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REVIEW

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Exploring the potential benefits of anthocyanins for individuals with cerebral small vessel disease

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Abstract

Several studies have demonstrated the antioxidant and anti-inflammatory properties of anthocyanins, as well as their potential phytoestrogenic activity, which could have positive effects on human health. These compounds have shown effectiveness against conditions such as obesity, diabetes, and high cholesterol, which are known risk factors for cardiovascular diseases, including stroke. Stroke is currently the second leading cause of death globally, and cerebral small vessel disease (CSVD) accounts for 20% of all strokes, and it often causes cognitive impairment and gait abnormalities in older adults. Anthocyanins and their metabolites can cross the blood–brain barrier and affect signaling pathways, gene expression, and protein function at the molecular level. In addition to their ability to enhance vascular flow, anthocyanins can also help mitigate the risk factors associated with CSVD by counteracting oxidative stress in the body. These findings exploring the potential benefits of anthocyanins for individuals with CSVD.

Keywords Anthocyanin, CSVD, Stroke

Introduction

Anthocyanins are water-soluble pigments that occur naturally in various plant-based sources, such as fruits, vegetables, flowers, and tubers. These pigment compounds, also known as anthocyanidins, give plants their vibrant red, purple, and blue hues [1]. Although they are commonly used as natural colorants in food and beverage applications [2], this discussion will focus on their potential health benefits.

In recent years, anthocyanins have gained considerable attention for their various biological activities that may protect against human pathological conditions. Research has shown that anthocyanins have antioxidant and anti-inflammatory properties and may exhibit phytoestrogenic activity, which could potentially benefit human health [3, 4]. They have been shown to be effective against conditions such as obesity [5], diabetes [6], and high cholesterol [7]. Furthermore, they can improve endothelial function leading to improvements in blood vessel vasomotor function, which could help

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reduce the risk of cardiovascular diseases, including strokes [8, 9].

Stroke is considered the second leading cause of death worldwide [10]. According to the World Health Organization (WHO), stroke is responsible for approximately 11% of total deaths worldwide, following coronary heart disease as the leading cause [10]. CSVD is a chronic and progressive condition that affects the small blood vessels supplying the white matter and deep structures of the brain [11, 12]. This disorder damages the white matter in the subcortical brain structures, and small vessels ranging from 50 to 400 μm in diameter are affected [13]. CSVD is responsible for 20% of all strokes, and it often causes cognitive impairment and gait abnormalities in older adults [13]. The condition is characterized by a redox imbalance that results in endothelial dysfunction and contributes to the development of atherosclerosis [8].

Taking proactive measures to prevent stroke and CSVD is crucial, including effectively managing risk factors and maintaining a healthy diet. These actions are instrumental in supporting the well-being of endothelial cell vasomotor function. Anthocyanins, known for their bioactive properties, have demonstrated beneficial effects on vascular health. Therefore, this review aims to explore the potential of anthocyanins for patients with cerebral small vessel disease.

Anthocyanin

The structure and properties of anthocyanins

Anthocyanins are water-soluble polyphenolic flavonoid plant pigments responsible for the red, purple, and blue colors of many fruits, vegetables, flowers, and leaves [1]. They get their name from the Greek words *anthos* means flower, and *kyanos* means blue [9, 14, 15]. There are currently 702 types of anthocyanins and 27 anthocyanidins discovered. The six most common types are cyanidin, delphinidin, malvidin, peonidin, petunidin, and pelargonidin, with cyanidin being the most prevalent (Table 1) [16, 17].

Anthocyanins are formed from anthocyanidins, which are the main components and are composed of two aromatic benzene rings (A and B) separated by an oxygenated heterocycle (C). These compounds also incorporate sugar groups and acyl conjugates (Fig. 1) [19, 20]. The structural diversity of anthocyanins comes from differences in the number and location of hydroxyl groups, the nature and position of sugars, and the nature and number of acids associated with these sugars. Commonly attached sugars include glucose, galactose, and rhamnose, and aromatic and aliphatic acids can be used for acylation [16, 17].

Anthocyanins are unstable compounds whose stability can be influenced by various factors such as pH, temperature, light, oxygen, enzymes, other flavonoids, proteins, and metal ions [17, 21]. When exposed to light, heat, or changes in pH, anthocyanins can undergo degradation reactions that result in the loss of their color. Similarly, changes in pH can also lead to the degradation of anthocyanins, with the pigment being most stable in acidic conditions [17].

Pharmacokinetic properties of anthocyanins: absorption, metabolism, and elimination pathways

The pharmacokinetic properties of anthocyanins, such as absorption, metabolism, elimination, bioavailability, and distribution, impact their biological activities. Anthocyanins undergo metabolic processes, including phase I (oxidation, reduction, and hydrolysis) and phase II (conjugation), which detoxify them and increase their hydrophilicity, leading to elimination from the body through urine and bile [22, 23].

