REVIEW article

Polyphenol-rich black chokeberry (*Aronia melanocarpa*) and its therapeutic potential in type 2 diabetes mellitus: A comprehensive review

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Article number: 15, **Received:** 04-09-2025, **Accepted:** 09-11-2025, **Published online:** 15-11-2025

HOW TO CITE THIS
Nizamuddin SFS. Polyphenol-rich black chokeberry (Aronia melanocarpa) and its therapeutic potential in type 2 diabetes mellitus: A comprehensive review. Mediterr J Med Med Sci. 2025; 1(3): 31-42.
[Article number: 15]. https://doi.org/10.5281/zenodo.17619107

Keywords: Antioxidant activity, *Aronia melanocarpa*, flavonoids, insulin sensitivity, polyphenols

Abstract: Diabetes mellitus is a global public health crisis, which we see mostly in Type 2 Diabetes (T2D) cases. Incidence of T2D is on the rise with the aging population, poor lifestyle choices, and bad diet, which in turn are health and economic issues. Black chokeberry (*Aronia melanocarpa*) has become a focus due to its high level of polyphenols, which include anthocyanins, proanthocyanidins, flavonols, and phenolic acids, known for their antioxidant, anti-inflammatory, hypoglycaemic and hypolipidemic actions. As to its flavonoid a-chokeberry, has been reported to do well in terms of digestive enzyme inhibition and also in improving insulin sensitivity. Anthocyanins have positively influenced glucose uptake, antioxidant properties, reduced inflammatory response, and improved lipid metabolism. Hydroxycinnamic acids, particularly chlorogenic acid, have also shown some evidence of supporting altered glucose homeostasis regulation, α-glucosidase inhibition, and gut microbiota. Additionally, experimental and clinical studies have shown combined hyperglycaemic effects with improved pancreatic β-cell function and improved lipid parameters as a result of supplemented chokeberry extract. Overall, the Black chokeberry presents favourable qualities regarding functional foods and adjunctive treatment in T2D; however, further clinical study is needed.

Introduction

Diabetes is a big health problem all over the world, with over 537 million people hit by it as of 2021 [1]. It shows up in a few ways, like type 1, type 2, and rare forms such as monogenic diabetes and gestational diabetes which comes during pregnancy. Type 1 happens when the body's own shields attack the cells that make insulin in the pancreas. On the other hand, type 2 (T2D) kicks in from a mix of insulin resistance, back and a drop in the pancreas's ability to make insulin. If not looked after well, gestational diabetes can change to T2D later [2]. Monogenic diabetes, which is not common, often gets mixed up with T1D or T2D [3]. Out of these, T2D is the most seen, about 90-95% of all cases that are known. Studies show that its numbers are going up, mainly because of older people, less moving, and bad diets. It is thought that by 2030, about 643 million people will have diabetes, and this might go up to 783 million by 2045 [4]. This rise is behind big health troubles like heart disease, harm to the kidneys, nerve problems, and loss of sight [5]. Also, diabetes costs a lot for healthcare, nearly $966 billion in 2021 alone [4]. Luckily, new drugs like SGLT2 stoppers, GLP, 1 mover, and tirzepatide (a drug that hits both GIP and GLP, 1 spots) have helped a lot in keeping blood sugar right and making life better for people with diabetes [6-11].

