Chapter 8

Beneficial Effects of Anthocyanin From Natural Products on Lifestyle-Related Diseases Through Inhibition of Protease Activities

Takuya Yamane[1]
Osaka Prefecture University, Sakai, Japan
[1]*Corresponding author: e-mail: tyt29194@osakafu-u.ac.jp*

Chapter Outline

INTRODUCTION

Intervention roles of enzyme inhibitors from natural products toward lifestyle-related diseases are known to be very important in the functional food area. Anthocyanins are one of the natural enzyme inhibitors. Anthocyanins are present in fruits and vegetables such as berries, grapes, cherries, aubergine, and onions. As shown in Fig. 8.1, anthocyanins are also categorized in glycosylated anthocyanidins. Although glycosylation often occurs on the hydroxyl group at the C3 position, 3,5-glycosylated and 3,7-glycosylated derivatives have also been identified [1]. Anthocyanins are present in foods of plant origin [2]. Chokeberry, elderberry, and purple corn contain very rich anthocyanin, and their contents are 410–1480, 664–1816, and 1642 mg/100 g, respectively (Table 8.1). The dietary intake and health effects of anthocyanins have been reviewed, and anthocyanin amount in human dietary sources is shown in Table 8.2 [33]. The amount of cyanidin-3-glucoside and cyanidin-3-galactoside is 794.1 and 557.7 g/100 g, respectively. Anthocyanins

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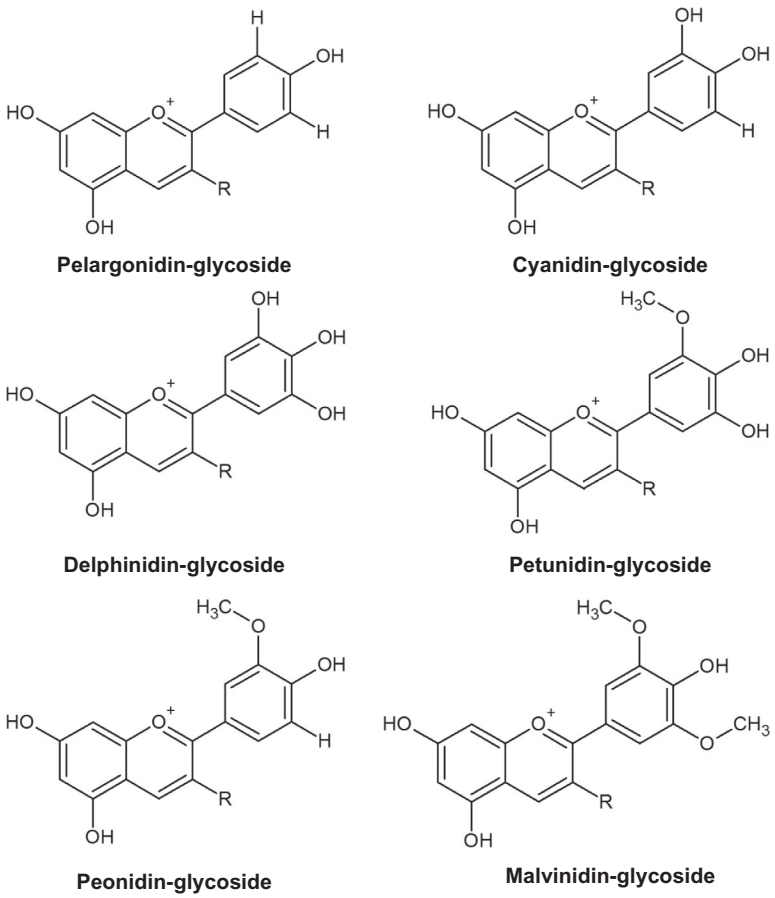

FIG. 8.1 Chemical structure of anthocyanins. R is one of the potential sugar binding sites in the chemical structure of anthocyanins.

have multiple effects on health such as the beneficial effect on various diseases (Table 8.3). Proteases inhibitors derived from natural products have beneficial effects on lifestyle-related diseases such as diabetes and hypertension. Angiotensin-converting enzyme (ACE) inhibitors are also contained in natural products and reduce the blood pressure level in hypertension patients through inhibiting conversion to angiotensin II. ACE is a zinc-containing peptidyl peptidase and is secreted from the lung and kidney. Angiotensin I is converted to angiotensin II by ACE. ACE activity is also inhibited by anthocyanins delphinidin- and cyanidin-3-O-sambubiosides from *Hibiscus sabdariffa* [38]. Dipeptidyl peptidase IV (DPP IV) inhibitors contained in natural products reduce the blood glucose level in diabetes patients through inhibiting degradation of incretins glucagon-like peptide-1 (GLP-1) and

