress in diabetes mellitus, not only in its initiation but also in its progression and the subsequent complications [41, 42]. More importantly, chronic hyperglycemia, the most obvious characteristic of diabetes, is associated with enhanced production of ROS, aggravating oxidative stress and the associated vascular, retinal and renal consequences [42]. ROS generation under hyperglycemic conditions can be of mitochondrial and non-mitochondrial origins. Hyperglycemia results in abundance of electron donors through metabolic pathways like Kreb’s cycle, consequently

increasing the inner mitochondrial membrane potential that is associated with mitochondrial dysfunction and increased ROS production. Moreover, the excessive generation of superoxide *via* the mitochondrial electron transport chain triggers additional biochemical pathways, such as the formation of advanced glycation end products and their precursors, the polyol pathway, the flux of the hexosamine pathway and the activation of protein kinase C and nuclear factor κβ [36, 43]. Further, mitochondrial ROS are suggested to cause insulin resistance, by regulating the mitogen-activated protein kinases MAPKs including JNK and p38, and oxidation of thioredoxin (TRX) and JNK inhibitor glutathione S-transferase [44]. Non-mitochondrial generation of ROS occur through xanthine oxidase, NAD(P)H oxidase, cyclooxygenase, lipoxygenase etc. [45].

Dietary antioxidants are reported to improve diabetic status by regulating oxidative stress markers and thus contributing to improved glucose metabolism and insulin secretion. Blueberries, being rich source of phytochemicals with antioxidant activities, are known to alleviate hyperglycemia and oxidative stress associated damage in the development of diabetes as demonstrated by various studies. The hypoglycemic as well as hypolipidemic properties of anthocyanin rich extracts of blue berry, and its constituent anthocyanins, malvidin-3-galactoside, malvidin- 3-glucoside and malvidin was investigated through in vitro as well as in vivo studies by Herrera-Balandrano et al. [8]. The study observed that there was a 6-fold enhancement in oxidative stress and reduced HepG2 (human hepatocarcinoma cell line) viability upon high glucose treatment. It was found that the pretreatments with anthocyanin rich extracts of blue berry, malvidin-3-glucoside, malvidin and malvidin-3-galactoside alleviate the damage by lowering the ROS levels and cell viability was enhanced. Furthermore, in HepG2 cells, the pre-treatments demonstrated the ability to mitigate hyperglycemia and hyperlipidemia by downregulating the expression of gluconeogenic and lipogenic enzymes, while simultaneously upregulating glycogenolytic and lipolytic enzymes via modulation of the adenosine monophosphate-activated protein kinase (AMPK) signalling pathway. Similarly, in high-fat diet-fed streptozotocin-induced diabetic mice, the administration of anthocyanin extracts from blueberries (200 mg/Kg and 400 mg/Kg) demonstrated in vivo hypoglycemic and hypolipidemic activities, evidenced by effects on body weight, enhanced AMPK activity, and reductions in levels of total cholesterol, triglycerides and glucose.

Inhibition of Carbohydrate Digestive Enzymes

Inhibiting α-amylase and α-glucosidase is considered as a potential strategy to regulate spikes in the blood glucose levels especially after a meal and thus in the dietary management of type II diabetes. α-Amylase secreted by the salivary gland and pancreas is involved in the hydrolysis of starch to oligosaccharides and disaccharides. α-Glucosidase, found in the intestinal brush border hydrolyses the oligo or disaccharides to glucose. Inhibition of these enzymes thus would help to regulate the blood glucose levels and hence in the management of post-prandial hyperglycemia and the oxidative stress mediated complications associated with diabetes. In their study, Pranaprawit et al. [16] evaluated the total phenolic content (TPC), antioxidant activities as well as in vitro α-amylase and α-glucosidase inhibitory potential of the aqueous extracts from eight varieties of Highbush blueberries from New Zealand. They found that the extracts of all the genotypes exhibited in vitro enzyme inhibitory potential at varying levels The eight varieties of frozen berries exhibited 10 to 40% α-glucosidase inhibitory activity and 11.2 to 36.2% α- amylase inhibitory at a concentration of 25 and 20 mg respectively. Further, no significant correlation between TPC, antioxidant activities and the enzyme inhibitory potential of the extracts across the studied genotypes were found. Hence it was suggested that the in vitro α-amylase and α-glucosidase inhibitory potential could be due to certain bioactive components such as glycosylated anthocyanins found in blueberries. Further, the α-glucosidase inhibitory role of anthocyanidins from blueberries was also demonstrated in the study by Zhang et al. [46].