Global diabetes is a public health concern with an estimate suggesting that at least 537 million people lived with diabetes worldwide in the year 2021 [1]. Diabetes can present as T1D, T2D, and some rare manifestations of diabetes including monogenic diabetes and gestational diabetes. Type 1 diabetes occurs when the body's defence mechanism attacks the beta cells for the production of insulin in the pancreas. Conversely, T2D diabetes occurs when one has insulin resistance with diminished beta-cell function for insulin secretion. Gestational diabetes mellitus must also be managed appropriately, or else it has the potential to develop into T2D after the maternal period [2]. Monogenic diabetes is uncommon and sometimes misdiagnosed as T1D or T2D [3]. Therefore, type diabetes is the most common presentation for the disease for approximately 90-95% of all diabetes cases. There has been evidence suggesting the increase in incidence of diabetes where the key causes will be an increasing population, physical inactivity, and unhealthy dietary intakes [5]. The predictions are dire- an estimated 643 million adults will have developed diabetes by the year 2030, and could increase by the year 2045 to 783 million adults [4]. Diabetes effects are not single but numerous including heart disease, nephropathy, neuropathy, and retinopathy [5], including also the effect on the health system estimated to reach $966 billion in the year 2021 [4]. In this review, it is aimed to assess the therapeutic attributes of the black chokeberry (*Aronia melanocarpa*), a rich source of polyphenols which may have a role in the management of T2D mellitus. We focus on how the bioactive constituents may influence glycemia, control oxidative stress, and help in the prevention of the complications of diabetes. We intend to reflect recent findings, with an emphasis on the experimental and clinical data, to better capture the potential of Aronia as a natural adjunct in diabetes management.

Black chokeberry: Part of the Rosaceae group, first grew wild in North America. For more than 400 years, people have grown it in Europe. It is also common in places like Canada, Russia, Bulgaria, Hungary, Poland, and the Czech Republic. The fruit shows a dark purple hue and is full of polyphenols. Many papers find that these polyphenols help a lot and act as extra help with many health problems [12-15]. Also, studies have told us that these bits help deal with things like high fat in the blood and high blood sugar [15, 16]. This paper has given a full and well-planned look at the studies on the things that stop harm and help our health in the black chokeberry. It has looked at and talked about the amounts and mix of chosen plant parts, like anthocyanins, proanthocyanidins, flavonols, flavanols, and acids, in chokeberry fruits, made goods, and taken out oils. It also went into how well the chokeberry fruits and their products fight harm to our cells in lab tests. It has shown how these parts could help make blood sugar levels stable, lessen swelling, and help with the health of our body, mainly when looking at T2D. While each part has been looked at a lot, this paper has underlined the joint power of the full mix of plant parts in chokeberries. The facts given here could help with more work on good foods and help make new chokeberry goods with greater health benefits.

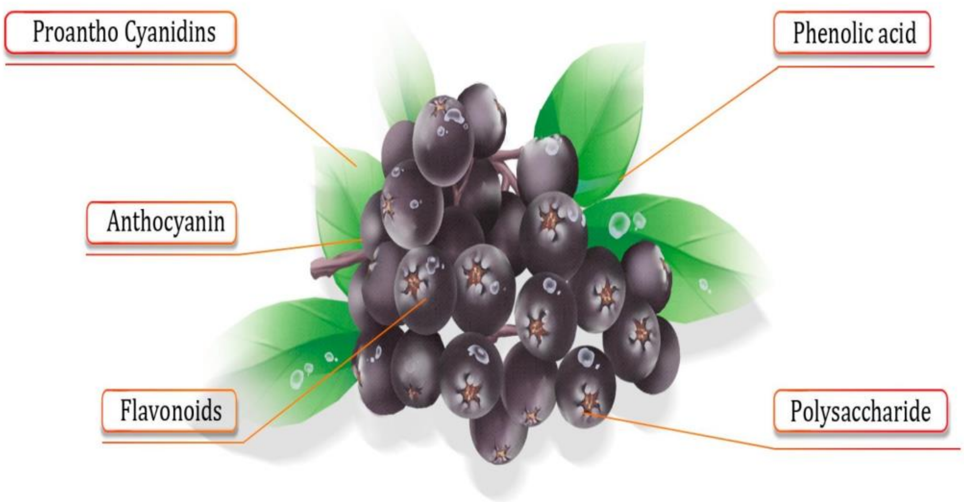

Figure 1: Black chokeberry polyphenols [17].