TABLE 8.1 Anthocyanin Contents in Foods of Plant Origin

Fruit	Content (mg/100 g)	References
Apple	0.0–60.0	[3,4]
Bilberry	300–698	[3,5]
Black bean	24.1–44.5	[6]
Blackcurrant	130–476	[7,8]
Black olives	42–228	[5]
Black rice	10–493	[9]
Blackberry	82.5–325.9	[10,11]
Blueberry	61.8–299.6	[12,13]
Bog whortleberry	154	[3]
Cherry	2–450	[5,14]
Chokeberry	410–1480	[3,8]
Cranberry	67–140	[3,8]
Crowberry	360	[12]
Eggplant	8–85	[3,8]
Elderberry	664–1816	[15]
Goji	49.4	[16]
Gooseberry	2.0–43.3	[8,17]
Grapefruit	5.9	[3]
Lettuce	2.5–5.2	[3,8]
Nectarine	2.4	[3]
Peach	4.2	[3]
Pear	5–10	[5]
Plum	2–25	[8]
Pomegranate	81.5–776	[18]
Purple corn	1642	[19]
Raspberry	20–687	[8,11]
Red cabbage	322	[8]
Redcurrant	22	[3]
Red grape	30–750	[20]
Red onion, processed	23.3–48.5	[8,21]

Continued

TABLE 8.1 Anthocyanin Contents in Foods of Plant Origin—Cont'd

Fruit	Content (mg/100 g)	References
Red radish	100–154	[8,22]
Rhubarb	4–200	[3]
Rowanberry	14	[3]
Saskatoon berry	234	[3]
Strawberry	19–55	[23]

Modified from S. de Pascual-Teresa, D.A. Moreno, C. García-Viguera, Flavanols and anthocyanins in cardiovascular health: a review of current evidence, Int. J. Mol. Sci. 11 (2010) 1679–1703.

TABLE 8.2 Principal Anthocyanins in Human Dietary Sources

Compounds	Amount (g/100 g FW)	Sources	References
Malvidin-3-glucoside	10.0	Red wine	[24]
	39.3	Black grapes	[24]
Cyanidin-3-glucoside	794.1	Elderberries	[25]
	405.0	Bilberries	[24]
	138.7	Blackberries	[26]
	25.1	Blackcurrants	[27]
	3.5	Blood orange	[28]
	0.7	Strawberry	[28]
	0.4	Red onion	[28]
Cyanidin 3-(6″-malonylglucoside)	1.6	Red onion	[29]
	15.0	Blood orange	[30]
Cyanidin-3-galactoside	557.7	Chokeberries	[26]
	370.0	Bilberries	[24]
	5.9	Pistachio	[31]
Cyanidin-3-rutinoside	160.8	Blackcurrants	[24]
	8.9	Blackberries	[24]
Cyanidin-3-arabinoside	252.8	Chokeberries	[24]

TABLE 8.2 Principal Anthocyanins in Human Dietary Sources—Cont'd

Compounds	Amount (g/100 g FW)	Sources	References
Cyanidin-3,5-diglucoside	24–236	Pomegranate juices	[18]
	30.0	Red cabbage	[32]
Cyanidin 3-(sinapoyl)-diglucoside-5-glucoside	31.0	Red cabbage	[32]
Cyanidin 3-(sinapoyl) (sinapoyl)-diglucoside-5-glucoside	28.0	Red cabbage	[32]
Cyanidin 3-(*p*-coumaroyl)-diglucoside-5-glucoside	25.0	Red cabbage	[32]
Peonidin-3-glucoside	365.0	Blueberries	[26]
Delphinidin-3-rutinoside	304.9	Blackcurrants	[24]
Delphinidin-3-glucoside	86.7	Blackcurrants	[24]
	5.0–104.0	Pomegranate juices	[18]
Delphinidin 3,5-diglucoside	37.0–530.0	Pomegranate juices	[18]
Pelargonidin-3-glucoside	47.2	Chokeberries	[25]
	15.9		[24]
Pelargonidin-3-rutinoside	3.6	Strawberry	[25]
Pelargonidin 3,5-diglucoside	0.7–9.0	Pomegranate juices	[18]