Anthocyanins in foods are released by chewing and degraded by saliva and oral microbiota [24]. Oral deglycosylation creates aglycones, which exhibit modified bioactivity [25]. In the stomach, anthocyanins remain

Table 1 Common types of anthocyanin [18]

Anthocyanidin (aglycone)	R group	Estimated distribution in fruits, vegetables, and tubers
Pelargonidin	R1 = R2 = H	~ 12%
Cyanidin	R1 = OH, R2 = H	~ 50%
Delphinidin	R1 = R2 = OH	~ 12%
Peonidin	R1 = OCH3, R2 = H	~ 12%
Petunidin	R1 = OH, R2 = OCH3	~ 7%
Malvidin	R1 = R2 = OCH3	~ 7%

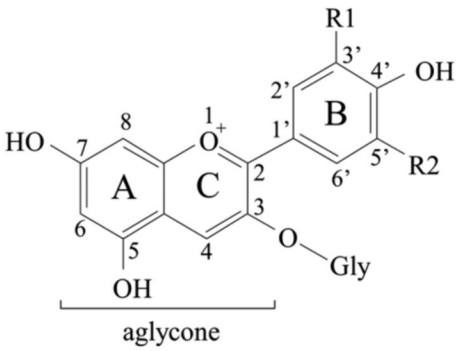

Fig. 1 Chemical structure of anthocyanidin [18]. Glycoside (Gly)

stable in glycoside form due to the low pH. They can be absorbed intact in this form, unlike other flavonoids [17, 26]. However, due to their hydrophilic nature, they require a carrier system to pass through cell membranes [17, 23]. The bilirubin transporter and glucose transporter-1 (GLUT-1) have been studied as potential carrier systems for anthocyanins [27]. However, the proposed mechanism for anthocyanin absorption in the stomach is based on in vitro studies, and its relevance to human absorption and metabolism is uncertain (Fig. 2).

Anthocyanins are mainly absorbed in the small intestine and can be broken down into aglycones through enzymes. The resulting aglycone can enter epithelial cells through passive diffusion or active transport by sodium/glucose cotransporter-1 (SGLT-1) or glucose transporter-2 (GLUT-2). However, it is uncertain whether SGLT-1 plays a role in absorption. Anthocyanin aglycones can be metabolized in the intestinal epithelial cells before entering the portal circulation, including phase I and II reactions [22, 26]. These reactions can also occur in the liver and kidney. After consuming a high anthocyanin-rich diet, the metabolized forms of anthocyanins can be detected in human plasma and urine [17, 22, 26].

Anthocyanin aglycones are degraded into phenolic acids and aldehydes by colon microbiota enzymes [26, 28]. These degradation products can be absorbed in the gut and metabolized in the liver or kidney, while unabsorbed anthocyanins are eliminated through feces [28, 29]. Anthocyanins can also participate in enterohepatic recycling, where they are secreted in bile after initial absorption and returned to the gastrointestinal tract [22]. Anthocyanin metabolites are eliminated from the body through urine, bile, feces, and breath [18, 29, 30], with urine being the primary elimination pathway within the first 6 h and feces being the primary pathway within the time intervals of 6–24 h and 24–48 h [30].

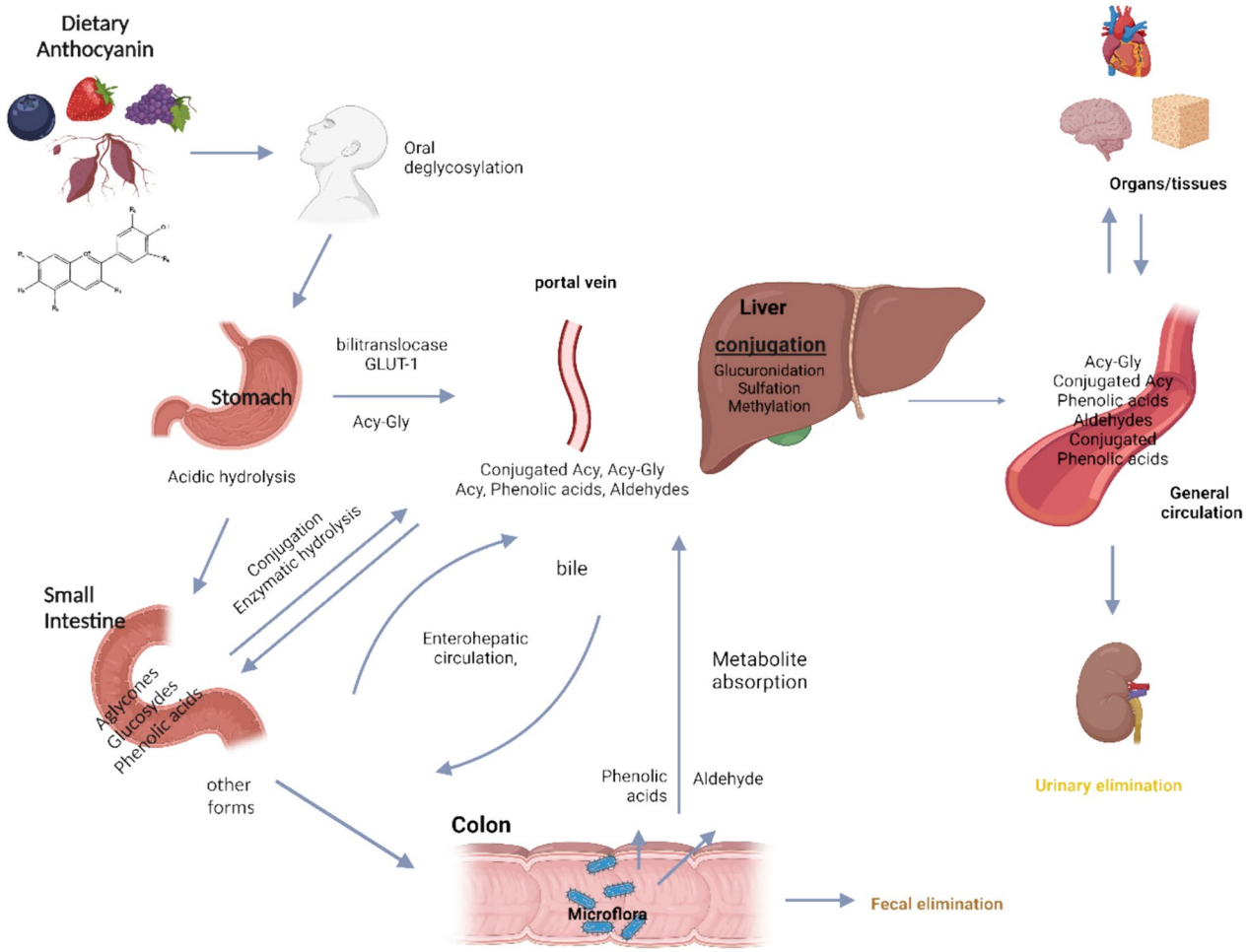

Fig. 2 Mechanism of absorption and metabolism of anthocyanin. Anthocyanidins (Acy); glycosides (Gly); glucose transporter-1 (GLUT-1)