Black chokeberry polyphenols for the treatment of type 2 diabetes mellitus

Flavonoids: Black chokeberry contains a high concentration of flavanols that include (+) catechins and (−) epicatechins, which are capable of forming proanthocyanidins (Pas) by condensation [18]. The Pas are abundant polyphenolic fractions and are present markedly in pomace, as opposed to juice [18]. Structure elucidation shows that the Pas are all procyanidins, since their oxidation products were derived from cyanidin [19]. Oligomeric Pas (degree of polymerization less than or equal to 4, e.g., procyanidin B2) are minor components, while polymeric Pas (degree of polymerization >4) are major components, making up >89.0% of total Pas [20, 21]. Although the polymeric Pas are present in a greater concentration, they have a large particle size, preventing effective bioavailability. Their bioactivity is confined to the human digestive tract, and Pas inhibit enzymes such as amylase and lipase, and modify glucose and lipid metabolism [21]. The unabsorbed Pas are catabolized by gut microbiota and converted to phenolic acids as an end product, but they have not established their impact on gut microbiota [21]. Epidemiology studies have demonstrated risk differentials and varied effects of flavonoid subclasses on the incidence of T2D. In the NHS cohorts, higher urinary metabolites of flavanones (naringenin, hesperetin) and flavonols (quercetin) were associated with a 39-48% lower risk of developing T2D during early follow-up (up to 4.6 years), but among these cohort studies, the association with T2D was not observed during the latter follow-up intervals [22]. Numerous foods high in anthocyanins, including apples and berries, were associated with a 26.0-28.0% lower risk of T2D in the Finnish cohort (n=10,054), and lower risk among U.S. (n=200,894) cohort studies [23, 24]. While no clear association was observed with total flavonoid intake [24, 25]. When red wine was consumed at least one serving per week, T2D risk was 16.0% lower, but the reduced incidence of T2D was likely from the alcohol intake stimulus on T2D, and not the polyphenol content [26]. These inconsistencies with the mentioned studies may be due to methodological concerns of a lack of positive controls and possibility of self-reporting dietary [23, 25]. Flavonoids are structural derivatives that were formed from the phenyl-propanoid pathway, and that exhibit diversity in structure and bioavailability of these compounds [27-33]. Though glycosides are poorly absorbed, they are either hydrolyzed by intestinal enzymes (e.g., SGLT1) or gut microbiota into bioactive aglycones [34-36]. There is clinical evidence that the antidiabetic effect of quercetin is via inhibition of α-glucosidase and improvement of insulin sensitivity [37-42]. Epicatechin improved β-cell function [43-47]. Anthocyanins (particularly berries) show a reduction of 15.0% in T2D risk [48-50]. As evidence accumulates for the beneficial effects of polyphenols on T2D risk and metabolic health, more work is needed to make definitive claims and develop therapeutic guidelines due to variability in study designs.

Anthocynins: are the main bioactive component in black chokeberries, are responsible for their distinctive pigmentation. These are present in the pomace instead of juice [51, 52]. Unlike other berries, the anthocyanins are spread throughout the flesh and peel of the fruit; the Viking cultivar has the highest concentration of anthocyanins [53]. Aside from trace amounts of pelargonidin-3-O-arabinoside and minor components, anthocyanins are cyanidin derivatives including cyanidin-3-O-galactoside (65.0-72.0% of total anthocyanins) and cyanidin-3-O-arabinoside. Delphinidin-3-O-rutinoside is a unique chemical [53-59]. By means of mechanisms including insulin sensitization by stimulating the AMPK/ACC/mTOR pathway, which factors into GLUT-4 mediated glucose uptake enhancement, anthocyanins can provide notable antidiabetic effects [60, 61]. In diabetic models, cyanidin-3-glucoside can lower bodyweight, hepatic steatosis, and hyper-glycaemia while raising adiponectin, inhibiting hepatic gluconeogenesis. By blocking the NFκB and JNK pathways, anthocyanins can also lower proinflammatory cytokines (TNFα, IL6) and chemokines (MCP1). Antioxidant enzymes (SOD, CAT) can accomplish the same thing by inhibiting the NFκB and JNK pathways [62-65]. Certain fermented anthocyanins found in berries, like delphinidin-3-arabinoside, have been shown to enhance glycaemic control by encouraging GLP1 release and lowering DPPIV [65-71]. Apart from glycaemic control, anthocyanins are found to lower obesity mediating metabolic diseases, as chokeberry and blueberry extracts clearly in high fat diet models, chokeberry and AMPK activation may explain blueberry extracts' reversal of mitochondrial malfunction and lowering of oxidative stress [72-79] **(Figure 2)**.