Modified from F. Ferreres, M.I. Gil, F.A. Tomas-Barberan, Anthocyanins and flavonoids from shredded red onion and changes during storage in perforated films, Food Res. Int. 29 (1996) 389–395.

gastric inhibitory polypeptide (GIP). DPP IV inhibitors have been discovered from natural products [39]. DPP IV activity is inhibited by anthocyanin such as cyanidin-3,5-O-diglucoside extracted from *Aronia melanocarpa* [40]. Thus, anthocyanins, which are contained in natural products, inhibit protease activities, leading to amelioration of lifestyle-related diseases. The objective in the chapter gives an overview of beneficial effects of anthocyanin on lifestyle-related diseases through inhibition of protease activities.

TABLE 8.3 Beneficial Effects of Anthocyanins on Lifestyle-Related Diseases

Life-Style Related Disease	Effects of Anthocyanins	References
Vision	Improvement of vision health	[34]
Type 2 diabetes	Prevention of type 2 diabetes and reduction of elevation for postprandial blood glucose level	[35]
Nonalcoholic fatty liver disease (NAFLD)	A 12-week supplement of purified anthocyanin improved insulin resistance, indicators of liver injury, and clinical evolution of NAFLD	[36]
Cardiovascular disease	Reduction of risk factors and prevention of cardiovascular health problems	[2]
Cancer	Anticancer in vitro and in vivo and improvement of life quality for cancer patients	[37]

BENEFICIAL EFFECTS OF ANTHOCYANINS ON HYPERTENSION AND CARDIOVASCULAR DISEASE

The renin–angiotensin–aldosterone system is one of the most important systems for the regulation of blood pressure (Fig. 8.2). Angiotensin I is cleaved at the C-terminal region, producing angiotensin II. Angiotensin II induces elevation of the blood pressure through various pathways. ACE inhibitors inhibit its activity and reduce angiotensin II levels in the blood, resulting in the reduction of the blood pressure level (Fig. 8.2). ACE-inhibitory activity has already been demonstrated in some compounds derived from plants such as flavonoids [41], terpenoids [42], peptides [43], and procyanidins [44].

ACE is a zinc-containing peptidyl dipeptidase. ACE-inhibitory activity of flavonoids is also carried out by generation of chelate complexes with the active center of ACE [45,46]. ACE-inhibitory activity of anthocyanins has been shown in *H. sabdariffa* [47–49]. *H. sabdariffa*, a traditional Chinese rose tea, has been used for treatment of hypertension. *H. sabdariffa* contains anthocyanins, including delphinidin-3-O-glucoside and delphinidin-3-O-sambubioside [38] (Fig. 8.3). Delphinidin-3-O-sambubioside and cyanidin-3-O-sambubioside are not detected in the plasma and urine of participants taking hibiscus tea [49]. These anthocyanins are degraded to anthocyanidins and further degraded to phenolic acids [50]. Anthocyanins are bioavailable as other flavonoid subclasses, including flavones and flavan-3-ols [51,52].

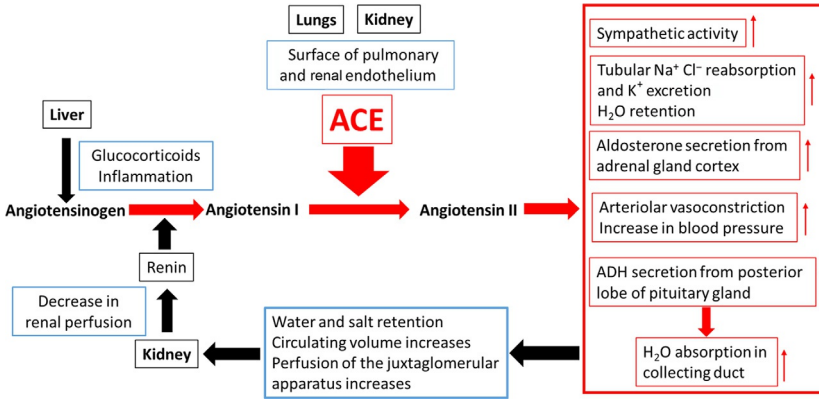

FIG. 8.2 Renin–angiotensin–aldosterone system.

