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Anthocyanin metabolism and vasorelaxant activity in cardiovascular related diseases: A systematic literature review

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ABSTRACT

In recent years, anthocyanin-rich diets have garnered increasing attention for their cardioprotective health benefits. The primary objective of this study is to systematically review the literature on the vasorelaxation effects of anthocyanins and evaluate their therapeutic potential in the prevention and management of cardiovascular-related diseases. To ascertain the rigor in its methodology, this systematic literature review (SLR) adhered to guidelines outlined in Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA); the research question was formulated based on the mnemonics of Population, Interest, and Context (PICO), the inclusion and exclusion criteria were based on timeline publication, document type, language, and focus of the study which is anthocyanin vasorelaxation effects on cardiovascular; the quality was appraised based on six criteria, namely: whether the study's purpose was clearly stated, the interest and usefulness of the work were presented, the methodology was clearly established, the core concepts were clearly defined, the work was compared with similar studies, and the study's limitations were clearly acknowledged. The quality assessment process was conducted by the lead researcher, with the assistance of two co-researchers. Data extraction and analysis were conducted using thematic analysis. The analytical outcomes yielded two main themes. First theme is anthocyanins in the prevention and management of specific CVD conditions, which consist of three sub-themes: atherosclerosis, hypertension, and endothelial dysfunction. The second theme is bioavailability and metabolism of anthocyanins, which later produced another three sub-themes, namely absorption, distribution, metabolism, excretion (ADME), influence of gut microbiota, and active metabolites and parent compounds. Referring to this SLR, there is an urgent need to identify the key anthocyanin-derived metabolites and clarify how gut microbiota influences their bioconversion and efficacy in cardiovascular protection. Further well-controlled human studies with standardized dosing and metabolite profiling are essential to validate these mechanisms and support their integration into personalized nutrition strategies.

Keywords: *Systematic literature review; cardiovascular diseases; anthocyanin; vasorelaxation effects and metabolism*

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of death worldwide, responsible for approximately 18.6 million deaths annually and accounting for 31% of global deaths in 2016 (Carvalho et al., 2024; do Rosario et al., 2020). CVDs encompass a broad spectrum of disorders affecting the heart and blood vessels, including coronary heart disease, stroke, hypertension, heart failure, and peripheral vascular disease (Carvalho et al., 2024; Woolf et al., 2023). The pathophysiology of CVD is multifactorial, involving modifiable risk factors such as diet, hypertension, and dyslipidemia, as well as non-modifiable factors like aging and genetics (Woolf et al., 2023). One of the earliest and most consistent features of CVD progression is vascular dysfunction, including endothelial dysfunction and arterial stiffening, both of which are predictive of adverse cardiovascular events (Woolf et al., 2023). Underlying mechanisms such as oxidative

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stress, inflammation, and gut microbiota dysbiosis have been shown to play critical roles in this vascular deterioration.

In recent years, dietary interventions incorporating polyphenol-rich foods have garnered increasing attention as complementary approaches to cardiovascular health management. Among these polyphenols, anthocyanins are naturally occurring flavonoid compounds responsible for the red, purple, and blue pigmentation in many fruits and vegetables that have demonstrated notable cardioprotective effects (Teixeira et al., 2023; Xiao, 2022). These compounds are primarily found in berries, cherries, grapes, and dark leafy vegetables and are known for their potent antioxidant, anti-inflammatory, antihypertensive, and antiatherogenic properties (Gai et al., 2023; Guo & Xia, 2018; Solverson et al., 2022; Wallace et al., 2020; Yousuf et al., 2016). Epidemiological, animal, and clinical studies suggest that diets rich in anthocyanins are associated with improvements in endothelial function, modulation of lipid profiles, reductions in blood pressure, and suppression of systemic inflammation (Festa et al., 2023; Woolf et al., 2023; Xin et al., 2024).

Vasorelaxation is the ability of blood vessels to dilate and increase blood flow. It is a crucial physiological process that contributes to the regulation of blood pressure and overall vascular homeostasis. Impairment of vasorelaxation is a hallmark of endothelial dysfunction and is strongly associated with hypertension and atherosclerosis (Festa et al., 2023; Xin et al., 2024). Anthocyanins have been shown to enhance nitric oxide (NO) bioavailability, suppress oxidative stress pathways, and modulate gut microbial metabolism, all of which contribute to improved vascular reactivity (Teixeira et al., 2023; Xu et al., 2019). Although native anthocyanins exhibit low bioavailability with less than 1% detected in plasma, emerging evidence suggests that their phenolic metabolites, formed through interactions with gut microbiota, may retain or even enhance biological activity (Festa et al., 2023).

