Structure and Physiological Activities of Anthocyanins

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Anthocyanidin is a kind of water-soluble natural pigment that widely exists in natural plants. Like other natural flavonoids, anthocyanin has a C6-C3-C6 carbon skeleton. Due to the different carbon substituents (-OH, -OCH3) on the B ring, different types of anthocyanins were derived. The six common anthocyanins were Pelargonidin (Pg), Cyanidin (Cy), Delphinidin (Dp), Peonidin (Pn), Petunidin (Pt), and Malvidin (Mv). In addition to giving food a variety of bright colors, anthocyanin also has important biological activities, such as antioxidant, anti-inflammatory, and anti-aging effects, among others. A large number of studies have shown that dietary anthocyanins have a good preventive effect on cardiovascular diseases.

anthocyanin | gut microbiota | vascular endothelial cells senescence | clearance of senescence cells | cardioprotection

1. Structure of Anthocyanin

Anthocyanin is a water-soluble flavanol compound that widely exists in fruits, vegetables, and flowers, such as blueberry, sunflower, grape, pitaya, purple sweet potato, and purple cabbage. It is an extremely important secondary metabolite in plants. The structure of anthocyanin is mainly composed of C6-C3-C6 as the basic C skeleton. The differences between anthocyanin molecules are mainly due to the number of hydroxyl groups, the type and bonding position of sugars, and the type and bonding position of acyl groups of modified sugar molecules. There are six kinds of anthocyanins in plants. When positions 3, 5, and 7 of a and C rings are Oh, anthocyanins are aglycones, mainly including delphinidin (12%), cyanidin (50%), pelargonidin (12%), petunidin (7%), malvidin (7%), and peonidin (12%) (**Figure 1** and **Table 1**). Delphinidin and its derivatives, petunidin and malvidin, are the sources of blue and purple, while cyanidin and pelargonidin are the main pigments of bright red fruits. Under natural conditions, the free anthocyanin is unstable, so it is rare that anthocyanin mainly exists in the form of glycoside. The hydroxyl at positions 3, 5, and 7 of anthocyanin can form anthocyanin through glycosidic bond with one or more monosaccharides (glucose, galactose, etc.), disaccharides (rutinose, etc.), or trisaccharides. Due to the different types, positions, and quantities of sugars that are glycosides of anthocyanin, the types of anthocyanin formed are also different. At present, there are more than 250 known natural anthocyanins.