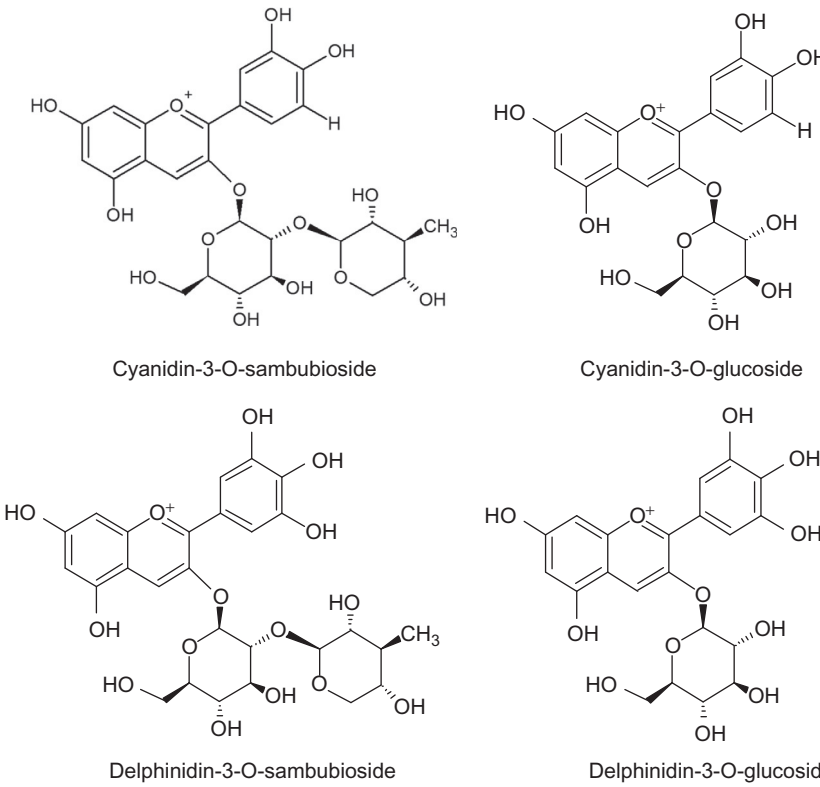

FIG. 8.3 Chemical structure of anthocyanins as ACE inhibitors from *Hibiscus sabdariffa*.

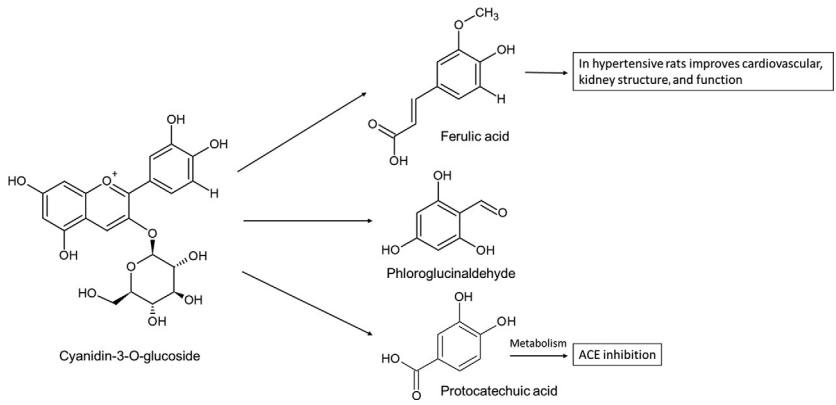

FIG. 8.4 Cyanidin-3-O-glucoside metabolites and antihypertensive functions.

Anthocyanin metabolites are bioactive at physiologically relevant concentrations [53]. Cyanidin-3-O-glucoside metabolites have been found to be protocatechuic acid, phloroglucinaldehyde, and ferulic acid [54] (Fig. 8.4). Ferulic acid has been shown to improve both endothelium-dependent relaxation and antioxidant status in hypertensive rats [55]. As shown in Table 8.4, protocatechuic acid is widely distributed in foods, including apple [58], blackberries [61], nipa palm nut [72], kiwi fruit [66], currents [73], blackberries and strawberries [74], jujube fruits [75], chokeberries [76], and olive oil [70]. Anthocyanin metabolites, including phenolic acids, have hypertensive and protective effects on maintaining vascular endothelial function, including the ACE-inhibitory effect [77].