Given the growing body of research and the expanding application of anthocyanins in nutraceuticals and functional foods, a systematic analysis of their vasorelaxation effects in cardiovascular-related diseases is timely and necessary. This review aims to consolidate and evaluate the current literature on anthocyanins' mechanisms of action, bioavailability, and their role in mitigating vascular dysfunction in CVD. By synthesizing findings across preclinical and clinical studies, this review aims to advance and enhance the understanding of anthocyanins' therapeutic potential and thereby support further translational research into their application for cardiovascular prevention and treatment.

This Systematic Literature Review (SLR) is warranted due to the inherent limitations associated with traditional literature reviews. These limitations include potential selection bias, limited comprehensiveness, lack of clarity, and inadequate quality control (Haddaway et al., 2018; Shaffril et al., 2021). As such, the SLR approach is adopted to address and mitigate these shortcomings through its structured and rigorous methodology. According to Higgins et al. (2011), a SLR is designed to thoroughly identify and synthesize relevant research using structured, transparent, and replicable methods throughout each stage of the process. Utilizing an SLR offers several advantages, including enhanced transparency, a strong emphasis on evidence, improved assessment of validity and causality, a comprehensive search approach, and greater control over review quality by ensuring the robustness of the evidence base (Shaffril et al., 2021). Besides that, compared to traditional literature reviews, SLRs stand out due to their distinct methodological steps. They encourage researchers to explore studies beyond their immediate disciplines and networks by employing broad search strategies, predefined search terms, and standardized inclusion and exclusion criteria (Robinson & Lowe, 2015).

The main objective of this SLR is to critically evaluate and synthesize existing scientific evidence on the vasorelaxation effects of anthocyanins, with a specific focus on their therapeutic potential in the prevention and management of cardiovascular-related diseases. This review aims to identify the underlying mechanisms of action of anthocyanins, assess the quality and outcomes of current *in vitro, in vivo*, and clinical studies, and highlight gaps in the literature in regards of anthocyanins in order to assist on the future research directions and clinical applications. Doing so contributes to a more comprehensive understanding of the role of anthocyanins in vascular health, supports the development of evidence-based dietary or nutraceutical interventions, and provides a foundation for future research and clinical applications in cardiovascular disease management.

MATERIALS AND METHODS

Review Protocol – PRISMA

This SLR refers to the Preferred Reporting Items for Systematic reviews and Meta-Analyses, also known as PRISMA. PRISMA was developed by Moher et al. (2010) and was later improved by Page et al. (2021). The updated version by Page offers several advantages, including its flexibility for application in the fields of health and medicine, its emphasis on a well-structured systematic methodology, and the selection of high-quality articles. Guided by the PRISMA framework, this SLR was conducted in the following four main methodological steps: formulation of the research question, systematic search strategy, quality assessment of the articles, and data extraction and analysis.

Formulation of the research question

The research question is a crucial component in a SLR, as it guides the study toward its defined objective. For this SLR, the PICO mnemonic was used as a reference. The PICO mnemonic was developed by Lockwood et al. (2015). In PICO, "P" stands for Population, "I" for Interest, and "CO" for Context. In the context of this SLR, "P" refers to individuals with cardiovascular-related diseases, "I" represents anthocyanins, and "CO" refers to the vasorelaxation effects. Based on these three elements, the researcher formulated the following research questions for this SLR: “What are the vasorelaxation effects of anthocyanins in the prevention and management of cardiovascular-related diseases?”, “How do anthocyanins influence vasorelaxation in individuals with cardiovascular-related diseases?”, or “What is the evidence for the vasorelaxant effects of anthocyanins in experimental and clinical models of cardiovascular disease?”

Systematic search strategies

To conduct a comprehensive search, the researcher carried out three main processes, namely identification, screening, and eligibility.

Identification

Identification is a process in which the researcher identifies relevant keywords to be used during the document search. Based on the research questions that have been developed, the researcher selected three appropriate keywords: *cardiovascular*, *anthocyanin*, and *vasorelaxation*.