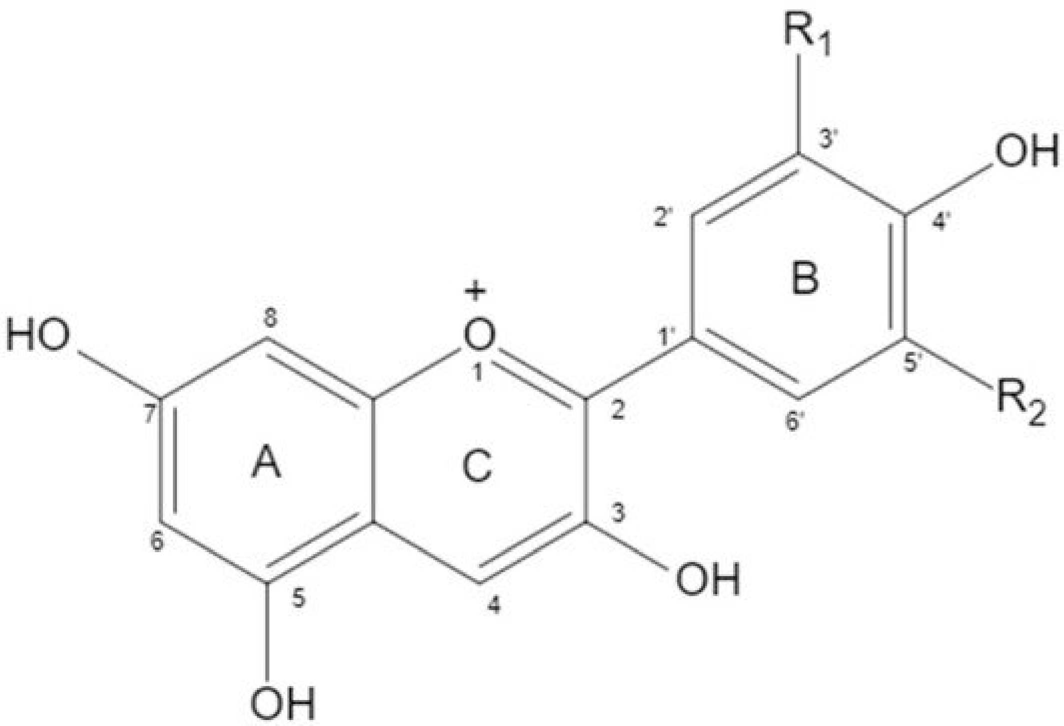

Figure 1. Chemical structure of anthocyanins.

Table 1. Chemical structure of anthocyanins.

Anthocyanin	Proportion	Substituents	
		R_1	R_2
Cyanidin	50%	OH	H
Delphindin	12%	OH	OH
Pelargonidin	12%	H	H
Peonidin	12%	OCH_3	H
Petunidin	7%	OCH_3	OH
Malvidin	7%	OCH_3	OCH_3

2. Physiological Activities of Anthocyanins

2.1. Anti-Cancer

Cancer is a disease caused by uncontrolled growth and progressive development of abnormal cells, killing millions of people every year. By 2030, there will be more than 20 million new cancer cases. Anthocyanins have been shown to have the ability to inhibit the initiation, promotion, and progression of various cancers, such as colon cancer [1], liver and bladder cancer [2], breast cancer [3], brain cancer [4], kidney cancer and skin cancer [5], gastric cancer [6], and thyroid cancer [7]. The ability of anthocyanins to inhibit tumorigenesis and development is closely related to their ability to enhance antioxidant defense; exert anti-inflammatory effects; and interfere with ERK, JNK, PI3K/Akt, MAPK, and NF-κB signaling pathways. Yun et al. reported that purple grape anthocyanins prevented tumor-necrosis-factor-α-induced NF-κB activation by inhibiting IκBα phosphorylation and resisted the invasion of human colon cancer cells in a dose-dependent manner [8]. Fragoso et al. proved through experiments that cyanidin-3-O-rutinoside at 25 μmol/L can effectively reduce the motility of human colon adenocarcinoma cells, reduce the metastasis of cancer cells, and play an anticancer effect [9]. Mazewski et al. reported that anthocyanins extracted from purple and red maize enhanced the expression of apoptotic factors BAX, Bcl-2, cytochrome C, and TRAILR2/D5 and inhibited vascular endothelial growth factor in HCT-116 and HT-29 human colorectal cancer cell (Tie-2, ANGPT2, and PLG) expression to achieve anti-cancer efficacy [10]. The results of Lage et al. showed that black sweet cherry anthocyanins can inhibit the growth of breast cancer cells and have no toxicity to normal MCF-10A breast cells. Anthocyanins work against cancer by reducing oxidative stress, regulation of Akt/mTOR, p38, and survivin, preventing cancer cell proliferation and promoting apoptosis. Anthocyanins can significantly downregulate the mRNA expression of invasive/metastatic biomarkers (Sp1, Sp4, VCAM-1), and anthocyanins from black sweet cherry can effectively prevent and treat cancer [3]. Su et al. reported that hibiscus calyx anthocyanin could inhibit the growth, metastasis, and angiogenesis of B16-F1 cells by triggering PI3K/Akt and Ras/MAPK signaling pathways and downregulating the expression of VEGF and MMP-2/-9, which could effectively prevent and treat melanoma cancer [11]. Sugata et al. found that purple sweet potato anthocyanin blocked all stages of cell cycle by acting on cell cycle regulators (such as p53, p21, p27, Cyclin D1, and Cyclin A), thereby inhibiting the proliferation of breast cancer, colon cancer, and gastric cancer cells in a concentration- and time-dependent manner [12].