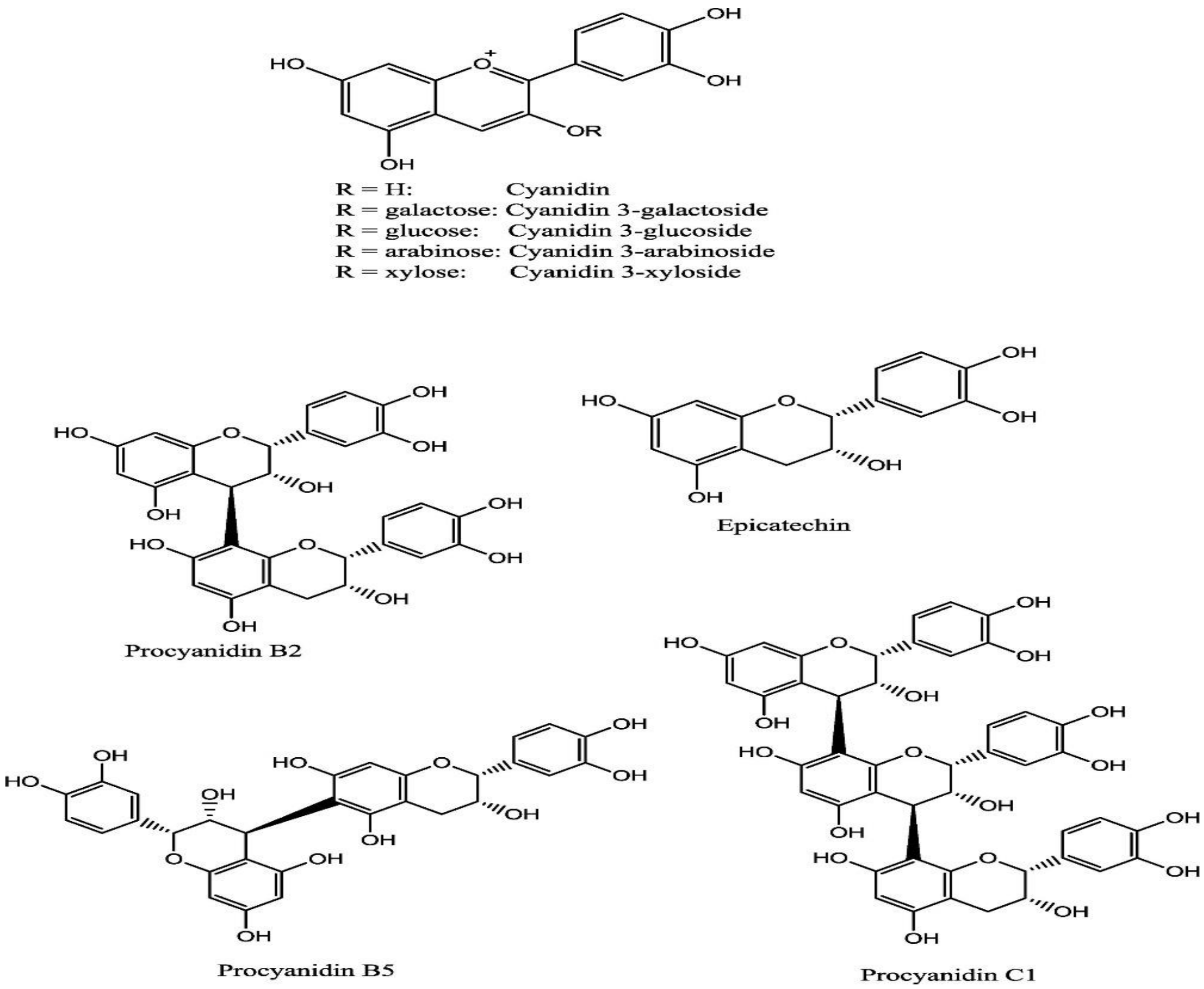

Figure 2: Major polyphenols occurring in *Aronia melanocarpa* berries [80].