Alleviation of Insulin Resistance

Secretion of insulin, which determines the rate of glucose diffusion, is one of the parameters for the utilization of glucose at the cellular level. Regulation of glucose metabolism is a multi-step procedure with the involvement of numerous glucoregulatory hormones including insulin, glucagon, GLP-1 among others. Insulin decreases gluconeogenesis while glucagon, adrenaline, cortisol and growth hormone counteract this process by various processes. This imbalance between glucose release and glucose uptake is an important factor in the pathophysiology of diabetes [47]. Insulin resistance, a condition characterized by inefficient uptake and utilization of glucose in response to insulin stimulation, at first manifests during the prediabetes stage [2]. This condition is known to be developed due to wide range of metabolic dysfunctions; instantly, obesity is one of the major risk factors in the development of insulin resistance. Insulin resistance is manifested with hyperinsulinemia, hyperglycemia, hypertension, dyslipidemia, visceral adiposity, hyperuricemia, etc. [48].

The beneficial effects of blueberries in ameliorating insulin resistance have been previously studied. The preclinical and clinical studies on blueberry mediated improvements

in insulin resistance have been reviewed earlier by Stull [2]. The effects of blueberry juice in imparting protection against early stages of diabetes (prediabetes) through amelioration of hepatic mitochondrial bioenergetics has been demonstrated by Nunes et al. [49]. They found that blueberry juice supplementation at 25 g/day for 14 weeks in hypercaloric diet induced prediabetic male Wistar rats could improve glucose tolerance as well as insulin sensitivity along with lowering of hypertriglyceridemia and liver lipid deposition. Also, the supplementation could effectively improve systemic as well as hepatic antioxidant status. The study observed an effective reduction in hepatic steatosis and mitochondrial dysfunction upon the supplementation.

Further, protein tyrosine phosphatase (PTB 1B) has been implicated as a negative regulator of insulin function, thus causing insulin resistance [50]. PTB 1B, an intracellular, non-transmembrane protein, is involved in the catalysis of dephosphorylation of activated insulin receptors as well as their corresponding substrates. Overexpression of PTB1B results inactivation of whole insulin signalling pathway and hence, PTB 1B inhibitors are potential therapeutic targets for T2D. The role of cyanidin-3-arabinoside, an anthocyanin extracted from blueberries in alleviating hyperglycemia and increasing insulin sensitivity by inhibiting PTB1B has been demonstrated by Tian et al. [51]. Through Lineweaver-Burk analysis and dialysis assay they showed that cyanidin-3-arabinoside is a reversible, mixed inhibitor of PTB1B. Further, the study demonstrated the potential role of cyanidin-3-arabinoside in promoting the synthesis of glycogen through enhancement of PTP1B-involved IRS1/PI3K/ Akt/GSK3β pathways. Furthermore, different anthocyanins at concentrations of 10, 20, and 40 μM enhanced glucose uptake by 9.2 to 26.7%, 22 to 35.1% and 36 to 49.7% respectively in HepG2 cells in a concentration-dependent manner.

The effects of acute consumption and short-term supplementation of fresh blue berries on post prandial glucose and insulinemic response were investigated in a study involving 10 sedentary human subjects [52]. Acute blueberry consumption trial included consumption of 150 g white bread and 150 g unprocessed frozen blueberries and the short-term supplementation trial included consumption of 150 g blueberries for a period of 6 days by the subjects. The results showed that acute consumption could significantly lower the blood glucose levels, while changes in the insulin levels. Short-term supplementation also showed positive effects on glucose management.

Studies suggest the alterations in the plasma sphingolipid profile under conditions of metabolic disorders. Obesity induced ceramide accumulation is known to trigger insulin resistance exacerbating the associated metabolic dysfunction; for instance, elevated levels of CERS6 (a ceramide synthase) mRNA expression as well as C16:0 ceramides in the adipose tissues of obese subjects have been reported [53]. Inhibition of *de novo* synthesis of ceramides reportedly attenuated insulin resistance and other obesity associated diseases. Si et al. [54] investigated the effect of supplementation of anthocyanin rich extracts from blue berries in modulating sphingolipid metabolism and the associated changes in insulin resistance in high fat induced hyperlipidemic mice. The study revealed that blue berry anthocyanin extracts at a dose of 200 mg/Kg could attenuate insulin resistance; at higher dose, administration of the extracts suppresses ceramide accumulation in the serum thus imparting hepatic protection and insulin signalling normalization effect.

In vitro and in vivo Studies

Several in vitro as well as in vivo studies link the effect of blueberries in ameliorating various metabolic processes associated with the pathogenesis of diabetes. Summary of blueberry's antidiabetic studies is depicted in Table 2. Besides producing direct hypo-glycemic effect, the anti-inflammatory and antioxidant activities of blueberry's bioactive compound also attribute to their anti-diabetic effect. Persistent high blood sugar levels result in increased oxidative stress and inflammation, creating a prooxidant environment. This scenario contributes to insulin resistance and compromised insulin secretion. Therefore, therapies that aim to inhibit the overproduction of reactive oxygen species (ROS) and inflammatory markers are crucial for delaying the onset and progression of T2DM and its associated complications [2, 3]. In studies conducted both in laboratory animals and human subjects, there are indications that consuming blueberries may lead to improvements in T2DM. Beverage produced by fermentation of blueberry and blackberry blend effectively reduced fasting glucose levels in blood and also prevented obesity in C57BL/6J mice [55].