Subsequently, the researcher sought to identify synonyms, related terms, and variations of these keywords. For this purpose, several sources were consulted, including ChatGPT, thesaurus, keywords from previous studies, as well as recommended terms (cardiac, cyanidin, vasodilation) from databases such as Scopus.

Through this effort, the researcher successfully identified several additional keywords, including *heart-related*, *cardiac*, *circulatory*, *heart and blood vessel*, *vascular*, *anthocyanin-rich*, *anthocyanidin*, *cyanidin*, *vasodilation*, *vessel relaxation*, *blood vessel relaxation*, and *vascular relaxation*.

Based on the identified keywords, the researcher searched for relevant documents or articles across several databases, namely Scopus, Web of Science (WoS), and Google scholar (GS).

Additionally, the researcher developed a search string to enhance the likelihood of retrieving a more comprehensive set of articles. The construction of this search string was guided by five fundamental functions: field codes, phrase searching, truncation, wildcards, and Boolean operators.

Table 1

The developed search string

Database	Search string
Scopus	TITLE-ABS-KEY (("cardiovascular" OR "heart-related" OR "cardiac" OR "circulatory" OR "heart and blood vessel*" OR "vascular") AND ("anthocyanin*" OR "anthocyanin-rich" OR "anthocyanidin" OR "cyanidin") AND ("vasorelaxation" OR "vasodilation" OR "vessel relaxation" OR "blood vessel relaxation" OR "vascular relaxation"))
WoS	TS=(("cardiovascular" OR "heart-related" OR "cardiac" OR "circulatory" OR "heart and blood vessel*" OR "vascular") AND ("anthocyanin*" OR "anthocyanin-rich" OR "anthocyanidin" OR "cyanidin") AND ("vasorelaxation" OR "vasodilation" OR "vessel relaxation" OR "blood vessel relaxation" OR "vascular relaxation"))
Google scholar	(("cardiovascular" OR "heart-related" OR "cardiac" OR "circulatory" OR "heart and blood vessel" OR "vascular") AND ("anthocyanin" OR "anthocyanin-rich" OR "anthocyanidin" OR "cyanidin") AND ("vasorelaxation" OR "vasodilation" OR "vessel relaxation" OR "blood vessel relaxation" OR "vascular relaxation"))

Note: ABS= Abstract; KEY= Keyword; TS= Topic

As a result of the identification process, the researcher successfully identified a total of 5942 potentially relevant articles, including 78 articles from Scopus, 114 articles from WoS, and 5750 articles from GS. Database-level inclusion criteria were subsequently applied to refine the search results. These criteria restricted the records to publication within the past five years, journal articles only, and articles written in English. After applying these criteria, 4980 articles were excluded, leaving 962 articles for further review (Scopus: n=14; WoS: n=26; GS: n=922). Due to the large volume of records retrieved from GS, and in line with commonly adopted practices in systematic review, only the first 30 pages of search results (300 articles) were screened, as relevance has been shown to decline substantially beyond this range. As a result, 340 articles were retained from all databases. After removing 21 duplicate articles, 319 unique articles were carried forward to the screening stage.

Table 2

Database-level inclusion criteria

Timeline publication	2020-2024
Document type	Article journals
Language	English
Focus of study	Anthocyanin vasorelaxation effects on cardiovascular
Type of data	Primary

Screening

In the screening stage, the titles and abstracts of the retained articles were reviewed to determine whether they were relevant to the study. All authors took part in the screening process. After this step, 250 articles were excluded, and 69 articles were selected for full test assessment.

Eligibility

The eligibility assessment was then conducted to further ensure that the selected articles matched the research questions and study objectives. At this stage, the full text of each article was carefully reviewed. Following this assessment, 18 articles were excluded because they were not in line with the study objectives. The remaining 51 articles were then included in the quality appraisal stage. All the articles selected from the eligibility process were assessed for quality based on six criteria established by Abouzahra et al. (2020). The six criteria are as follows:

QA1. Is the purpose of the study clearly stated?
QA2. Is the interest and usefulness of the work clearly presented?
QA3. Is the study methodology clearly established?
QA4. Are the concepts of the approach clearly defined?
QA5. Is the work compared and measured with other similar work?
QA6. Are the limitations of the work clearly mentioned?

