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Beneficial effects of anthocyanins against diabetes mellitus associated consequences-A mini review

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ABSTRACT

Anthocyanins (ACN) are water-soluble pigments, belonging to flavonoids, and are present in almost all fruits, and vegetables at varying concentration. About 635 ACN were distinguished based on the position and number of methoxyl and hydroxyl moieties in the basic structure of ACN. Pelargonidin, cyanidin, delphinidin, malvidin, peonidin, and petunidin are extensively studied anthocyanidins. The absorption, bioavailability, metabolism, pharmacokinetics, molecular mechanism, and analytical techniques of several phytochemicals were described. The biological benefits (antidiabetic, anti-neuro-disorder, anti-cardiovascular diseases, anti-gastrointestinal diseases, and disorders) of flavonoids and ACN have been reported. Several *in vitro*, and *in vivo* reports demonstrated that ACN-rich plant extracts ameliorate the diabetes-associated consequences by reducing the glucose absorption, ROS production, oxidative stress, glomerular angiogenesis, lipid synthesis, and FoxO1 and adipose triglyceride lipase expressions, and improve the insulin secretion, insulin sensitivity, glucose tolerance, glucose uptake, glucose consumption, antioxidant activity. The literature search was made in Scopus, Google Scholar, PubMed using the keywords "anthocyanin" and "diabetes". The documents were carefully checked for the relevance to the current manuscript and the selection was made without any chronological restriction. The present manuscript summarizes the updated reports on antihyperglycemic properties of ACN.

1. Introduction

Anthocyanins (ACN) are water-soluble flavonoids and are responsible for the pigmentation in plant tissues. ACN are present in almost all plants at varying concentration, and are widely present in fruits, and vegetables[1]. The distribution of ACN varies based on plant species, cultivars, cultivation area, and climate. The delivery of ACN in Thai rice varieties has been reported[2]. ACN have a heterocyclic, and two benzyl rings, and are connected by a carbon bridge (3n of C). Anthocyanidins are aglycon forms of ACN,

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architecturally based on the 2-phenylbenzopyrilium or flavylium ion, and consist of methoxyl and hydroxyl groups in different positions. About 635 ACN were identified based on the position and number of methoxyl and hydroxyl moieties. Pelargonidin, cyanidin, delphinidin, malvidin, peonidin, and petunidin are commonly found and most described anthocyanidins in plants[3,4].

ACN are easily susceptible to deprivation, and biological (enzymes), and physical (pH, temperature and light) factors, which can trigger the degradation of ACN. The pH is responsible for color of the ACN and also prompts the degradation. It is known that ACN are more stable in acidic pH compared to alkaline condition. The temperature and oxygen also play a crucial role in ACN stability, and the anaerobic condition comparatively protects the ACN from degradation. Studies on the factors affecting the stability of ACN suggested that heat facilitates the deformation of ACN quickly compared to other physical factors like sonication and microwave[4,5].

The absorption, bioavailability, metabolism, pharmacokinetics, molecular mechanism, and analytical techniques of several phytochemicals were described previously[6-9]. The biological benefits (antidiabetic, neuroprotective activity, anti-cardiovascular diseases, antioxidant, antimicrobial, anti-gastrointestinal diseases and disorders) of flavonoids, and ACN have been reported[10-15].

Diabetes mellitus (DM) is a disorder characterized by hyperglycemia due to the fault in insulin secretion and action, and untreated DM condition causes organ damage, and dysfunction. As per the International Diabetes Federation, the prevalence of DM may raise up to 552 million by 2030[16]. The plasma glucose level, glucose tolerance, and HbA1c testing were used to determine the DM. The intravenous insulin infusion is the current eventual treatment for management of the hyperglycemic condition[16]. Several alternative and complementary treatment strategies have been reported to manage and treat the DM condition[17,18]. The plant based alternative formulas, treatment methods, and clinical outcomes have been reported to manage the DM[19-24]. The current manuscript summarizes the reported anti-hyperglycemic properties of ACN. The literature search was made in Scopus, Google Scholar, PubMed using the keywords "anthocyanin" and "diabetes". The documents were carefully checked for the relevance to the current manuscript and the selection was made without any chronological restriction.