2.2. Anti-Inflammatory

Inflammation is usually regulated by the body to secrete inflammatory cytokines and mediators. Therefore, it is generally believed that the downregulation of factor secretion may contribute to the treatment of diseases such as inflammation [13]. Epidemiology and research have shown that anthocyanin has an anti-inflammatory effect and can improve a variety of inflammation-related diseases, such as colitis [14], periodontitis, pharyngitis, and postprandial inflammatory response. Anthocyanin can change the redox state of cells and affect redox-sensitive inflammatory mediators through Nrf2-ARE signal modulation [15]. Hou et al. showed that anthocyanin inhibited COX-2 by inhibiting C/EBP, AP-1, and NF-κB, thereby reducing the production of pro-inflammatory cytokines IL-1β, IL-6, IL-8, and TNF-α [16]. Min et al. found that cyanidin-3-glucoside showed an effective anti-inflammatory effect by regulating NF-κB and MAPK activity [17]. Studies have shown that fenugreein can inhibit HcPT degradation, p65 nuclear translocation, and JNK phosphorylation, showing an indigenous anti-inflammatory activity [18]. In general, B-ring o-dihydroxyphenyl anthocyanin, such as fayashinin and cyanidin, has strong anti-inflammatory activity, while geranium pigment, peony pigment, and kumquat pigment do not show the above activity without o-dihydroxy structure [19]. Aboonabi et al. showed that 320 mg anthocyanidin daily intake in people with metabolic syndrome can significantly inhibit the expression of NF-κB-pathway-related proinflammatory factor genes and enhance the expression of *PPAR-γ* gene to reduce the risk of inflammation [20]. Duarte et al. showed that geranium pigment-3-O-glucoside in strawberry could inhibit the activation of IkB-α and reduce the phosphorylation of JNK-MAPK, leading to the decrease in NF-κB and AP-1 activation factors in the inflammatory pathway stimulated by TLR4, indicating that geranium pigment-3-O-glucoside had an anti-inflammatory effect [21]. The study of Karnarathne and other studies have shown that anthocyanin from *Hibiscus* can inhibit the secretion of nitric oxide and prostaglandin E2 in LPS-induced endotoxic shock zebrafish, while down-regulating the expression of inducible nitric oxide synthase and cyclooxygenase 2. Furthermore, LPS inhibited the production of pro-inflammatory cytokines such as TNF-α, IL-6 and IL-12 in RAW 264.7 macrophages. Anthocyanin also inhibits LPS-induced TLR4 dimerization or cell surface formation, thereby reducing MyD88 growth and IRAK4 phosphorylation, thereby inhibiting NF-κB activity [22].