The quality assessment process was conducted by the lead researcher, with the assistance of two co-researchers. All assessors independently evaluated the 51 articles, after which they convened to compare their evaluation results. For each evaluation criterion, the assessors had three possible responses: yes (1.0 mark), partly (0.5 mark), and no (0 mark). According to Abouzahra et al. (2020), only articles that scored a minimum of 3.0 points and above were selected to be included in this systematic literature review. The results of the assessment revealed that 12 articles met the required minimum score and were carried forward to the next stage, which is data extraction and quality assessment.

Data extraction and quality assessment

This SLR employed a deductive thematic analysis as the primary analytical method. This approach enables researchers to determine themes that align with the research questions and objectives set at the outset. The deductive thematic analysis process adopted in this review was guided by the recommendations of Braun & Clarke (2006). These recommendations include: (1) identification of themes and sub-themes, (2) validation of themes and sub-themes, (3) data extraction for thematic analysis, and (4) reporting of themes in the SLR article.

For the first step, theme identification, the researchers referred to several sources, including ChatGPT and previous studies such as Alam et al. (2021), Woolf et al. (2023), Oumeddour et al. (2024), and Xin et al. (2024). From this process, a total of 2 themes were selected.

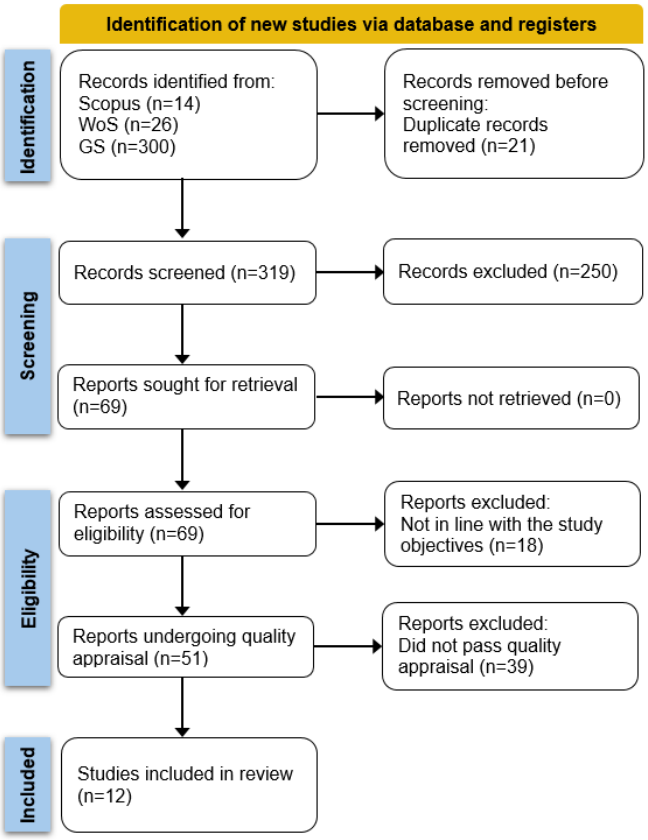
For the validation and verification of themes, the primary researcher, along with two co-researchers, conducted a thorough review and evaluation of all the selected themes. During this process, all researchers examined the suitability and relevance of each theme in relation to the established research objectives and questions. Any theme deemed less appropriate was either excluded or refined for improved alignment.

Subsequently, the primary researcher proceeded with data extraction based on the finalized themes. This phase focused specifically on reviewing the results and discussion sections of the selected articles to extract relevant information corresponding to each theme.

The final step involved reporting the identified themes, which were presented in the form of a literature-based thematic review under the findings section of the study.

Figure 1

The flow diagram



Note: Systematic search strategies carried out by three main processes, namely identification, screening, and eligibility.

RESULTS

Background of the selected studies

The developed themes

Based on the thematic analysis, the following two main themes were identified: (1) the role of anthocyanins in the prevention and management of specific CVD conditions, and (2) the bioavailability and metabolism of anthocyanins. Based on the results, two themes and six sub-themes provided answers to the main research question of this SLR, "What are the vasorelaxation effects of anthocyanins in the prevention and management of cardiovascular-related diseases?". The background of the selected studies explained in the following section.