Anthocyanin bioavailability and absorption in the human body

Bioavailability refers to the extent to which consumed anthocyanins are available to target tissues [23]. Anthocyanin bioavailability has been reported to be very low in the past, with less than 1% recovery of the ingested dose [23]. It was found that anthocyanin metabolism is extensive, and a recovery rate of up to 12.4% can be achieved [30]. Anthocyanin absorption primarily occurs in the stomach and small intestine, but it can also reach the large intestine and produce some metabolites. This suggests that anthocyanin bioavailability is greater than previously thought and includes microbiota catabolites [17].

The fate of anthocyanins in the human body: distribution and transport across the blood–brain barrier

After consuming anthocyanin-rich foods, anthocyanins and their metabolites quickly appear in human circulation, reaching a maximum concentration within 1.5 h and disappearing from the bloodstream within 6 h. Studies show that phenolic acids can also be detected in plasma as metabolites of anthocyanins [18]. Metabolites, especially those derived from microbial metabolism, are the dominant circulating form of anthocyanins and have the potential to contribute to beneficial health effects. Anthocyanins are distributed throughout the body's organs, with the liver being the dominant target organ and the brain allowing anthocyanins to reach crucial regions [31]. However, the findings of the distribution of anthocyanin in tissues were conducted in animals, but never in humans.

Anthocyanins and their metabolites can cross the blood–brain barrier and affect signaling pathways, gene expression, and protein function at the molecular level [20]. Several in vitro studies using cell culture models that mimic the blood–brain barrier have been conducted to evaluate the uptake of anthocyanins by brain cells. The study reveals that cyanidin-3-rutinoside, pelargonidin-3-glucoside, and some other flavonoids can cross the blood–brain barrier [32, 33].

A study suggests that some drugs conjugated with glucose can access the brain through the GLUT-1 transporter, which may also be the case for anthocyanins [34]. Anthocyanins can be transported actively through the stomach and small intestine, which depend on GLUT-1 [35, 36]. Another possible mechanism is bilitranslocase, which has been reported to transport some anthocyanins in human endothelial cells [37].

The significance of anthocyanins in our diets and food sources

Anthocyanins, which are essential components of our diets, can be found in common sources such as fruits like blueberries, blackberries, cherries, raspberries, strawberries, and grapes, as well as vegetables and tubers like eggplant, red cabbage, red onions, and purple sweet potatoes [38, 39]. Anthocyanins' solubility in water makes them widely used in the food industry as a natural colorant for food and beverages, with no harmful effects reported. Additionally, anthocyanins can be found in beverages such as red wine or juices, and in processed foods such as jams [18].

The absence of dietary recommendations for anthocyanins can be attributed to the fact that they have not been identified as essential nutrients, despite their significance [24]. Cyanidin is the most consumed anthocyanin, followed by delphinidin, malvidin, petunidin, peonidin, and pelargonidin [40]. The daily intake of anthocyanins in the US has decreased from an estimated 180–215 mg per day in 1976 to approximately 12.5 mg per day, according to a recent report from the United States Department of Agriculture (USDA) [41, 43]. In Europe, the average anthocyanin intake varies by country, around 31 mg/day [24]. The estimated average daily anthocyanin intake in Australia and China was 24.2 mg/day and 27.6 mg/day, respectively, which closely aligns with European levels.

The potential benefits of anthocyanins for cerebral small vessel disease

Cerebral small vessel disease (CSVD)

CSVD is a group of age-related neuropathological processes that affect small arteries, arterioles, capillaries, and venules with a diameter of less than 50 μm in the brain parenchyma [12, 42]. CSVD is a major cause of disability, cognitive impairment, and loss of functional ability in the elderly [43]. CSVD also contributes up to 25% of all ischemic stroke cases [13], making it the second leading cause of death in the world after ischemic heart disease, i.e., stroke [43]. Although most cases of CSVD are asymptomatic in the early stages of the disease, CSVD can develop over years until sequelae symptoms appear [43, 44].

Cognitive impairment is one of the consequences of CSVD. The range of severity of cognitive deficits in CSVD consists of a spectrum that spans from mild cognitive impairment (MCI) to dementia [13]. Some CSVD patients may appear asymptomatic in the cognitive domain. In patients with CSVD, the pattern of cognitive deficits involves information processing; the ability to focus, sustain, or shift attention; and the ability to manipulate, organize, and select information [45]. Gait disturbance is the second most common problem in CSVD patients after cognitive impairment [46]. About 35% of CSVD patients experience gait disturbance. Gait disturbance in CSVD primarily manifests as motor dysfunction, including reduced stride length, balance

impairment, and a tendency to fall [47]. It is essential to address these issues early on to prevent or minimize the impact of disabilities on individuals with CSVD.