2. Anti-diabetic properties of ACN

2.1. In vitro studies

Cyanidin-3-*O*-β-glucoside (C3G) treatment introverted the glycerol and free fatty acid release in mouse embryo 3T3-L1 cells in a dose-dependent manner during hyperglycemic condition, which also increased the adenosine monophosphate (AMP)-activated protein kinase, as well as suppressed the hexosamine biosynthesis and FoxO1 activation and adipose triglyceride lipase expression. The results suggested that ACN controls FoxO1-mediated adipocyte lipolysis, which helps to manage or reduce the diabetes-associated hyperlipidemia[25]. The short-term exposure of 0.125%, w/v ACN-rich berry extract (ARBE) decreased the glucose uptake via both in sodium-dependent and independent manner in human intestinal Caco-2 cells. The ARBE exposure further reduced the transcriptional expression of SGLT1 and GLUT2. The results suggested that the ARBE modified post-prandial glycemia via reducing the glucose transporter expression[26].

ACN-rich purple corn extract (APCE) treatment reduced the expression of vascular endothelial growth factor (VEGF), and hypoxia-inducible factor-1a, and also inhibited the integrin β3 and platelet endothelial cell adhesion molecule. The study also proved that the APCE exposure interrupted the endothelial tube formation in high glucose condition. The results suggested that APCE supplementation may protect from diabetic nephropathy[27]. Delphinidin inhibits the glucose absorption in a free fatty acid receptor-1 (FFAR-1) dependent way, which also distresses the function of sodium-glucose cotransporter 1. The study revealed that the mechanism behind the ACN delphinidin mediated anti-hyperglycemic effect is associated with FFAR-1[28].

Recently, Luna-Vital and Gonzalez de Mejia[29] demonstrated that APCE and pure ACN compounds improved the glucose-stimulated insulin secretion and glucose absorption in INS-1E, and HepG2 cells, respectively. Delphinidin-3-*O*-glucoside and APCE effectively activated the FFAR-1 and stimulated the FFAR1-dependent insulin secretory pathway. APCE significantly reduced the gluconeogenesis by suppressing the PEPCK expression and AMPK phosphorylation in HepG2 cells. The study proved that APCE supplementation could protect the DM associated consequences[29].

Protocatechuic acid (PCA) exposure normalized the insulin-induced phosphorylation in obese visceral adipose tissue. PCA exposure reduced the activity of protein-tyrosine phosphatase 1B, and phospho-p65 NF-κB and IL-6 in obese visceral adipose tissue. Moreover, it also increased the secretion of adiponectin in normal visceral adipose tissue. The results suggested that ACN treatment reduced the inflammation and insulin resistance in obesity[30].

3T3-Ll cells exposed to black soybean seed coat extract (BSSCE) showed adipocytes differentiation, which is associated with amplified expression of *PPAR γ* and *C/EBP α* genes, increased secretion of adiponectin, insulin signaling, and glucose uptake, and reduced TNF-α secretion. The study also found that BSSCE treatment increased the *SIRT1*, *PGC-1 α*, and *UCP-3* genes expressions. It has been proved that BSSCE has potent antidiabetic activity[31]. C3G-rich blood orange variety Moro juice activated the AMP-activated protein kinase and suppressed the mTOR/S6K kinase, which increased the expression of *glut 1* and *glut 4*, as well as glucose tolerance, thereby exhibiting antidiabetic property in BNL CL.2 murine hepatocytes and Hela cells[32].

ACN-rich mulberry extract (AME) exposure improved the glucose uptake, consumption, glycogen content and diminished

Table 1

Anti-diabetic properties of ACN: *In vitro* studies.