Anthocyanins in prevention and management of specific CVD conditions

Under the theme of anthocyanins in the prevention and management of specific CVD conditions, three sub-themes were generated, namely atherosclerosis, hypertension, and endothelial dysfunction.

Atherosclerosis

Atherosclerosis is a progressive vascular disease increasingly seen in younger populations (Xin et al., 2024). Anthocyanins, naturally occurring flavonoids in berries, have shown potential in preventing or slowing their progression. Berry polyphenols, especially anthocyanins and resveratrol, inhibit thrombin activity, reduce atherosclerosis, lower low-density lipoprotein (LDL) oxidation, and promote NO production (Kocabas & Sanlier, 2024). They exert anti-atherosclerotic effects by reducing inflammation, inhibiting cholesterol synthesis, improving oxidative balance, and protecting vascular endothelium (Oumeddour et al., 2024; Xin et al., 2024). It works by suppressing free radicals, decreasing reactive oxygen species (ROS) production, and inhibiting the nuclear factor-kappa B (NF-κB) signalling pathway (Oumeddour et al., 2024; Xin et al., 2024). Animal studies report improved lipid profiles and reduce arterial plaque, while human trials show mixed outcomes, with benefits more evident in dyslipidemic individuals. Although promising, further clinical research is needed to confirm their efficacy and therapeutic potential (Xin et al., 2024).

Table 3

The developed themes and sub-themes

Authors/Theme	**Anthocyanins in the prevention and management of specific CVD conditions**			**Bioavailability and metabolism of anthocyanins**		
Sub-themes	**AS**	**HT**	**ED**	**ADME**	**GM**	**AMPC**
Xin et al., 2024	✓	✓	✓		✓	
Kocabas and Sanlier, 2023	✓					
Oumeddour et al., 2024	✓			✓	✓	
Onuh et al., 2023		✓	✓			
Alam et al., 2021		✓			✓	
Carvalho et al., 2024		✓	✓			
Festa et al., 2022		✓				
Woolf et al., 2023			✓		✓	✓
Ockermann et al., 2021				✓		
Grosso et al., 2022					✓	
Garcia et al., 2021						✓
Festa et al., 2023						✓

Note: AS=Atherosclerosis; HT=Hypertension; ED=Endothelial dysfunction; ADME=Absorption, distribution, metabolism, excretion; GM=Gut microbiota; AMPC=Active metabolites and parent compounds

Hypertension

Hypertension is a major global risk factor for cardiovascular disease. Dietary interventions, particularly those rich in flavonoids such as polyphenols found in pigmented fruits like berries, have shown potential in lowering blood pressure in people with hypertension and may also help prevent high blood pressure in healthy or pre-hypertensive individuals (Alam et al., 2021; Onuh et al., 2023; Xin et al., 2024). Anthocyanins help regulate blood pressure by increasing NO production via endothelial nitric oxide synthase (eNOS) activation, promoting vasodilation and endothelial function (Alam et al., 2021; Carvalho et al., 2024; Festa et al., 2022; Xin et al., 2024). Anthocyanins may also block the renin-angiotensin system (RAS) by inhibiting angiotensin-converting enzyme (ACE) and reducing endothelin-1 (ET-1), which are linked to blood vessel constriction, resulting in reducing vasoconstriction naturally and promoting vasorelaxation (Carvalho et al., 2024; Xin et al., 2024).

Endothelial dysfunction

Endothelial function is a key indicator of vascular health, helping regulate blood flow, inflammation, and clotting. Dysfunction of the endothelium is an early sign of atherosclerosis and CVD (Onuh et al., 2023). Studies suggest that anthocyanin-rich fruits such as blueberries can improve endothelial function primarily by reducing vasoconstriction and enhancing vasorelaxation, which ultimately reduces the risk of CVD (Onuh et al., 2023; Woolf et al., 2023). Anthocyanins enhance endothelial function through the NO synthesis, which enhances eNOS expression, increasing NO bioavailability and improving vascular tone (Carvalho et al., 2024; Xin et al., 2024).

Bioavailability and metabolism of anthocyanins

The second theme is related to bioavailability and metabolism of anthocyanins, and it consists of three sub-themes, namely absorption, distribution, metabolism, excretion (ADME), influence of gut microbiota, and active metabolites and parent compounds.