The high incidence of CSVD is related to the main risk factors for CSVD, some of which are non-modifiable such as advanced age and gender, while others are modifiable such as hypertension, diabetes mellitus (DM), hypercholesterolemia, and obesity [12]. Studies have revealed that the endothelium is the main target of inadequate oxidation, which accelerates the degenerative effects on central nervous system blood flow in CSVD patients. Arterial hypertension, the oxidation of low-density lipoproteins (oxLDL), and diabetes mellitus promote monovalent reactive forms of free radicals [48]. Accordingly, excessive reactive oxygen species (ROS) formation underlies the pathology of cerebral small vessel disease.

A redox imbalance is a contributing factor to several conditions that are associated with endothelial dysfunction, leading to atherosclerosis [49]. Endothelial dysfunction refers to a state in which the endothelial cells exhibit a pro-inflammatory and pro-thrombotic phenotype, reduced bioavailability of nitric oxide (NO), and impaired vascular tone [50]. It is known that the decrease in cerebral vasomotor reactivity (cVMR) due to endothelial dysfunction contributes to the ischemic process in CSVD. A decrease in cVMR is linked to higher levels of white matter hypersensitivity (WMH) severity, greater damage to white matter integrity, and an increased occurrence of lacunar infarcts in CSVD [51].

Improvement in cVMR is characterized by an increase in the expression of endothelial nitric oxide synthase (eNOS) through an increase in NO and an increase in eNOS expression in catalyzing the oxidation of L-arginine, which ultimately increases NO production more optimally. In addition, an increase in adiponectin also plays a role in improving cVMR through the phosphorylation and activation of Akt (Ak strain transforming), which directly phosphorylates and activates eNOS. The presence of NO in the endothelium of intracranial blood vessels can increase cVMR and intracranial blood flow. An increase in NO levels also affects vasodilation, which can increase perfusion and cerebral blood flow (CBF) to neuronal cells [52–54]. This is expected to improve the vasomotor reactivity (VMR) of cerebral blood vessels and improve the outcomes of stroke patients.

Previous studies have found that cVMR measurement using the Breath Holding Index (BHI) technique is an accurate assessment in assessing cVMR capability. The ability of cVMR was assessed by looking at changes in CBFV during hypercapnia using transcranial Doppler [76]. It found that a 10% reduction in CBFV increased respondents' risk of stroke by 64%. This suggests that cVMR disruption is independently associated with an increased risk of ischemic stroke [76]. Thereby, ensuring the effects of anthocyanin on CSVD could be assessed by measuring BHI to evaluate the cVMR using transcranial Doppler.

It is evident that oxidative stress and endothelial dysfunction play a crucial role in the development and progression of CSVD. Fortunately, there is growing evidence that certain bioactive compounds, such as anthocyanins, possess antioxidant, anti-inflammatory, and phytoestrogenic properties that may combat the pathology of CSVD. The discussion below will explore the potential of anthocyanins for individuals with cerebral small vessel disease.

Biomolecular effects of anthocyanin

Anthocyanins exert their biological effects through their direct antioxidant properties by neutralizing reactive oxygen species. The imbalance between the production of reactive oxygen species and antioxidant defenses leads to oxidative stress, which is associated with inflammatory reactions, endothelial dysfunction, and atherosclerosis [55]. Anthocyanins and their aglycones possess antioxidant properties by neutralizing free radicals and terminating chain reactions [56]. The antioxidant activity of anthocyanins is linked to the presence of hydroxyl groups in positions 3, 4, and 5 in ring B, and acylation of sugar residues with aromatic hydroxy acids further enhances their antioxidant properties [57].

Anthocyanins and cyanidin-3-O-glucoside (C3G) have been linked to a decreased risk of cerebral ischemia. The neuroprotective effects of anthocyanins are thought to be due to their ability to suppress neuroinflammation and oxidative stress. Studies have shown that anthocyanins and C3G can inhibit the production of pro-inflammatory cytokines and molecules associated with high levels of oxidative stress, thereby preventing neuronal damage in models of cerebral ischemia [58, 59].

Phytoestrogens are plant compounds that can mimic or modulate the actions of estrogen by binding to estrogen receptors [60]. They have been gaining attention for their potentially beneficial effects on diseases like cancer and cardiovascular disease [61, 62]. Estrogen activates estrogen receptors and stimulates intracellular signaling pathways, resulting in increased synthesis of endothelial NO through the activation of the enzyme eNOS. This increase in NO production is crucial for maintaining vasodilation, regulating blood pressure, and improving blood flow [63–65].

Anthocyanins, such as cyanidin and delphinidin, are plant pigments that belong to the flavonoid family and can exhibit phytoestrogenic activity [4]. Structurally, anthocyanins resemble phytoestrogens like genistein, which is considered the prototype phytoestrogen that

can produce estrogenic effects [66, 67]. This suggests that anthocyanins may have vasodilatory effects like estrogen, which is known to cause rapid vasodilation in vascular areas through two receptor-mediated mechanisms that explain its non-genomic vasodilatory action.

A recent study found that delphinidin and its derivatives have vasodilatory effects with similar production times, with the large sugar group in delphinidin possibly contributing to its effectiveness as a vasodilator [68–71]. Another study showed that delphinidin can activate molecular pathways leading to NO production and vasorelaxation by interacting with estrogen receptor alpha (ER-α) [72]. This suggests that anthocyanins, whether glycosylated or not, can act as ERα or G protein-coupled estrogen receptor (GPER) ligands (Fig. 3).

Menopause and estrogen deficiency have been associated with the development of leukoaraiosis, and early menopause increases the risk of silent infarcts in the elderly. Estrogen has been found to reduce the risk of cerebral small vessel disease or delay its progression [73]. As anthocyanins exhibit phytoestrogenic effects and have shown potential as vasodilatory compounds, they may have beneficial effects on CSVD.