S. No.	Model	Study materials	Outcomes	Ref.
1	Mouse embryo 3T3-L1 cells	C3G	Inhibited the free fatty acids and glycerol discharge ↓ Glutamine: fructose 6-phosphate aminotransferase activity Suppressed hexosamine biosynthesis pathway ↓ FoxO1 and adipose triglyceride lipase expression	[25]
2	Human intestinal Caco-2 Cells	ACN-rich berry extract	↓ Sodium-dependent and sodium-independent ^{3}H-D-glucose uptake ↓ SGLT1, GLUT2 expression ↓ Glucose transporter expression	[26]
3	Human umbilical vein endothelial cells, human renal mesangial cells	ACN-rich purple corn extract	↓ Vascular endothelial growth factor, and hypoxia-inducible factor-1 α expression ↓ Integrin β 3 and platelet endothelial cell adhesion molecule Disrupted the endothelial tube formation	[27]
4	Human intestinal cell lines HT-29, Caco-2, and NCM460	Delphinidin	↓ Glucose absorption via free fatty acid receptor -1 (FFAR-1) dependent way Distressed the function of sodium-glucose cotransporter 1	[28]
5	Caco-2 cells, INS-1E or HepG2 cells	ACN-rich purple corn extract	↑ Glucose-stimulated insulin secretion, and glucose uptake Activated the FFAR1-dependent insulin secretory pathway ↓ AMPK phosphorylation and PEPCK expression	[29]
6	Visceral adipose tissue (VAT)	Protocatechuic acid	↓ PTP1B activity in obese-VAT ↓ phospho-p65 NF-κB and IL-6 in obese-VAT ↑ adiponectin secretion in normal-VAT ↓ IL-1 β in normal-VAT	[30]
7	3T3-Ll cells	Black soybean seed coat extract	↑ *PPAR γ* and *C/EBP α* gene expressions ↑ Adiponectin secretion ↑ Glucose uptake ↑ *PGC-1 α* , *SIRT1* and *UCP-3* genes ↓ Tumor necrosis factor- α secretion	[31]
8	BNL CL.2 murine hepatocytes and Hela cells	C3G-rich blood orange variety Moro juice	Activated the AMP-activated protein kinase ↓ mTOR/S6K expression ↑ *glut 1* and *glut 4* expression ↑ Glucose tolerance ↑ Insulin sensitivity	[32]
9	HepG2 cells	ACN-rich mulberry extract	↑ Glucose uptake, consumption, glycogen content ↓ Insulin resistance ↓ Glucose-6-phosphatase, and phosphoenolpyruvate carboxykinase activities ↑ Protein kinase B (AKT) and glycogen synthase kinase-3 β activation	[33]
10	HK-2 cells	Grape seed procyanidin, and C3G	↑ Antioxidant activity ↓ ROS production, apoptosis, and expression of cleaved caspase-3 and the Bax/Bcl-2 ratio ↑ Cytochrome c expression ↑ p38 MAPK, thioredoxin 2 and ERK1/2 oxidase	[34]

the insulin resistance in HepG2 cells. AME exposure inhibited the forkhead box protein O1 (FOXO1), and PPAR γ coactivator 1 α (PGC-1 α) followed by reducing the glucose-6-phosphatase, and phosphoenolpyruvate carboxykinase activities. AME treatment also improved the protein kinase B (AKT) and glycogen synthase kinase-3 β activation. The results suggested that AME exhibited strong anti-hyperglycemic property[33].

The grape seed procyanidin and C3G inhibited the ROS production, apoptosis, and expression of cleaved caspase-3 and the Bax/Bcl-2 ratio, and enhanced cytochrome c expression. C3G treatment activated the p38 MAPK, thioredoxin 2 and ERK1/2 oxidase in HK-2 cells under high glucose condition. The results revealed that intervention of grape seed procyanidin and C3G protects diabetic nephropathy via antioxidant system[34] (Table 1).

2.2. *In vivo studies*

ACN-rich grape-bilberry juice (AGBJ) was supplemented to male Fischer rats for ten weeks and assessed for the several risk factors related to obesity-associated diseases. The study proved that AGBJ intervention effectively reduced the serum cholesterol, triglycerides, leptin, and resistin levels while glucose, insulin, adiponectin, adipokines secretion and non-esterified fatty acids were not affected. Moreover, AGBJ improved the polyunsaturated fatty acids content and reduced the saturated fatty acids content in plasma. Collectively, the results revealed that AGBJ could be active against obesity-associated metabolic diseases[35].

Male Sprague-Dawley rats were fed with a fructose-enriched diet for four weeks and ensured the fructose-induced insulin resistance. ACN-rich black rice extract (ABRE) was supplemented to rats fed with a fructose-enriched diet. ABRE supplementation improved the glucose intolerance and hyperlipidemia but hyperinsulinemia was not reverted. ABRE supplemented rats displayed less oxidative stress, plasma thiobarbituric acid reactive substances and blood oxidized glutathione[36].

C3G treatment enhanced the secretion of leptin and adiponectin in rat adipocytes and increased the expression of adipocyte-specific gene. The mice fed with C3G showed the increased expression of

adiponectin in white adipose tissue. The authors claimed that the changes in activation of AMP-activated protein kinase and decreased AMP: ATP ratio are greatly associated with ACN supplementation, and ACN could be a potent therapeutic agent to prevent the obesity and diabetes[37].