Absorption, distribution, metabolism and excretion (ADME)

Anthocyanins are commonly consumed through fruits, vegetables, and supplements, and are subject to extensive transformation as they pass through the gastrointestinal tract. Their absorption, distribution, metabolism, and excretion are influenced by various physiological and chemical conditions. In general, anthocyanins exhibit low oral bioavailability, often due to poor stability in the gastrointestinal environment and rapid metabolism. For example, Ockermann et al. (2021) noted that only 0.1% of orally administered cyanidin-3-O-glucoside (C3G), a major anthocyanin that was recovered in urine, with plasma concentrations ranging from 10 to 50 nM after doses of 150 mg to 2 g.

However, when isotopically labelled C3G was used (500 mg), researchers observed a more comprehensive metabolic profile. A study by Ockermann et al. (2021) reported that approximately 43.9% of the labelled compound was recovered through urine, breath, and feces combined, with a relative bioavailability of 12.38%. Importantly, C3G was not the only active compound detected. A wide range of 24 labelled metabolites, including phase II conjugates (e.g., cyanidin-glucuronide) and degradation products like protocatechuic acid, vanillic acid, and ferulic acid were also identified. These findings support the idea that anthocyanin bioactivity may result from both the parent compounds and their metabolites.

Further supporting this complexity, Oumeddour et al. (2024) highlighted those anthocyanins undergo significant metabolism via intestinal enzymes and gut microbiota. Anthocyanins were absorbed rapidly, particularly in the stomach and small intestine. Studies suggested the involvement of specific transporters, such as bilitranslocase and glucose transporters (GLUT1 and GLUT3), in gastric absorption. The small intestine was also shown to play a key role, with some anthocyanins being absorbed intact via sodium-dependent glucose transporters (SGLT1), while others were hydrolyzed by intracellular enzymes.

Experimental models showed that anthocyanins are generally stable in gastric conditions but degrade significantly in the intestine due to pH and enzymatic activity (Ockermann et al., 2021). For instance, 8 out of 12 anthocyanins decreased within 30 minutes in simulated duodenal juice, and nearly all were undetectable after 24 hours. Metabolism continued in the liver via phase I (cytochrome P450) and phase II (e.g., UGT, COMT) reactions, followed by enterohepatic recirculation, which contributes to the persistence and complexity of anthocyanin-derived metabolites in the systemic circulation.

Influence of gut microbiota

Food matrix, genetic variations, and gut microbiota all influence anthocyanin absorption and metabolism. Studies suggest that differences in human gut microflora and gene polymorphisms can affect bioavailability. Gut microbiota can metabolize anthocyanins into smaller, more bioavailable products like phenolic acids, which retain antioxidant and anti-inflammatory properties (Alam et al., 2021).

Gut microbiotas play a pivotal role in the metabolic transformation and bioavailability of dietary anthocyanins. Following ingestion, anthocyanins are only partially absorbed in the stomach and small intestine, with the majority reaching the colon, where they undergo extensive microbial metabolism (Oumeddour et al., 2024; Woolf et al., 2023; Xin et al., 2024). In the colon, specific gut bacteria facilitate enzymatic processes such as deglycosylation, demethylation, and dehydroxylation, converting anthocyanins into more bioavailable and bioactive compounds, including aglycones and various phenolic acids, such as protocatechuic acid, gallic acid, and ferulic acid (Woolf et al., 2023; Xin et al., 2024). These microbial metabolites are believed to have superior antioxidant, anti-inflammatory, and vasodilatory properties compared to the parent compounds (Oumeddour et al., 2024; Xin et al., 2024).

Several bacterial species, including *Clostridium sphenoides*, *Lactobacillus plantarum*, and *Bifidobacterium longum*, have been identified as key players in this metabolic transformation (Woolf et al., 2023). These microbial processes not only enhance the systemic absorption of anthocyanin-derived metabolites but also influence their eventual distribution and excretion via urine or feces. Despite these transformations, less than 1% of intact anthocyanins are recovered in the urine, underscoring the importance of gut microbial metabolism in determining their physiological effects (Woolf et al., 2023).

Importantly, the interaction between anthocyanins and the gut microbiota is bidirectional. While gut bacteria metabolize anthocyanins, the anthocyanins themselves can modulate the composition and function of the microbiota, promoting the growth of beneficial bacteria (Xin et al., 2024). This positive modulation can enhance the production of health-promoting microbial metabolites such as short-chain fatty acids (SCFAs), which are involved in inflammation regulation, lipid metabolism, and vascular function, all of which are relevant to cardiovascular health and diseases like atherosclerosis and hypertension (Grosso et al., 2022; Xin et al., 2024).