Anthocyanin effect study in human

The impairment of cerebral vasomotor reactivity is implicated in the ischemic process associated with CSVD. In a meta-analysis study, it was discovered that acute supplementation of anthocyanins yielded a noteworthy increase in flow-mediated dilation (FMD), a widely recognized non-invasive measure of vasomotor reactivity (VMR). The study observed a significant improvement in FMD within the range of 1–8 h after consuming anthocyanin doses ranging from 7 to 724 mg. Moreover, chronic intervention studies involving anthocyanins also reported improvements in vascular function [53]. The duration of these interventions ranged from one week to six months, and the use of anthocyanin doses between 12 and 320 mg/day was found to significantly enhance FMD compared to the control group. The meta-analysis study demonstrated a statistically significant increase in vasomotor reactivity, as measured by FMD, resulting from both acute and chronic anthocyanin supplementation [53].

In addition to studies involving patients with chronic conditions, Guo et al. conducted a study specifically targeting healthy young adults. The study aimed to evaluate the dose–response relationship of anthocyanins and its effects on markers of inflammation, oxidative stress, and metabolic risk [74]. Participants were given anthocyanin capsules at doses of 20, 40, 80, 160, and 320 mg daily for 14 days. The study concluded that anthocyanin administration above 80 mg/day proved to be an effective and efficient dose in promoting antioxidant and anti-inflammatory functions in healthy young adults. The study also mentioned that higher doses of

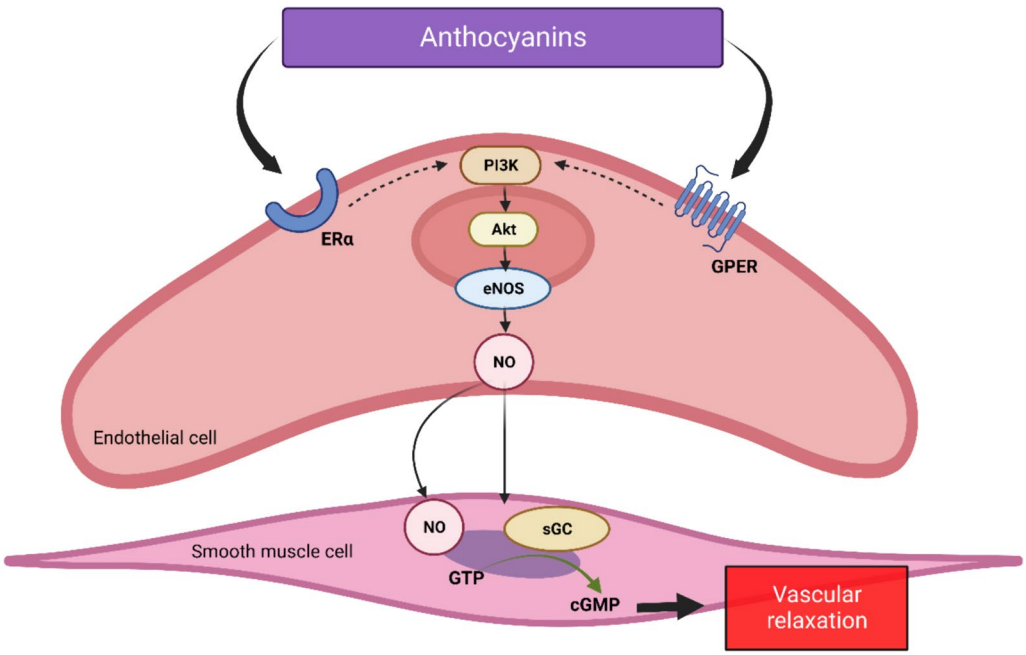

Fig. 3 Anthocyanins activate membrane estrogen receptors to induce non-genomic vascular responses through the generation of nitric oxide (NO). Phosphatidylinositol 3-kinase (PI3K); soluble guanylate cyclase (sGC); guanosine triphosphate (GTP); cyclic guanosine monophosphate (cGMP)

320 mg/day were required in other studies to achieve the maximal effects of anthocyanins in addressing oxidative stress and acting as anti-inflammatory agents aimed at improving metabolic profiles in patients with chronic diseases [74].

The structure and functional of the human nervous system can be directly visualized by neuroimaging. The recent study's fMRI demonstrate that blood oxygenation increased following high flavonol consumption, with the most significant changes observed in the lateral frontal regions [75].

Conclusion

The association between oxidative stress, endothelial dysfunction, and the development of cerebral small vessel disease (CSVD) is firmly established. Considering the wide array of actions demonstrated by anthocyanins, including their antioxidant, anti-inflammatory, and phytoestrogenic properties, it becomes evident that anthocyanins hold promising potential in providing substantial benefits to individuals affected by CSVD. In addition to their capacity to enhance vascular flow, anthocyanins can also aid in mitigating the risk factors linked to CSVD by counteracting oxidative stress in the body. Conducting future studies is crucial to further explore the potential of anthocyanins in this regard.