C3G treatment reduced the glycerol-3-phosphate acyltransferase 1 activity by preventing the translocation of mitochondrial acyl-CoA: glycerol-sn-3-phosphate acyltransferase 1 (mtGPAT1) activity and suppressed the lipid synthesis in hepatoma cell lines. C3G exposure increased the protein kinase C ζ phosphorylation by which prevents the mtGPAT1 activation. C3G supplementation suppressed the hepatic mtGPAT1 activity and reduced the hepatic steatosis in diabetic KKAy mice model[38].

The supplementation of APCE (10 mg/kg) for eight weeks inhibits the glomerular angiogenesis in mice via VEGF and hypoxia-inducible factor-1 α attenuation. APCE intervention condensed the endothelial proliferation and activation of VEGF receptor 2. The suppression of glomerular angiogenesis in mice by APCE intervention was associated with renal VEGF receptor 2 signaling pathway[27].

Wistar rats were fed with an ACN-rich extract from Kamchatka honeysuckle berry extract (AKHBE) (2 g/kg) for four weeks along with control and high-fructose diet. AKHBE supplementation increased the mucosal lactase activity, and bacterial α and β glucosidase activity when compared to control. The dietary AKHBE interventions stabilized the plasma triglyceride concentration and atherogenicity, while insulin concentration and resistance, and plasma non-HDL cholesterol were amended when compared to control. AKHBE supplementation improved the glucose metabolic status and gut enzymatic activities in rats fed on a high-fructose diet[39].

The supplementation of C3G improved the free radical scavenging status and inhibited the mitochondria-mediated apoptotic pathway via inactivation of c-Jun N-terminal kinase pathway and activation of phosphatidylinositol 3-kinase/Akt pathway, which prevented the high glucose-induced hepatic damages in C57BL/J mice[40].

The supplementation of 30 mg/kg of BSSCE for 30 d reduced the adipose tissue mass in BKS.Cg-Dock7^{m}+/+ Lepr^{db}/J male mice. The study proved that BSSCE have antidiabetic activity by encouraging adipocyte differentiation[31]. The supplementation of ACN-rich blood orange juice (ABOJ), especially rich in C3G, and PCA, activated the AMP-activated protein kinase and suppressed mTOR/S6K. ABOJ intervention improved the glucose tolerance, augmented the *glut 1* and *glut 4* expressions, and increased the insulin sensitivity in mice. The results suggest that the ABOJ could be used to improve the health status of DM patients[32].

The supplementation of 50 and 125 mg/kg body weight per day of AME reduced the blood glucose, serum insulin, triglyceride, cholesterol, and leptin level in experimental mice via AKT activation[33]. The intervention of 20 mg/100g of body weight of purple sweet potato extract reduced the blood glucose level significantly and improved the histopathological parameters of pancreatic β cells in alloxan-induced diabetic Wistar rat model[41].

Pre-administration of blackcurrant polyphenol extract, rich in delphinidin 3-rutinoside, effectively improved the glucose tolerance in rats, which is associated with glucagon-like peptide-1 activation and insulin secretion. The study claimed that the delphinidin 3-rutinoside is responsible for the increased secretion of glucagon-like peptide-1, and blackcurrant polyphenol extract could be used as an adjuvant therapeutic agent to manage the hyperglycemic condition[42].

The intervention of C3G (20 mg/kg/day for 12 weeks) to db/db mice significantly reduced the body mass, glucose, HbA1c, C-peptide, serum insulin, blood pressure, and kidney related pathological biomarkers such as serum creatinine, urinary albumin, blood urea nitrogen, albumin/creatinine ratio, fibronectin, collagen Ⅳ, TGF β 1, matrix metalloprotein 9, TNF α , monocyte chemotactic protein-1, IL-1 α , and α -smooth muscle actin expressions. Further, C3G treatment improved the glutathione (GSH) level in db/db mice. The protective effect of C3G has been attributed to the elevation of GSH in db/db mice, which has been demonstrated using GSH inhibitors. The study suggested that the C3G supplementation could be an effective treatment strategy to prevent or protect diabetes associated nephropathy[43]. Another study by Wei *et al*.[34] also demonstrated that the supplementation of C3G and grape seed procyanidin protects the db/db mice from diabetic nephropathy by activating the antioxidant system (Table 2).