Furthermore, gut microbiota composition can influence the efficiency of anthocyanin metabolism. A healthy and diverse microbiome tends to support greater transformation of anthocyanins into active metabolites, while dysbiosis may impair this process and reduce their effectiveness (Oumeddour et al., 2024). Additionally, polyphenols, including anthocyanins have been shown to reduce harmful microbial metabolites such as trimethylamine-N-oxide (TMAO), which is associated with vascular inflammation, and to increase SCFA production by stimulating the growth of microbes such as *Lactobacillus* and *Bifidobacterium* (Grosso et al., 2022).

Active metabolites and parent compound

Anthocyanins, primarily found in berries and other colourful fruits, are bioactive polyphenols known for their cardiovascular benefits. However, their parent compounds, defined as the intact dietary anthocyanins present as glycosylated anthocyanidins (e.g., cyanidin, delphinidin, pelargonidin, peonidin, petunidin, and malvidin), are poorly absorbed, with only a small fraction detected in plasma after ingestion. Instead, the health effects of anthocyanins are attributed mainly to their metabolites, which are formed during digestion and metabolism. These metabolites include phenolic compounds such as protocatechuic acid (PCA), vanillic acid (VA), hippuric acid, and ferulic acid, which are more bioavailable and possess antioxidant and anti-inflammatory properties (Garcia & Blesso, 2021; Woolf et al., 2023).

Following ingestion, anthocyanins undergo extensive metabolism in the gastrointestinal tract, where they are broken down by gut microbiota into smaller phenolic metabolites, many of which circulate in plasma and contribute to vascular health. These metabolites are detected in plasma and urine within hours of consumption, with peak concentrations typically reached between 2- and 30-hours post-ingestion (Festa et al., 2023; Garcia & Blesso, 2021). Despite the low bioavailability of parent anthocyanins, circulating metabolites have been shown to improve endothelial function, reduce oxidative stress, and modulate NO signalling, which is crucial for vascular health (Festa et al., 2023).

One of the key pathways through which anthocyanin metabolites exert their effects is the protein kinase B (Akt)-eNOS-NO pathway. Metabolites like PCA and VA, which are more stable and bioavailable than their parent compounds, have been shown to enhance NO bioavailability by reducing oxidative stress and suppressing superoxide production (Festa et al., 2023). These metabolites are believed to restore eNOS activity, which is essential for maintaining vascular tone and function. Furthermore, these metabolites, particularly PCA, also inhibit the adhesion of monocytes to endothelial cells, a critical early step in atherosclerosis, by reducing the expression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) (Festa et al., 2023).

In addition to the Akt-eNOS-NO pathway, NF-κB signalling also plays a critical role in the inflammatory processes underlying atherosclerosis. Anthocyanin metabolites like PCA and VA have been shown to modulate NF-κB activation, reducing the phosphorylation of its p65 subunit and thereby decreasing the expression of proinflammatory cytokines and adhesion molecules (Festa et al., 2023). This reduction in NF-κB activity leads to less monocyte adhesion and attenuates the progression of atherosclerosis, highlighting the potential of anthocyanin metabolites as anti-inflammatory agents (Woolf et al., 2023). Moreover, in animal models, PCA has been demonstrated to lower the expression of VCAM-1 and intercellular adhesion molecule-1 (ICAM-1), key markers of endothelial dysfunction and atherosclerosis (Festa et al., 2023).

Another important pathway activated by anthocyanin metabolites is nuclear factor erythroid 2-related factor 2 (Nrf2), a transcription factor that regulates antioxidant defences. Anthocyanin-derived metabolites, such as PCA and VA, activate the Nrf2 pathway, leading to the upregulation of antioxidant enzymes like heme oxygenase-1 (HO-1) and superoxide dismutase (SOD). These enzymes protect endothelial cells from oxidative damage, enhance vascular function, and reduce inflammation (Festa et al., 2023; Garcia & Blesso, 2021). For instance, VA has been shown to scavenge free radicals and restore SOD activity in diabetic hypertensive rats, while PCA activates Nrf2 in endothelial cells, improving their resistance to oxidative stress (Festa et al., 2023; Garcia & Blesso, 2021).