Anthocyanins with inhibiting ACE activity include delphinidin-3-O-glucoside, cyanidin-3-O-glucoside, pelargonidin-3-O-glucoside, malvidin-3-O-glucoside, and peonidin-3-O-glucoside [78] (Fig. 8.5). Flavonol glycoside and phenolic acids have lower inhibitory activities against ACE than do anthocyanins [38,78]. IC_{50} values of these anthocyanins are shown in Table 8.5, and the strongest inhibitor of ACE activity in anthocyanin is delphinidin-3-O-glucoside ($IC_{50} = 65.4 \pm 4.0\ \mu M$). The production level of angiotensin 1–7 (Ang 1–7) heptapeptide is reduced by inhibition of ACE activity. Mas receptor-mediated vasodilation is decreased by reduction of Ang 1–7 production, and therefore the essential role of Ang 1–7 in hypertension is to modulate renal flow by prompting vasodilation and counterbalancing Ang II-induced vasoconstriction [79]. Inhibition of ACE activity also increases the bioavailability of bradykinin (BK), leading to reduction of BK degradation by ACE inhibitors [80].

Many kinds of anthocyanins have ACE inhibitory activities. Since these anthocyanins are included in many plants and foods, the prevention effect of these anthocyanins on hypertension has been expected. Elevated blood pressure plays a significant role in the pathogenesis of cardiovascular

TABLE 8.4 Food Sources of Protocatechuic Acid [56]

Source	Content	References
Açai pulp	11.7 µmol/L	[57]
Apple	31 µmol/kg	[58]
Avocado	2.4 µmol/kg	[59]
Beer	3 µmol/L	[60]
Bilberries	111 µmol/kg	[61]
Bitter melon, ripe	970 µmol/kg	[62]
Blackberries	127 µmol/kg	[61]
Blueberries, *Vaccinium arctostaphylos L.*	9.5 µmol/kg	[63]
Buckwheat, whole grain	600 µmol/kg	[64]
Currants, black	78 µmol/kg 357 µmol/kg	[61] [58]
Garlic	23 µmol/kg	[65]
Gooseberry	405 µmol/kg	[58]
Grapes, white	22 µmol/kg	[58]
Honeysuckle, blueberries	140 µmol/kg	[61]
Juneberries, European	159 µmol/kg	[61]
Kiwi juice	39 µmol/L	[66]
Lingonberries	195 µmol/kg	[67]
Mango pulp	2.5 µmol/kg	[59]
Mangosteen pulp	91 µmol/kg	[68]
Medlar, ripe	6 µmol/kg	[69]
Mulberries, black	119 µmol/kg	[61]
Oil, Açai—phenol rich	4 µmol/mL	[57]
Oil, olive—virgin	3–11.5 µmol/kg	[70]
Onion, red	50 µmol/kg	[65]
Onion, white	1.2 µmol/kg	[65]
Pear	3 µmol/kg	[58]
Raspberry	270 µmol/kg	[58]
Strawberry	112 µmol/kg	[58]
Wine, red	0.3–0.8 µmol/L	[71]
Wine, white	0.1–0.5 µmol/L	[71]