2.3. Anti-Oxidation

Humans produce free radicals during metabolism. Excessive free radicals can lead to lipid, protein, DNA, RNA, and sugar oxidation, which is closely related to cancer, Alzheimer′s disease, Parkinson′s disease, autoimmune deficiency, diabetes, obesity, and other diseases. As a natural plant pigment, anthocyanin not only can be used as a colorant, but also has prominent antioxidant activity. Anthocyanins can scavenge reactive oxygen species (ROS) and reactive nitrogen (RNS), such as superoxide anion (O_2^-), singlet oxygen ($^1O_2$), peroxide free radical ($RCOO^·$), hydrogen peroxide, hydroxyl free radical ($OH^·$), and peroxynitrite anion ($ONOO^-$) [23]. The phenolic ring, hydroxyl side chain, and double bond in the glycosylation reaction of anthocyanin are helpful to scavenge free radicals. Compared with cyanidins and philoxerin, anthocyanin lacking O-phenyl structure in the B ring (sunflower pigment, geranium pigment, petunia pigment, and peony pigment) had low DPPH radical scavenging efficiency. Peonidin has methyl at 3′ position and OH at 4′ position, which is more active than pelargonidin. As reported by Fukumoto and Mazza, the hydroxyl at the third position of the B ring enhances the activity. Similarly, delphinidin with hydroxyl at 3′, 4′, and 5′ is more effective than cyanidin with hydroxyl at only 3′ and 4′ [24]. Harakotr et al. reported that the anthocyanin extract of purple corn had strong DPPH radical scavenging activity, and the anthocyanin content in the extract was positively correlated with antioxidant capacity [25]. Matera et al. reported that cyanidins in radish buds could significantly inhibit the automatic oxidation of linoleic acid and scavenge hydrogen-peroxide-free radicals [26]. Coklar et al. reported that anthocyanin extracts from *Mahonia aquifolium* (cyanidins, delphinidin, malvidin, peonidin, pelargonidin) had strong DPPH and ABTS radical scavenging ability and FRAP reduction ability [27]. Lu et al. fed D-galactose-induced aging mice black rice anthocyanin extract (cyanidin-3-O-glucoside). The activities of superoxide dismutase and catalase in mice were significantly improved, and the content of malondialdehyde and the activity of monoamine oxidase were reduced. Black rice anthocyanin extract showed a strong anti-aging effect in mice [28]. Huang et al. studied the antioxidant effect of main anthocyanins in blueberry on endothelial cells. The results showed that brocade pigment and its two glycosides decreased the levels of reactive oxygen species (ROS) and xanthine oxidase-1 (XO-1), but increased superoxide dismutase (SOD) and heme oxygenase-1 (HO-1). Moreover, the presence of glycoside greatly improved the antioxidant capacity of malvidin [29].

2.4. Protective Effect on the Liver

Daveri et al. fed high-fat diet mice with 40 mg anthocyanin/kg BW (cyanidins and delphinidins). The changes of chemokine MCP-1, cytokine TNF-α, macrophage marker F4/80, and enzyme NOS2 were measured. The results showed that anthocyanin played a role in preventing liver injury [30]. Jiang et al. showed that when carbon tetrachloride-induced liver injury mice were fed with cyanidin-3-O-glucoside 800 mg/kg BW, cyanidin-3-O-glucoside could significantly alleviate liver injury and prevent fibrosis in mice. Cyanidin-3-O-glucose can protect the liver by reducing liver oxidative stress, reducing liver cell apoptosis, inhibiting liver inflammatory response, and ultimately inhibiting the activation of liver star [31]. Arjinajarn et al. showed that the anthocyanin extract of riceberry bran could prevent gentamicin-induced liver injury in rats by inhibiting intracellular oxidative stress and the activation of NF-κB factor, reducing liver cell inflammation and apoptosis [32]. Zhang et al. found that purple sweet potato anthocyanin could effectively inhibit the production of reactive oxygen species in mice and inhibit the accumulation of liver fat induced by high-fat diet by activating adenosine-monophosphate-activated protein kinase (AMPK) signaling pathway [33]. Cai et al. studied the effects of different doses of purple sweet potato anthocyanin on the main liver function indexes, liver histological changes, and oxidation state of mice with alcoholic fatty liver, finding that medium dose of purple sweet potato anthocyanin had an obvious protective effect on the release of alanine aminotransferase (ALT) in the mice with liver injury [34].

2.5. Lowering Blood Glucose

Diabetes is a non-infectious endocrine metabolic disease that can lead to serious complications of various organs, and the number of patients with diabetes is increasing. Maintaining normal blood glucose level is a necessary condition for maintaining body function. In the human body, glucose homeostasis is controlled by various organs, including the pancreas, liver, and other tissues, as well as complex networks of hormones and neuropeptides. The pancreas plays a key role in glucose homeostasis by secreting hypoglycemic hormone insulin [35]. Purple corn anthocyanins have significant effects on β-cell function and insulin secretion, which can protect pancreatic β cells from high-glucose-induced oxidative stress and improve insulin secretion ability of β cells [36]. The liver is the main part of human body and plays a fundamental role in glycogen storage, plasma protein synthesis, and detoxification [37]. Studies have shown that anthocyanin-rich mulberry extract inhibits gluconeogenesis and stimulates glycogen synthesis by increasing AMPK phosphorylation in the liver [38].