Phenolic acids: Black chokeberry has been discovered to contain considerable quantities of phenolic acids. Chlorogenic acid and neochlorogenic acid are the predominant phenolic acids, with caffeic acid occurring in trace amounts, and cryptochlorogenic acid also [81-85]. As the bioactive compounds, these phenolic acids are responsible for the antioxidant along with anti-diabetic effects of chokeberry, but the mechanisms for this activity are an area for future studies. Of the known phenolic acids, the most investigated has been the chlorogenic acid due to the promise for modulating the numerous metabolic processes playing roles for diabetes [84, 86]. There has been evidence suggesting the potential for controlling type T2D with the assistance of the phenolic acids, particularly the chlorogenic acid, by its reinforcement on the hepatic glucose homeostasis with the inhibition of the carbohydrate hydrolysing enzyme (i.e., α-glucosidase along with α-amylase) activities [87, 88]. Chlorogenic effects have been confirmed with human clinical studies suggesting that the dose of the chlorogenic acid (400-1200 mg/day) greatly reduced the fasting blood glucose with reinforcement on the insulin sensitivity whereby the Matsuda index progression improved [89, 90]. From animal studies, evidence indicates that chlorogenic acid modulates gut microbiota, by increasing Lactobacillus and Blautia populations which are positively associated with glucose tolerance [90]. Although some metabolic outcomes remain inconsistent with respect to chlorogenic acid's activity, and phenolic acids in general, the anti-diabetic properties of phenolic acids remain supported with respect to the regulation of glycemia and inflammation [86, 91]. Epidemiologic type studies have consistently shown an association with consumption of both, caffeinated and decaffeinated coffee, and with green tea in reduced risk of T2DM to be dose-dependent [92-98]. Meta-analyses show that drinking 3-6 cups of coffee per day decreased T2DM risk up to 33.0%; while drinking ≥3 cups/day of green tea decreased T2DM risk by 16.0% [93-95]. These effects, along with the physiological mechanisms that promote reduced risk of T2DM, were independent of BMI which suggests a direct influence on metabolism [93, 96-100].

Table 1: The main ingredients and their contents in black chokeberry are listed

Compound	Sugars g/L	Ref.
(−) Epicatechin	1.74 (DW)	[81]
(+) Catechin	0.24 (DW)	[81]
Cyanidin 3-arabinoside	0.50 3.99 (FW)	[101] [20]
Cyanidin 3-galactoside	1.49 9.89 (FW)	[101] [20]
Cyanidin 3-glucoside	0.12 0.07 (DW)	[101] [59]
Chlorogenic acid	1.38 1.64 (FW)	[101] [102]
Delphinidin-3-O-rutinoside	6.90 (FW)	[103]

Pharmacological actions of black chokeberry in diabetes management: Pharmacological actions of black chokeberry have been most attributed to polyphenolic compounds (chiefly anthocyanins, procyanidins, phenolic acids, and flavonols. These phytochemicals are powerful antioxidants, anti-inflammatories, hypoglycaemic, and hypolipidemic agents, and these interactions work in concert to help prevent or manage metabolic disorders, primarily diabetes mellitus.

Antioxidant and anti-inflammatory properties: Black chokeberry extracts have strong radical scavenging activity and decreased lipid peroxidation. Anthocyanidins and ellagic acid have been documented to reduce oxidative stress levels through the increase of endogenous antioxidants (superoxide dismutase, catalase and glutathione peroxidase) and through reductions in ROS. Antioxidant factors intended to prevent oxidative stress is important in diabetic subjects, as excessive oxidative stress results in hyperglycaemia-induced damage in the β-cell of the pancreas and hepatic tissue, lowering the capacity to manage insulin tolerance and cellular function.