Blueberry consumption enhanced insulin sensitivity in obese induced mice by downregulating the expression of genes encoding inflammatory cytokines (TNF-α and IL-10) [10]. In the context of diabetes, high blood sugar triggers chronic inflammation that plays a significant role in the development of insulin resistance and other complications. Polyphenols help combat this inflammation by inhibiting inflammatory reactions in the body [56].

Phytochemicals from blueberries mitigate endothelial inflammation and restore cell surface glycosaminoglycan in diabetic human aortic endothelial besides reducing the levels of VCAM-1 and inflammatory cytokines such as IL-8 [57]. In a study, blueberry supplementation increased β-cell survival and halted high-fat diet-induced β-cell expansion in mice. Particularly notable was the discovery of small,

Table 2 Antidiabetic studies of blueberries' bioactive compounds

Bioactive compounds	In vitro / in vivo study	Effective concentration	Anti-diabetic Effect	Antidiabetic Mechanism	References
Anthocyanin	Rat model	20, 40, and 80 mg/kg body weight	Improved retinal cell viability, decrease in glucose levels	Increase in the levels of glutathione peroxidase, improved antioxidant activity, reduced ROS and MDA levels. Increase in Nrf2 and HO-1 mRNA levels.	Song et al. [61]
Anthocyanin extract, malvidin, malvidin-3-galactoside and malvidin-3-glucoside	Streptozotocin induced diabetic mice and in human hepatocarcinoma cell line (HepG2)	5 µg/mL	Insulin independent hypoglycemic effect, suppression of gluconeogenesis, reduced cellular cytotoxicity	Activation of AMPK signalling. Inhibition of FOXO1, PGC-1α and genes involved in gluconeogenesis (PEPCK, G6Pase)	Herrera-Balandrano et al. [8]
Blueberry methanolic extract (quninic acid and flavonoid glycosides)	Human non-tumor hepatic LO2 cells	-	Hypoglycemic effect due to the enhanced expression of GLUT-2 and PPARγ.	Inhibition of NF-κB activity, reduced inflammatory cytokines and increased peroxisome proliferator response element (PPRE) activity	Huang et al. [13]
delphinidin-3-*O*-(glucoside, galactoside) petunidin-3-*O*-(galactoside, glucoside), and malvidin-3-*O*-galactoside	In vitro α-glucosidase inhibitory activity	IC_{50} range from 68.33 to 218.2 µM	-	Inhibition of α-glucosidase enzyme	Zhu et al. [60]
Cyanidin-3-arabinoside	HepG2 cells	IC50 = 8.91 ± 0.63 µM	Enhanced glucose consumption in HepG2 cells, PTP1B inhibitory activity more than the positive control (oleanolic acid)	Inhibition of Protein tyrosine phosphatase 1B (PTP1B)	Tian et al. [51]
Cyanidin-3-O-β-glucoside (C3G)	Mice	50 µM C3G	Decreased the toxicity of high glucose in hepatocytes	50 µM Cyanidin-3-O-β-glucoside inactivated caspases, and Bax protein, inhibited c-Jun N-terminal protein kinase (JNK)	Jiang et al. [59]
Aqueous extract (Highbush blueberry)	In vitro	α-glucosidase inhibitory (10 to 40% at 25 mg concentration of frozen berries) and α- amylase inhibitory (11.2 to 36.2% at 20 mg frozen berries) activity.	α-glucosidase, α-amylase inhibitory activity, radical scavenging activity	Inhibition of enzyme activity by phytochemicals present in blueberries	Pranprawit et al. [16]