Abbreviations

Acy	Anthocyanidins
Akt	Ak strain transforming/ protein kinase B
C3G	Cyanidin-3-O-glucoside
CBF	Cerebral blood flow
cGMP	Cyclic guanosine monophosphate
CSVD	Cerebral small vessel disease
cVMR	Cerebral vasomotor reactivity
DM	Diabetes mellitus
eNOS	Endothelial nitric oxide synthase
ERα	Estrogen receptor alpha
GLUT-1	Glucose transporter-1
GLUT-2	Glucose transporter-2
Gly	Glycoside
GPER	G protein-coupled estrogen receptor
GTP	Guanosine triphosphate
MCI	Mild cognitive impairment
mg	Milligram
NO	Nitric oxide
oxLDL	Oxidation of low-density lipoproteins
PI3K	Phosphatidylinositol 3-kinase
ROS	Reactive oxygen species
sGC	Soluble guanylate cyclase
SGLT-1	Sodium/glucose cotransporter-1
USDA	United States Department of Agriculture
VMR	Vasomotor reactivity
WHO	World Health Organization
WMH	White matter hyperintensity

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Author contributions

TM analyzed and interpreted the data, SH, AR, AG, WK, FW, H, NA, LA contributed to manuscript editing. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Khoo HE, Azlan A, Tang ST, Lim SM. Anthocyanidins and anthocyanins: colored pigments as food, pharmaceutical ingredients, and the potential health benefits. Food Nutr Res. 2017;61(1):1361779.
2. Chisté RC, Lopes AS, De Faria LJG. Original article: thermal and light degradation kinetics of anthocyanin extracts from mangosteen peel (*Garcinia mangostana* L.). Int J Food Sci Technol. 2010;45(9):1902–8. https://doi.org/10.1111/j.1365-2621.2010.02351.x.
3. Alam MK. A comprehensive review of sweet potato (Ipomoea batatas [L.] Lam): revisiting the associated health benefits. Trends Food Sci Technol. 2021;115:512–29.
4. Schmitt E, Stopper H. Estrogenic activity of naturally occurring anthocyanidins. Nutr Cancer. 2001;41(1–2):145–9.
5. Lee YM, Yoon Y, Yoon H, Park HM, Song S, Yeum KJ. Dietary anthocyanins against obesity and inflammation. Nutrients. 2017;9(10):1089.
6. Guo H, Xia M. Chapter 12—anthocyanins and diabetes regulation. In: Watson RR, Preedy VR, Zibadi S, editors. Polyphenols: mechanisms of action in human health and disease. 2nd ed. Academic Press; 2018. p. 135–45.
7. Liu C, Sun J, Lu Y, Bo Y. Effects of anthocyanin on serum lipids in dyslipidemia patients: a systematic review and meta-analysis. PLoS ONE. 2016;11(9): e0162089.
8. Manolescu BN, Oprea E, Mititelu M, Ruta LL, Farcasanu IC. Dietary anthocyanins and stroke: a review of pharmacokinetic and pharmacodynamic studies. Nutrients. 2019;11(7):1479.
9. Kimble R, Keane KM, Lodge JK, Howatson G. Dietary intake of anthocyanins and risk of cardiovascular disease: a systematic review and meta-analysis of prospective cohort studies. Crit Rev Food Sci Nutr. 2019;59(18):3032–43.
10. Murphy SJX, Werring DJ. Stroke: causes and clinical features. Medicine. 2020;48(9):561–6.
11. Cuadrado-Godia E, Dwivedi P, Sharma S, Santiago AO, Gonzalez JR, Balcells M, et al. Cerebral small vessel disease: a review focusing on