Enzymes and regulation of glucose metabolism: Aronia extracts and juice products have inhibition against carbohydrate hydrolysing enzymes such as α-glucosidase and dipeptidyl peptidase-IV (DPP-IV); as a result, slowing the absorption of carbohydrates in the intestine and halting the degradation of incretins. Evidence of inhibition exists against ACE inhibiting enzymes which has demonstrated vasomodulation effects and reduction of blood pressure, which is critical in diabetic subjects. Evidence of these effects have been demonstrated in vitro dissections and in vivo through clinical trials in humans, including Postprandial glucose excursion was significantly reduced in subjects who consumed chokeberry juice.

Modulation of insulin signaling: A few specific phenolics, such as α-pentagalloylglucose (α-PGG) and manufactured phenolics like modified 6Cl-TGQ, have been dieselley defined as insulin mimetics. These compounds engage directly with the insulin receptor (IR) and activate it, leading to downstream activation of the PI3K/Akt/GLUT4 pathway. Increased glucose uptake into skeletal muscle and adipose tissue results in increased insulin sensitivity and overall glycaemic control. The activation of IR by arginine and these compounds associated with insulin secretion, has been documented in T1D (autoimmune β-cell loss) and T2D (insulin resistance) diabetic models.

Protection of pancreatic β cells: In diabetic models, produced from streptozotocin, daily gavage of Aronia has been shown to significantly decrease hyperglycaemia and protect pancreatic β-cells against oxidative apoptosis. Restoration of pancreatic architecture and partial preservation of insulin secretion have been shown. From these studies, it appears that chokeberry may have cytoprotective effects beyond glycaemic regulation.

Improvement of lipid homeostasis: In addition to glucose regulation, black chokeberry, has improved lipid profiles in different experimental and clinical contexts. The extracts have been shown to decrease triglycerides, total cholesterol and LDL while increasing HDL. One mechanism for this hypolipidemic action has been attributed to the decreased oxidative modification of lipoproteins and better hepatic lipid metabolism [104, 105] **(Figure 3)**.