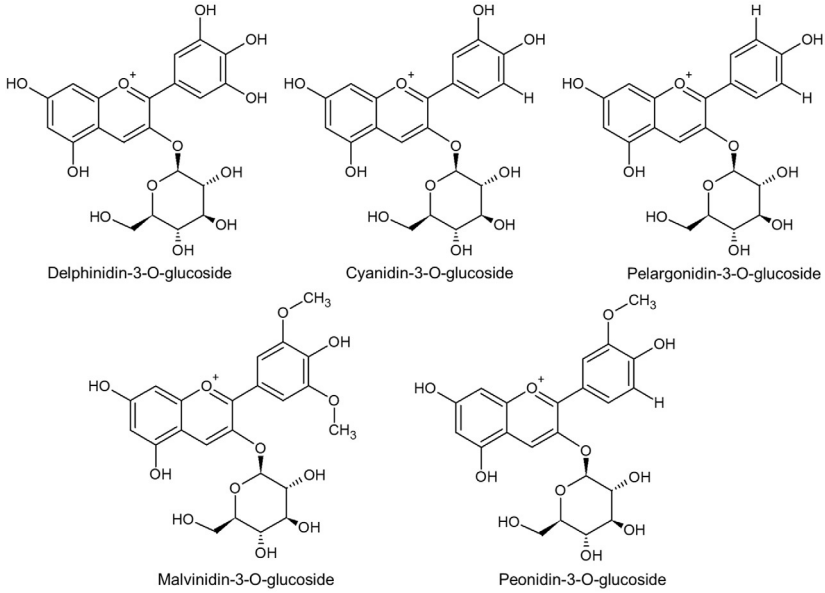

FIG. 8.5 Chemical structures of anthocyanins as ACE inhibitors.

TABLE 8.5 IC_{50} Values of Anthocyanins and Phenolic Acids as ACE Inhibitors

Inhibitor	IC_{50} (μM)	References
Gallic acid	332.4 ± 40.1	[78]
Caffeic acid	157.3 ± 16.1	[78]
Coumaric acid	504.2 ± 31.5	[78]
Malvidin-3-O-glucoside	83.9 ± 5.1	[78]
Delphinidin-3-O-glucoside	65.4 ± 4.0	[78]
Cyanidin-3-O-glucoside	70.8 ± 2.0	[78]
Pelargonidin-3-O-glucoside	77.7 ± 2.3	[78]
Peonidin-3-O-glucoside	104.6 ± 5.8	[78]
Delphinidin-3-O-sambubioside	141.61 ± 0.003	[38]
Cyanidin-3-O-sambubioside	117.75 ± 0.004	[38]

disease (CVD). CVD is the number one cause of death worldwide according to reports from the World Health Organization (WHO). The WHO predicts that by 2030, over 28 million individuals will die from CVD annually [81]. In previous studies, beneficial effects of anthocyanin on hypertension and CVD have been shown. Shaughnessy et al. reported that treatment of spontaneously hypertensive stroke-prone rats (SHRs) with blueberry-enriched diet inhibits systolic blood pressure and suggested that blueberry-enriched diet is used for prevention of hypertension and CVD [82]. Other studies using SHRs are shown in Table 8.6. In human study, blood pressure is significantly reduced in blueberry-treated patients [86]. Since SHRs are hypertension model rats resembling phenotypes of human hypertension, inhibition of conversion from angiotensin I to angiotensin II by ACE inhibitors leads to amelioration of hypertension in SHRs. Furthermore, blood pressure and some CVD markers, including 8-isoprostanes, oxLDL, high-sensitivity C-reactive protein (hsCRP), and monocyte chemostatic protein 1 (MCP-1), are decreased after survival of myocardial infarction patients who were treated with chokeberry (*A. melanocarpa*) extract [87]. Systematic reviews regarding effects of anthocyanins show that berries, vegetables, parts of plants, juice, or purified anthocyanin-rich extracts have intervention effects against CVDs in human studies and animal models, demonstrating significant improvements in LDL oxidation, VLDL, CRP, and blood pressure [88]. However, to adequately determine supplementation effects of these food and their extracts, more careful trials with controlled longer duration assessing a dose–response across various populations are needed [89].

TABLE 8.6 Effects of Anthocyanins on Cardiovascular Disease in Spontaneously Hypertensive Stroke-Prone Rats

Source of Anthocyanins	Effects	References
Blueberry extract	Blueberry-fed rats reduce markers of renal oxidative stress such as proteinuria and kidney nitrites	[82]
Black and green tea	Both black and green tea polyphenols attenuate blood pressure increases	[83]
Rice bran	Rice bran fractions appear to have beneficial dietary components that improve hypertension, hyperlipidemia, and hyperglycemia	[84]
Oak bark extract	Oak bark extract containing ellagitannins improves cardiovascular, metabolic, and liver parameters	[85]

BENEFICIAL EFFECTS OF ANTHOCYANINS ON TYPE 2 DIABETES AND OBESITY

Anthocyanins have beneficial effects on type 2 diabetes and obesity in animals and humans through inhibition of body weight gain and improvement of insulin resistance. Dietary cyanidin-3-O-glucoside-rich purple corn color prevents obesity and ameliorates hyperglycemia in mice fed a high-fat diet (HFD) [90]. Both HFD-induced body weight gain and fat accumulation in white and brown adipose tissues are reduced and obesity is prevented in mice by supplementation of anthocyanin extracts from blackberries, blueberries, and blood orange [91–94]. The beneficial effects of anthocyanins on weight gain are shown in Table 8.7.