3. Conclusion and future perspectives

Several *in vitro* and *in vivo* reports proved that ACN-rich plant extracts ameliorate the diabetes-associated consequences via suppressing the glucose absorption, hepatic steatosis, free fatty acids and glycerol discharge, oxidative stress, glomerular angiogenesis, ROS production, TNF- α secretion, phospho-p65 NF-κB, IL-6, IL-1 β expression, lipid synthesis, and FoxO1 and adipose triglyceride lipase expressions, and improve the insulin secretion, insulin sensitivity, glucose tolerance, glucose uptake, glucose consumption, antioxidant activity.

A cohort study conducted on more than 187 382 human subjects revealed that consumption of ACN-rich whole fruits, such as blueberries, grapes, raisins, prunes, reduced the risk of development of DM while the consumption of fruit juice increased the incidents of DM[44]. Another study suggested that supplementation of protocatechuic acid significantly reduced the insulin resistance, and inflammation in the visceral adipose tissue of obese subjects[30]. The clinical studies to explain the antidiabetic properties of ACN are very limited, and the direct evidence is inadequate. Further, extended clinical studies are required to explore the detailed health benefits of ACN, which helps to develop an effective and alternative treatment procedure to manage or to prevent the incidence of DM.

Table 2

Anti-diabetic properties of ACN: *In vivo* studies.

S. No.	Model	Study materials	Outcomes	Ref.
1	db/db mice	ACN-rich purple corn extract	↓ Glomerular angiogenesis ↓ Endothelial proliferation	[27]
2	db/db mice	Black soybean seed coat extract	↓ Adipose tissue mass ↑ Adipocyte differentiation	[31]
3	C57BL/6 mice	C3G-rich blood orange variety Moro juice	Activated the AMP-activated protein kinase ↓ mTOR/S6K expression ↑ *glut 1* and *glut 4* expression ↑ Glucose tolerance ↑ Insulin sensitivity	[32]
4	db/db mice	ACN-rich mulberry extract	↓ Fasting blood glucose ↓ Serum insulin ↓ Triglyceride ↓ Cholesterol ↓ Leptin ↑ Phosphorylation of protein kinase B (AKT)	[33]
5	db/db mice	Grape seed procyanidin, and C3G	↑ Antioxidant activity	[34]
6	Male Fischer rats	ACN-rich grape-bilberry juice	↓ Serum cholesterol and triglycerides level ↓ Serum leptin and resistin ↑ Proportion of polyunsaturated fatty acids ↓ Plasma saturated fatty acids	[35]
7	Male Sprague-Dawley Rats	ACN-rich black rice extract	Prevented the fructose-induced insulin resistance Improved the glucose intolerance ↓ Oxidative stress	[36]
8	Rat Adipocytes, Mice	C3G	↑ Adipocytokine secretion ↑ Expression of adipocyte specific gene Altered AMP-activated protein kinase activation ↓ AMP: ATP ratio	[37]
9	Hepatoma cell lines and KKAy mice	C3G	↓ Glycerol-3-phosphate acyltransferase 1 activity ↓ Lipid synthesis ↑ Protein kinase C ζ phosphorylation ↓ Hepatic steatosis	[38]
10	Male Wistar rats	ACN-rich extract from Kamchatka honeysuckle berry extract	↑ Mucosal lactase activity, and bacterial α and β glucosidase activity Stabilized plasma triglyceride concentration and atherogenicity Insulin concentration and resistance, and plasma non-HDL cholesterol were altered positively	[39]
11	C57BL/6J mice	C3G	Inactivated the c-Jun N-terminal protein kinase ↓ Free radical generation ↓ Pro-apoptotic Bax protein ↓ Caspase-3 and -9 activity ↑ Hepatoprotection	[40]
12	Wistar rats	Purple sweet potato extract	↓ Blood glucose Improved the histopathological parameters of pancreatic β cells	[41]
13	Sprague-Dawley rats	Blackcurrant polyphenol extract	↑ Glucose tolerance ↑ Insulin secretion ↑ Glucagon-like peptide-1 (GLP-1) activation	[42]
14	db/db mice	C3G	↓ Body weights ↓ Fasting blood glucose, serum insulin, C-peptide, glycosylated hemoglobin A1c, and blood pressure ↓ Blood urea nitrogen, serum creatinine, urinary albumin content and albumin/creatinine ratio ↓ Pathological changes of kidneys ↑ Glutathione level	[43]

Conflict of interest statement

The authors declare that there is no conflict of interests.

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