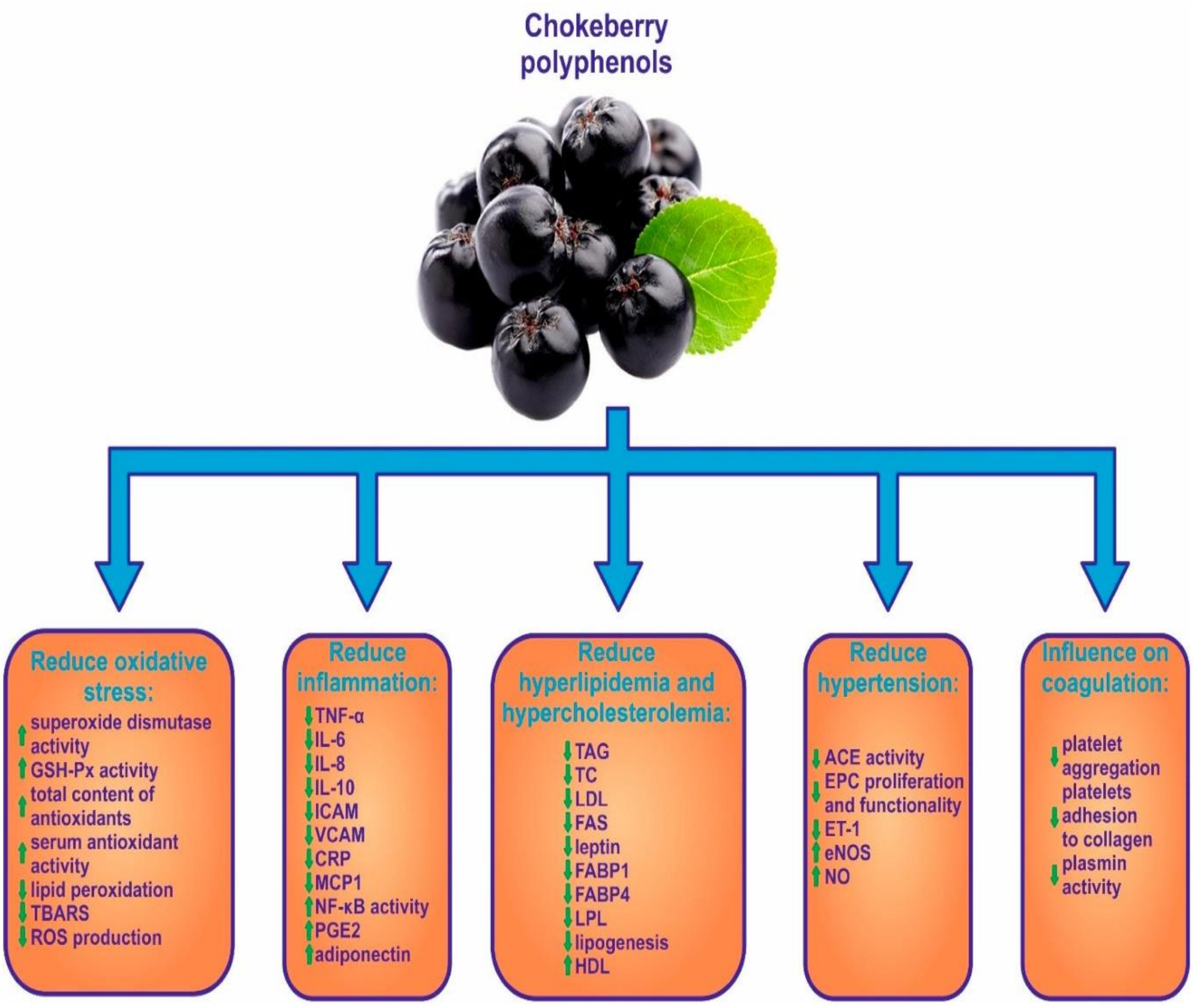

Figure 3: Pharmacological actions of *Aronia melanocarpa* [106].

Conclusion: The rapid spread of type 2 diabetes has highlighted the necessity of new preventive and treatment approaches just as the utilization of Black chokeberry has come under the spotlight. Black chokeberry, the main factor behind the marked improvement in glycose, regulation along with metabolic health, among others, is the natural polyphenolic profile of the chokeberry which is characteristically rich in phytochemicals. The same compounds have not only inhibited enzymes that promote the digestion of carbohydrates but also facilitated insulin sensitivity besides oxidative stress reduction and regulation of inflammatory pathways.

In clinical and experimental studies, the main outcomes related to the control of blood glucose, the lipid profile, and the protection of pancreatic β-cells were reported after the supplementation with the chokeberry. In addition, the lowering of triglycerides and LDL cholesterol together with the rise in HDL cholesterol have contributed to the hypothesis that the chokeberry may have a role in the reduction of cardiovascular risk in diabetics. Though quite positive, the differences in dosage, bioavailability, and study design have posed a problem in setting up unified clinical guidelines. As a result, more studies are needed to standardize extracts, conduct long-term clinical trials, and investigate gut microbiota interactions. According to available studies, we can say that black chokeberry is not an enemy but a friend of type 2 diabetes.

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Acknowledgements: The author is especially grateful for the academic support and resources that made this work possible.
Conflict of interest: The authors declare the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Ethical issues: The authors completely observed ethical issues, including plagiarism, informed consent, data fabrication or falsification, and double publication or submission.
Data availability statement: The raw data that support the findings of this article are available from the corresponding author upon reasonable request.
Author declarations: The authors confirm that they have followed all relevant ethical guidelines and obtained any necessary IRB and/or ethics committee approvals.
Generative AI disclosure: No Generative AI was used in the preparation of this manuscript.