2.6. Anti-Aging

Oxidative stress is one of the main inducing factors of aging, and excessive expression of inflammatory factors, DNA damage, and a series of inflammatory reactions activated by NLPR3 and NF-κB can also promote the aging of the body [39]. Many studies have shown that anthocyanin has an anti-aging effect. Jin et al. fed aged mice with anthocyanin from purple sweet potato and found that compared with the control group, anthocyanin from purple sweet potato could significantly reduce the serum MDA level and improve the activities of SOD and GSH-PX, and low-dose anthocyanin could achieve the same effect as the equivalent amount of vitamin, indicating that anthocyanin from purple sweet potato could play a role in delaying aging by improving antioxidant activity [40]. Wang et al. showed that Cy-3-glu and Pg-3-glu treatments could significantly inhibit the galactosidase in the aging process of human retinal pigment epithelium (RPE) cells induced by visible light irradiation and play a protective role in anti-aging [41]. Gao et al. found that Ribes meyeri anthocyanins can promote the proliferation of neural stem cells, improve cell senescence phenotype, reduce ROS and senescence-associated *P16Ink4a* gene expression levels, increase DNA synthesis, and prolong telomeres [42]. Wei et al. showed that anthocyanin could maintain the stability of the redox system in plasma and liver structure, as well as reduce the levels of inflammatory factors such as IL-1, IL-6, and TNF-α in the liver. At the same time, the decrease in the expression levels of sensors (ATM and ATR), media (H2AX and γ-H2AX), and effectors (Chk1, Chk2, p53 and p-p53) in the DNA damage signaling pathway indicate that anthocyanin can slow down aging by inhibiting DNA damage [43].

2.7. Other Effects

Qin et al. used purple sweet potato anthocyanin (PSPC 500 mg/kg/day) to orally take high-fat model mice. The results showed that PSPC corrected the abnormal metabolic indexes induced by HFD, including improving obesity, reducing fasting blood glucose concentration, and improving glucose tolerance [44]. Lee et al. found the effect of black soybean anthocyanin on obesity. The results showed that TC/HDLc/LDLc/HDLc of obese patients taking black soybean anthocyanin were significantly decreased [45]. Farrell et al. established a mouse model of hyperlipidemia and high-density lipoprotein dysfunction to explore and determine that an anthocyanin-rich blackcurrant extract (BEE) (13% anthocyanin) can prevent inflammation-related HDL functional damage and apolipoprotein E atherosclerosis. The results showed that the total cholesterol content in the aorta of mice was significantly decreased, and the aspartate aminotransferase (AST) and fasting blood glucose were decreased, indicating that blackberry may affect chronic inflammation-related HDL dysfunction by affecting liver gene expression [46]. In addition, studies have shown that purple sweet potato anthocyanin has a protective effect on the kidneys. Qun and other studies have found that purple sweet potato anthocyanin can significantly improve kidney injury in mice fed with high fat diet by reducing the production of AGEs and ROS and improving insulin sensitivity. Its protective effect is played by inhibiting the expression of TXNIP and RAGE and further inhibiting the activation of NLRP3 inflammasome and IKKb/NFκB pathway [39].

The physiological activities of anthocyanins are summarized in **Table 2**.

Table 2. Physiological activities of anthocyanins.