pathophysiology, biomarkers, and machine learning strategies. J Stroke. 2018;20(3):302.
12. Li Q, Yang Y, Reis C, Tao T, Li W, Li X, et al. Cerebral small vessel disease. Cell Transplant. 2018;27(12):1711–22.
13. Chojdak-Łukasiewicz J, Dziadkowiak E, Zimny A, Paradowski B. Cerebral small vessel disease: a review. Adv Clin Exp Med. 2021;30(3):349–56.
14. Kong JM, Chia LS, Goh NK, Chia TF, Brouillard R. Analysis and biological activities of anthocyanins. Phytochemistry. 2003;64(5):923–33.
15. Strygina KV, Kochetov AV, Khlestkina EK. Genetic control of anthocyanin pigmentation of potato tissues. BMC Genet. 2019;20(1):27. https://doi.org/10.1186/s12863-019-0728-x.
16. Andersen ØM, Jordheim M. Basic anthocyanin chemistry and dietary sources. Anthocyanins Health Dis. 2013;1:13–89.
17. Fang J. Bioavailability of anthocyanins. Drug Metab Rev. 2014;46(4):508–20.
18. Krga I, Milenkovic D. Anthocyanins: from sources and bioavailability to cardiovascular-health benefits and molecular mechanisms of action. J Agric Food Chem. 2019;67(7):1771–83.
19. Li P, Feng D, Yang D, Li X, Sun J, Wang G, et al. Protective effects of anthocyanins on neurodegenerative diseases. Trends Food Sci Technol. 2020;2021(117):205–17.
20. Liu Y, Tikunov Y, Schouten RE, Marcelis LFM, Visser RGF, Bovy A. Anthocyanin biosynthesis and degradation mechanisms in Solanaceous vegetables: a review. Front Chem. 2018;6(MAR).
21. de Pascual-Teresa S, Sanchez-Ballesta MT. Anthocyanins: from plant to health. Phytochem Rev. 2008;7:281–99.
22. Lila MA, Burton-Freeman B, Grace M, Kalt W. Unraveling anthocyanin bioavailability for human health. Annu Rev Food Sci T echnol. 2016;7:11–7.
23. Passamonti S, Vrhovsek U, Mattivi F. The interaction of anthocyanins with bilitranslocase. Biochem Biophys Res Commun. 2002;296(3):631–6.
24. Riaz M, Zia-Ul-Haq M, Saad B. Anthocyanins and Human Health: Biomolecular and therapeutic aspects. Springer Briefs in Food, Health and Nutrition. 2016.
25. Mallery SR, Budendorf DE, Larsen MP, Pei P, Tong M, Holpuch AS, et al. Effects of human oral mucosal tissue, saliva, and oral microflora on intraoral metabolism and bioactivation of black raspberry anthocyanins capacity for enteric recycling in human oral mucosa. Cancer Prev Res. 2011;4(8):1209–21.
26. Hribar U, Poklar UN. The metabolism of anthocyanins. Curr Drug Metab. 2014;15(1):3–13.
27. Oliveira H, Fernandes I, Bras NF, Faria A, De Freitas V, Calhau C, et al. Experimental and theoretical data on the mechanism by which red wine anthocyanins are transported through a human MKN-28 gastric cell model. J Agric Food Chem. 2015;63(35):7685–92.
28. Faria A, Fernandes I, Norberto S, Mateus N, Calhau C. Interplay between anthocyanins and gut microbiota. J Agric Food Chem. 2014;62(29):6898–902.
29. De Ferrars RM, Czank C, Zhang Q, Botting NP, Kroon PA, Cassidy A, et al. The pharmacokinetics of anthocyanins and their metabolites in humans. Br J Pharmacol. 2014;171(13):3268–82.
30. Czank C, Cassidy A, Zhang Q, Morrison DJ, Preston T, Kroon PA, et al. Human metabolism and elimination of the anthocyanin, cyanidin-3-glucoside: a 13C-tracer study. Am Clin Nutr. 2013;97(5):995–1003.
31. Henriques JF, Serra D, Dinis TCP, Almeida LM. The anti-neuroinflammatory role of anthocyanins and their metabolites for the prevention and treatment of brain disorders. Int J Mol Sci. 2020;21:1–31.
32. Steiner O, Coisne C, Engelhardt B, Lyck R. Comparison of immortalized bEnd5 and primary mouse brain microvascular endothelial cells as in vitro blood–brain barrier models for the study of T cell extravasation. J Cereb Blood Flow Metab. 2011;31(1):315–27.
33. Faria A, Pestana D, Teixeira D, Azevedo J, Freitas V, Mateus N, et al. Flavonoid transport across RBE4 cells: a blood-brain barrier model. Cell Mol Biol Lett. 2010;15(2):234–41.
34. Patching SG. Glucose transporters at the blood-brain barrier: function, regulation and gateways for drug delivery. Mol Neurobiol. 2017;54(2):1046–77.
35. Oliveira H, Roma-Rodrigues C, Santos A, Veigas B, Brás N, Faria A, et al. GLUT1 and GLUT3 involvement in anthocyanin gastric transport-Nanobased targeted approach. Sci Rep. 2019;9(1):1–14.
36. Zou TB, Feng D, Song G, Li HW, Tang HW, Ling WH. The role of sodium-dependent glucose transporter 1 and glucose transporter 2 in the absorption of cyanidin-3-O-β-glucoside in Caco-2 cells. Nutrients. 2014;6(10):4165–77.
37. Smeriglio A, Barreca D, Bellocco E, Trombetta D. Chemistry, pharmacology and health benefits of anthocyanins. Phytother Res. 2016;30(8):1265–86.
38. Manolescu BN, Oprea E, Mititelu M, Ruta L, Farcasanu I. Dietary anthocyanins and stroke: a review of pharmacokinetic and pharmacodynamic studies. Nutrients. 2019;11(7):1–35.
39. He J, Giusti MM. Anthocyanins: natural colorants with health-promoting properties. Annu Rev Food Sci Technol. 2010;1:163–87.
40. Wu X, Beecher GR, Holden JM, Haytowitz DB, Gebhardt SE, Prior RL. Concentrations of anthocyanins in common foods in the United States and estimation of normal consumption. J Agric Food Chem. 2006;54(11):4069–75.
41. Kuhnau J. Flavonoids. A class of semi-essential food components: their role in human nutrition. World Rev Nutr Diet. 1976;
42. Charidimou A, Pantoni L, Love S. The concept of sporadic cerebral small vessel disease: a road map on key definitions and current concepts. Int J Stroke. 2016;11(1):6–18.
43. Nie S, Shen C, Guo Y, Hou X, Hong Y, Xu S, et al. Preliminary findings on visual event-related potential p3 in asymptomatic patients with cerebral small vessel disease. Neuropsychiatr Dis Treat. 2021;17:3379–94.
44. Mustapha M, Nassir CMNCM, Aminuddin N, Safri AA, Ghazali MM. Cerebral small vessel disease (CSVD)—lessons from the animal models. Front Physiol. 2019;10:1–29.
45. Verdelho A, Wardlaw J, Pavlovic A, Pantoni L, Godefroy O, Duering M, et al. Cognitive impairment in patients with cerebrovascular disease: a white paper from the links between stroke ESO Dementia Committee. Eur Stroke J. 2021;6(1):5–17.
46. Okroglic S, Widmann C, Urbach H, Scheltens P, Heneka M. Clinical symptoms and risk factors in cerebral microangiopathy patients. PLoS ONE. 2013;8: e53455.
47. Hatate J, Miwa K, Matsumoto M, Sasaki T, Yagita Y, Sakaguchi M, et al. Association between cerebral small vessel diseases and mild parkinsonian signs in the elderly with vascular risk factors. Parkinsonism Relat Disord. 2016;1:26.
48. Grochowski C, Litak J, Kamieniak P, Maciejewski R. Oxidative stress in cerebral small vessel disease. Role of reactive species. Free Radic Res. 2018;52(1):1–13.
49. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. Circ Res. 2000;87(10):840–4.
50. Incalza MA, D'Oria R, Natalicchio A, Perrini S, Laviola L, Giorgino F. Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases. Vascul Pharmacol. 2018;100:1–19.
51. Smith EE, Beaudin AE. New insights into cerebral small vessel disease and vascular cognitive impairment from MRI. 2017;1–8.
52. Jawi IM, Yasa IWPS, Mahendra AN. Antihypertensive and antioxidant potential of purple sweet potato tuber dry extract in hypertensive rats. Bali Med J. 2016;5(2):65.
53. Fairlie-Jones L, Davison K, Fromentin E, Hill AM. The effect of anthocyanin-rich foods or extracts on vascular function in adults: a systematic review and meta-analysis of randomised controlled trials. Nutrients. 2017;9(8):908.
54. Ghimire K, Altmann HM, Straub AC, Isenberg JS. Nitric oxide: what's new to NO? Am J Physiol Cell Physiol. 2017;312(3):C254–62.
55. Hadi HAR, Carr CS, Al SJ. Endothelial dysfunction: cardiovascular risk factors, therapy, and outcome. Vasc Health Risk Manag. 2005;1(3):183–98.
56. Wang H, Cao G, Prior RL. Oxygen radical absorbing capacity of anthocyanins. J Agric Food Chem. 1997;45(2):304–9.
57. Garcia-Alonso M, Rimbach G, Sasai M, Nakahara M, Matsugo S, Uchida Y, et al. Electron spin resonance spectroscopy studies on the free radical scavenging activity of wine anthocyanins and pyranoanthocyanins. Mol Nutr Food Res. 2005;49(12):1112–9.
58. Shin WH, Park SJ, Kim EJ. Protective effect of anthocyanins in middle cerebral artery occlusion and reperfusion model of cerebral ischemia in rats. Life Sci. 2006;79(2):130–7.
59. Min J, Yu SW, Baek SH, Nair KM, Bae ON, Bhatt A, et al. Neuroprotective effect of cyanidin-3-O-glucoside anthocyanin in mice with focal cerebral ischemia. Neurosci Lett. 2011;500(3):157–61.