On the other hand, the improvement of insulin resistance is also important in preventing the development of type 2 diabetes and the insulin resistance-related obesity. Improvement effects of anthocyanins on insulin resistance in animals are shown in Table 8.8.

TABLE 8.7 Beneficial Effects of Anthocyanins on Weight Gain

Anthocyanins	Animal Models	References
Cyanidin-3-O-glucoside-rich purple corn color (2 g/kg diet)	C57BL/6J mice fed an HFD for 12 weeks	[90]
Anthocyanin extracts from blueberries	C57BL/6J mice fed an HFD for 72 days	[91]
Anthocyanin extracts from blueberries	C57BL/6 mice fed an HFD for 12 weeks	[92]
Anthocyanin extracts from mulberries	C57BL/6 mice fed an HFD for 12 weeks	[93]
Anthocyanin extracts from blood oranges	C57BL/6 mice fed an HFD for 12 weeks	[94]
Cyanidin-3-O-glucoside-rich from honeysuckle	C57BL/6 mice fed an HFD for 8 weeks	[95]
Cyanidin-3-O-glucoside-rich blackberries	Ovariectomized rats	[96]
Anthocyanin extracts from black soybean	Sprague–Dawley rats	[97]
Anthocyanins from aronia berries	C57BL/6 mice fed an HFD for 4 weeks	[98]
Anthocyanins from aronia juice	KK-A^y diabetic mice	[99]

TABLE 8.8 Improvement Effects of Anthocyanins on Insulin Resistance in Animals

Anthocyanins	Animal Models	Evidence	References
Anthocyanins from black soybean seed coat extract	KK-A^y diabetic mice with 1 g/kg	Significantly induced AMPK activation and glucose uptake	[100]
Anthocyanin-rich black rice extract	High-fructose diet-fed mice with 5 g/kg	Preventing and ameliorating the hyperlipidemia and insulin resistance	[101]
Cyanidin-3-O-glucoside	High-fat diet-induced obese mice	Modulating the c-Jun N-terminal kinase/forkhead box O1 signaling pathway and the related inflammatory adipocytokines	[102]
	Genetically diabetic db/db mice with 2 g/kg diet for 5 weeks		
Cyanidin-3-O-glucoside	KK-A^y diabetic mice with 2 g/kg	The regulation of Glut4–RBP4 system and the related inflammatory adipocytokines	[103]
Black soybean anthocyanins	STZ-induced diabetic rats	Regulation of glucose transporter 4	[104]

Furthermore, antimetabolic syndrome potentials of anthocyanins in clinical trials are shown in Table 8.9 [117].

DPP IV is a protease that regulates blood glucose levels via degradation of incretins. DPP IV inhibitors have been reported as peptide inhibitors and medicines for therapeutics of type 2 diabetes. Polyphenols also inhibit DPP IV activities and reduce blood glucose levels. Anthocyanins, its aglycons (anthocyanidins), and related flavonol and phenolic acids inhibit DPP IV activity [39]. IC_{50}, K_i values, and binding energy of DPP IV inhibitory activities by anthocyanins and anthocyanidins are shown in Table 8.10. One of anthocyanin cyanidin-3-O-glucoside inhibits DPP IV activity [39].

Cyanidin-3,5-diglucoside from aronia juice also inhibits DPP IV activity [40]. Chemical structure of cyanidin-3,5-diglucoside is shown in Fig. 8.6.

Some anthocyanins such as cyanidin-3-O-galactoside, cyanidin-3-O-arabinoside, cyanidin-3-O-glucoside, cyanidin-3-O-xyloside, pelargonidin-3-O-galactoside, and pelargonidin-3-O-arabinoside are included in aronia