Effects		Source	Mechanisms	Ref.
Anti-cancer	colon cancer	Purple grape anthocyanins	• Inhibited IκBα phosphorylation • Prevented tumor necrosis factor α-induced NF-κB activation	[8]
	colon cancer	Cyanidin-3-O-rutinoside	• Reduced the motility and the metastasis	[9]
	colon cancer	Purple and red maize anthocyanins	• Enhanced BAX, Bcl-2, cytochrome C, and TRAILR2/D5 • Inhibited Tie-2, ANGPT2, and PLG	[10]

Effects		Source	Mechanisms	Ref.
	breast cancer	Black sweet cherry anthocyanins	• Downregulated Sp1, Sp4, and VCAM-1	[3]
	melanoma cancer	Hibiscus calyx anthocyanin	• Triggered PI3K/Akt and Ras/MAPK signaling pathways • Downregulated VEGF and MMP-2/-9	[11]
		Purple sweet potato anthocyanin	• Acted on cell cycle regulators (such as p53, p21, p27, Cyclin D1, and Cyclin A)	[12]
Anti-inflammatory			• Nrf2-ARE signal modulation	[15]
			• Inhibited C/EBP, AP-1, and NF-κB • Inhibited COX-2 • Reduced IL-1β, IL-6, IL-8, and TNF-α • Enhanced *PPAR-γ* gene	[16] [19]
		Cyanidin-3-glucoside	• Regulated NF-κB and MAPK activity	[17]
		Geranium pigment-3-O-glucoside in strawberry	• Inhibited the activation of IkB-α • Reduced the phosphorylation of JNK-MAPK	[21]
		Hibiscus anthocyanin	• Inhibited the secretion of nitric oxide and prostaglandin E2 • Reduced MyD88 growth and IRAK4 phosphorylation • Inhibited NF-κB activity	[22]
Anti-oxidation		Purple corn anthocyanin	• Had DPPH radical scavenging activity	[25]

Effects	Source	Mechanisms	Ref.
	Cyanidins in radish buds	• Inhibited the automatic oxidation of linoleic acid • Scavenged hydrogen peroxide free radicals	[26]
	Mahonia aquifolium anthocyanin	• Had DPPH and ABTS radical scavenging ability • Had FRAP reduction ability	[27]
	Black rice anthocyanin extract (cyanidin-3-O-glucoside)	• Improved the activities of superoxide dismutase and catalase • Reduced the content of malondialdehyde and the activity of monoamine oxidase	[28]
	Blueberry anthocyanins	• Decreased the levels of ROS and XO-1 • Increased SOD and HO-1	[29]
Protective effect on liver	Cyanidin-3-O-glucoside	• Prevented fibrosis • Reduced liver oxidative stress • Reduced liver cell apoptosis • Inhibited liver inflammatory response	[31]
	Riceberry bran anthocyanin	• Inhibited intracellular oxidative stress and the activation of NF-κB factor • Reduced liver cell inflammation and apoptosis	[32]

Effects	Source	Mechanisms	Ref.
	Purple sweet potato anthocyanin	• Activated adenosine-monophosphate-activated protein kinase (AMPK) signaling pathway • Inhibited the production of reactive oxygen species • Inhibited the accumulation of liver fat	[33]
	Purple sweet potato anthocyanin	• Had obvious protective effect on the release of alanine aminotransferase (ALT)	[34]
Lowering blood glucose	Purple corn anthocyanins	• Protected pancreatic β cells from high-glucose-induced oxidative stress • Improved insulin secretion ability of β cells	[47]
	Mulberry anthocyanin	• Increased AMPK phosphorylation • Inhibited gluconeogenesis and stimulated glycogen synthesis	[36]
Anti-aging	Purple sweet potato anthocyanin	• Reduced the serum MDA level • Improved the activities of SOD and GSH-PX • Delayed aging by improving antioxidant activity	[40]
	Cy-3-glu Pg-3-glu	• Inhibited the galactosidase	[41]
	Ribes meyeri anthocyanins	• Promoted the proliferation of neural stem cells • Improved cell senescence phenotype	[42]

Effects	Source	Mechanisms	Ref.
		• Reduce ROS • Reduced senescence-associated *P16Ink4a* gene expression levels • Increased DNA synthesis • Prolonged telomeres	
		• Maintained the stability of redox system • Reduced the levels of IL-1, IL-6, and TNF-α • Decreased in the expression levels of sensors, media, and effectors in the DNA damage signaling pathway • Slowed down aging by inhibiting DNA damage	[43]

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