60. Kuhnle GGC, Dell'Aquila C, Runswick SA, Bingham SA. Variability of phytoestrogen content in foods from different sources. Food Chem. 2009;113(4):1184–7.
61. Adlercreutz H. Assay of lignans and phytoestrogens in urine of women and in cow milk by GC/MS (SIM). In: Advances in Mass Spectrometry-85 Proceedings of the 10th International Mass Spectrometry Conference, 1986. John Wiley; 1986. p. 661–2.
62. Anthony MS. Phytoestrogens and cardiovascular disease: where's the meat? Arteriosclerosis, thrombosis, and vascular biology. Am Heart Assoc. 2002;22:1245–7.
63. Paterni I, Granchi C, Katzenellenbogen JA, Minutolo F. Estrogen receptors alpha (ERα) and beta (ERβ): subtype-selective ligands and clinical potential. Steroids. 2014;90:13–29.
64. Saczko J, Michel O, Chwiłkowska A, Sawicka E, Mączyńska J, Kulbacka J. Estrogen receptors in cell membranes: regulation and signaling. Transport Across Natural and Modified Biological Membranes and its Implications in Physiology and Therapy. 2017;93–105.
65. Li L, Haynes MP, Bender JR. Plasma membrane localization and function of the estrogen receptor α variant (ER46) in human endothelial cells. Proc Natl Acad Sci. 2003;100(8):4807–12.
66. Dixon RA, Ferreira D. Genistein. Phytochemistry. 2002;60(3):205–11.
67. Andersen OM, Markham KR. Flavonoids: chemistry, biochemistry and applications. CRC Press; 2005.
68. Walle T, Walle UK. The β-D-glucoside and sodium-dependent glucose transporter 1 (SGLT1)-inhibitor phloridzin is transported by both SGLT1 and multidrug resistance-associated proteins 1/2. Drug Metab Dispos. 2003;31(11):1288–91.
69. Cunningham P, Afzal-Ahmed I, Naftalin RJ. Docking studies show that D-glucose and quercetin slide through the transporter GLUT1. J Biol Chem. 2006;281(9):5797–803.
70. Maestro A, Terdoslavich M, Vanzo A, Kuku A, Tramer F, Nicolin V, et al. Expression of bilitranslocase in the vascular endothelium and its function as a flavonoid transporter. Cardiovasc Res. 2010;85(1):175–83.
71. Ziberna L, Lunder M, Tramer F, Drevenšek G, Passamonti S. The endothelial plasma membrane transporter bilitranslocase mediates rat aortic vasodilation induced by anthocyanins. Nutr Metab Cardiovasc Dis. 2013;23(1):68–74.
72. Chalopin M, Tesse A, Martínez MC, Rognan D, Arnal JF, Andriantsitohaina R. Estrogen receptor alpha as a key target of red wine polyphenols action on the endothelium. PLoS ONE. 2010;5(1): e8554.
73. Seo SK, Jung I, Lee SM, Cho S, Choi YS, Chung TS, et al. Relationship between leukoaraiosis and menopause in healthy middle-aged women. Fertil Steril. 2013;100(2):500–4.
74. Guo Y, Zhang P, Liu Y, Zha L, Ling W, Guo H. A dose-response evaluation of purified anthocyanins on inflammatory and oxidative biomarkers and metabolic risk factors in healthy young adults: a randomized controlled trial. Nutrition. 2020;27(74): 110745.
75. Gratton G, Weaver SR, Burley CV, Low KA, Maclin EL, Johns PW, et al. Dietary flavonols improve cerebral cortical oxygenation and cognition in healthy adults. Sci Rep. 2020;10:19409.
76. Reinhard M, Schwarzer G, Briel M, Altamura C, Palazzo P, King A, Bornstein NM, Petersen N, Motschall E, Hetzel A, Marshall RS. Cerebrovascular reactivity predicts stroke in high-grade carotid artery disease. Am Acad Neurol. 2014;16:1424–31.

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