TABLE 8.9 Antimetabolic Syndrome Potentials of Anthocyanins in Clinical Trials

Subjects (Numbers)	Study Design	Intervention Duration	Evidence	References
Diabetic patients ($n=33$)	Case–control study	2 months	Reduction of serum free radical levels	[105]
Healthy volunteers ($n=28$)				
Diabetic patients ($n=19$)	Cross reference	6 weeks	Reduction of body weight, blood pressure and HbA1c	[106]
Women with metabolic syndrome ($n=16$)	Cross reference	4 weeks	Reduction of lipid peroxidation	[107]
Adults with metabolic syndrome ($n=44$)	Randomized, controlled study	8 weeks	Reduction of oxidized LDL	[86]
Obese adults ($n=16$)	Randomized, controlled study	4 weeks	Improvement of LDL, blood pressure and C-reactive protein	[108]
Adults with metabolic syndrome ($n=44$)	Randomized, controlled study	8 weeks	Reduction of serum hsCRP, IL-6, IL-12, and LPS concentration	[109]
Overweight men ($n=18$)	Randomized, controlled, crossover study	8 weeks	Increased the resistance to oxidatively induced DNA damage	[110]
Young adults with features of nonalcoholic fatty liver disease ($n=44$)	Randomized, controlled, crossover study	4 weeks	Improvement of the plasma antioxidant status and inhibiting the inflammatory and apoptotic responses	[111]
Obese adults with hyperlipidemia ($n=80$)	Randomized, controlled study	2 months	Improvement of lipid profile	[112]
Overweight adults with hyperlipidemia ($n=120$)	Randomized, double-blind, controlled study	12 weeks	Improvement of LDL- and HDL-cholesterol concentrations	[113]
Overweight adults with hypercholesterolemia ($n=150$)	Randomized, double-blind, controlled study	24 weeks	Improvement in the serum lipid profile and reduction of the inflammatory response	[114–116]

TABLE 8.10 DPP IV Inhibitory Activities and Binding Energy by Anthocyanins and Anthocyanidins [39]

Anthocyanins	IC_{50} (μM)	K_i (μM)	Binding Energy (kcal/mol)
Cyanidin	1.41 ± 0.25	43.43	−5.95
Cyanidin-3-glucoside	0.42 ± 0.09	22.23	−6.35
Malvidin	1.41 ± 0.44	21.64	−6.36

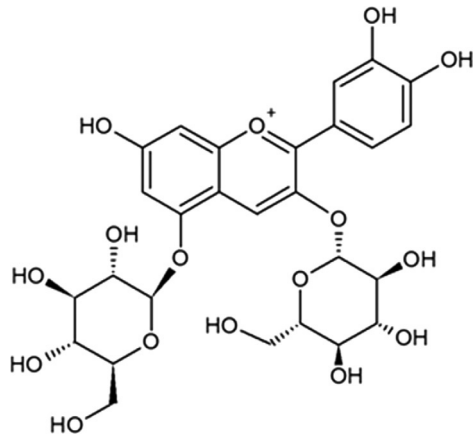

FIG. 8.6 Chemical structure of cyanidin-3,5-diglucoside.

juice [118]. The blood glucose levels are reduced in aronia juice-administered KK-Ay obesity and type 2 diabetes mouse models through inhibition of DPP IV activity in the small intestine [99]. Thus, various kinds of anthocyanins inhibit DPP IV activities. DPP IV inhibitory mechanisms of these anthocyanins will be revealed in future studies.

CONCLUDING REMARKS

Anthocyanins have beneficial effects on lifestyle-related diseases. Anthocyanins inhibit protease activities such as ACE and DPP IV. ACE inhibitors such as anthocyanins inhibit ACE-induced degradation of angiotensin I, leading to reduction of elevation of blood pressure and hypertension. Elevation of blood glucose levels and hyperglycemia are prevented by DPP IV inhibitors such as anthocyanins. Degradation of incretins is reduced by DPP IV inhibitory activities of anthocyanins. Furthermore, prevention of hypertension and

hyperglycemia by anthocyanin consumption also prevents the onset of CVD and obesity. In addition, since anthocyanins are abundantly included in berries, intake of anthocyanin-rich berries as a part of diet is very important for prevention of lifestyle-related diseases.

ABBREVIATIONS

ACE	angiotensin-converting enzyme
ADH	antidiuretic hormone
CVD	cardiovascular disease
DPP IV	dipeptidyl peptidase IV
GIP	gastric inhibitory polypeptide
GLP-1	glucagon-like peptide-1
HFD	high-fat diet
hsCRP	high-sensitivity C-reactive protein
MCP-1	monocyte chemotactic protein 1
NAFLD	nonalcoholic fatty liver disease
oxLDL	oxidized low-density lipoprotein
WHO	World Health Organization

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