dispersed islets in obese mice treated with blueberry, suggesting a possible role of blueberry in regenerating pancreatic β-cells [58]. Malvidin, known for its antioxidant properties exhibited protective effect in mice with streptozotocin induced diabetes and in human hepatocarcinoma cell line (HepG2). Approximately 76 to 91% reduction in reactive oxygen species (ROS) levels and 73 to 98% increased cell viability was observed following pretreatment with blueberries anthocyanins including anthocyanin extract, malvidin (Mv), malvidin-3-galactoside and malvidin-3-glucoside (Mv-3-glc). Furthermore, anthocyanin rich extracts upregulated the adenosine monophosphate-activated protein kinase (AMPK) signalling pathway in HepG2 cells as well as in diabetic mice and thereby resulted in lowering of glucose levels in blood and urine. In HEPG1 cells induced with high glucose levels, anthocyanins from blueberries demonstrated a suppressive impact on the transcription factor FOXO1 and its co-activator (PGC-1α), which are involved in regulating the expression of genes related to gluconeogenesis (such as PEPCK and G6Pase). This resulted in a hypoglycemic effect through a pathway that does not rely on insulin [8]. Furthermore, protein tyrosine phosphatase 1B (PTP1B) represents a potential target for therapeutic intervention in T2DM. In a study by Tian et al. [51], anthocyanins (cyanidin-3-arabinoside) isolated from blueberries selectively inhibited PTP1B with an IC50 of 8.91 µM as demonstrated by molecular docking studies. A concentration-dependent rise in glucose consumption in HepG2 cells was observed in the treated cells.Cyanidin-3-glucoside (C3G) at 50 µM concentration, suppressed mitochondria mediated apoptosis

of primary hepatocytes in mice fed with high fat diet under hyperglycemic conditions by producing inhibitory action on caspase-3, caspase-9 and Bax protein besides modulating phosphatidylinositol 3-kinase (PI3K)/Akt signalling [59].

Five anthocyanins (delphinidin-3-*O*-glucoside, petunidin-3-*O*-galactoside, petunidin-3-*O*-glucoside, delphinidin-3-*O*-galactoside, and malvidin-3-*O*-galactoside) isolated from rabbit eye blueberry (*Vaccinium virgatum*) exhibited α-glucosidase inhibitory activity in vitro with IC_{50} of 239.7, 68.54, 218.2, 68.33 and 184.6 µM respectively. Moreover, some compounds improved glucose uptake and attenuated lipid accumulation in high glucose and oleic acid-treated HepG2 cells [60]. The methanolic extract from blueberry, containing caffeoylquinic acid derivatives and flavonoid glycosides stimulated GLUT-2 expression and reduced the LPS induced inflammatory response induced in LO2 normal liver cell line. Furthermore, extract also reduced the NF-κB activity and thereby decreased the levels of proinflammatory mediators such as nitric oxide (NO), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β). Interestingly, when quinic acid and flavonoid glycosides fractions were separated, no inhibitory effect on NF-κB activity was observed, highlighting a synergistic effect between quinic acid derivatives and flavonoids in repressing NF-κB activity [13].

Prevention of diabetes induced retina damage is one of the protective effects of blueberry anthocyanins. The anthocyanins enhance the retina's antioxidant capacity by increasing glutathione (GSH) levels and glutathione peroxidase (GPx) activity, along with decreasing the levels of malondialdehyde (MDA) and reactive oxygen species (ROS). Additionally, blueberry anthocyanins significantly reverse the upregulation of vascular endothelial growth factor (VEGF) and interleukin-1β (IL-1β) in the serum of diabetic rats, and increase the mRNA levels of Nrf2 and HO-1. Blueberry anthocyanins protected retinal cells of male rats with streptozotocin-induced diabetes and also reduced blood glucose elevation [61]. Blueberry anthocyanins (malvidin, malvidin-3-glucoside (Mv-3-glc) and malvidin-3-galactoside (Mv-3-gal) and anthocyanin extract) reduce the ROS levels in the retinal cells, enhance the activity of antioxidant enzymes (catalase, superoxide dismutase) and thereby mitigate high glucose induced injury in human retinal capillary endothelial cells and improve cell viability. The potential mechanisms of protection involve the attenuation of oxidative damage, modulation of retinal enzyme activity and suppression of inflammation. Furthermore, anthocyanins and Mv-3-glc influence angiogenesis by reducing VEGF levels and inhibiting the Akt pathway, resulting in decreased nitric oxide levels. Additionally, Mv and Mv-3-glc exhibit anti-inflammatory properties and thereby inhibit high glucose-induced intercellular adhesion molecule-1 (ICAM-1) and nuclear factor-kappa B (NF-κB) in retinal cells [12].

Conclusion

In conclusion, blueberries have emerged as a promising natural remedy with significant potential in managing diabetes. The bioactive components present in blueberries, such as anthocyanins, flavonols and phenolic acids, contribute to their antidiabetic effects by targeting various pathways involved in glucose metabolism and insulin sensitivity. Studies have consistently demonstrated the ability of blueberry extracts to inhibit gluconeogenesis, improve insulin sensitivity and reduce inflammation as well as oxidative stress, all of which are crucial in diabetes management. Furthermore, the evidence from in vivo as well as preclinical and clinical studies supports the notion that regular consumption of blueberries or their derivatives may offer therapeutic benefits in preventing and managing diabetes. However, further research, including large-scale clinical trials, is warranted to fully elucidate the mechanisms and optimize the use of blueberries as an adjunct therapy for diabetes.

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Declarations

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