DISCUSSION

The present review highlights two central and interconnected themes related to anthocyanins and cardiovascular health: their vasculoprotective effects and the complexities of their bioavailability and metabolism. While anthocyanins have garnered attention for their antioxidant and anti-inflammatory properties, their efficacy *in vivo* is intricately linked to their biotransformation within the human body, particularly via gut microbiota. Understanding both their direct vascular actions and their metabolic fate is critical to appreciating their potential therapeutic roles in atherosclerosis and hypertension.

Anthocyanins and vascular function

A growing body of evidence supports the role of anthocyanins in improving endothelial function and mitigating vascular inflammation; two key factors in the pathogenesis of atherosclerosis and hypertension. *In vitro* and *in vivo* studies consistently demonstrate that anthocyanins can enhance eNOS activity and NO bioavailability, contributing to vasodilation and improved vascular tone (Carvalho et al., 2024; Festa et al., 2022; Xin et al., 2024). These effects are primarily mediated via activation of the phosphoinositide 3-kinase (PI3K)/Akt-eNOS-NO signalling pathway, as well as the suppression of oxidative stress, which otherwise impairs NO signaling (Festa et al., 2023).

Moreover, anthocyanins and their metabolites modulate inflammatory signaling by inhibiting the activation of NF-κB, thereby reducing the expression of vascular adhesion molecules such as VCAM-1 and ICAM-1. These adhesion molecules are implicated in leukocyte recruitment and the early stages of atherogenesis (Festa et al., 2023). Animal studies further confirm that anthocyanin supplementation reduces inflammatory cytokine expression, improves lipid profiles, and inhibits plaque formation, which supports their potential application in cardiovascular disease prevention.

Bioavailability and metabolism: A critical consideration

Despite the compelling evidence of vascular benefits, anthocyanins are characterized by low oral bioavailability, which is often cited as a limitation to their clinical application. Studies report that only a small fraction of ingested anthocyanins, often less than 1%, is detectable in plasma or urine in their native form (Ockermann et al., 2021). However, this perceived limitation is counterbalanced by extensive metabolism that occurs throughout the gastrointestinal tract, liver, and especially the colon.

Anthocyanins are absorbed in the stomach and small intestine via active transporters such as bilitranslocase and glucose transporters (GLUT1/3, SGLT1), though this absorption is limited by their instability at neutral pH and rapid enzymatic degradation (Oumeddour et al., 2024). Following absorption, they undergo Phase I and II hepatic metabolisms, generating various conjugates that re-enter the gut via enterohepatic circulation. These processes result in a diverse array of metabolites with potential bioactivity, rather than reliance on the parent anthocyanin structure alone (Ockermann et al., 2021).

Notably, isotopically labeled studies (e.g., Ockermann et al., 2021) have demonstrated that anthocyanins are extensively metabolized into over 20 distinct compounds, including PCA, VA, ferulic acid, and hippuric acid. These metabolites are often more stable and bioavailable than the parent compound and are likely the true mediators of the health effects observed in vivo.

The role of gut microbiota

The gut microbiota serves as a central hub in anthocyanin metabolism. After escaping absorption in the upper gastrointestinal tract, the majority of anthocyanins reach the colon, where they are catabolized by bacterial enzymes into low-molecular-weight phenolic compounds. Bacterial species such as *Clostridium sphenoides*, *Lactobacillus plantarum*, and *Bifidobacterium longum* have been implicated in these transformations, producing metabolites that retain and often exceed the bioactivity of their precursors (Woolf et al., 2023).

These microbial-derived phenolic acids exhibit anti-inflammatory, antioxidant, and vasodilatory effects, making them key contributors to the anthocyanins' vascular benefits. For example, PCA and VA have been shown to restore eNOS activity, enhance NO production, reduce ROS, and suppress the expression of inflammatory markers by modulating NF-κB and Nrf2 signaling pathways (Festa et al., 2023; Garcia & Blesso, 2021; Woolf et al., 2023). In this context, anthocyanins can be viewed as prebiotic-like agents that not only depend on but also modulate gut microbial composition to promote vascular health.

Importantly, the interaction between anthocyanins and gut microbiota is bidirectional. While microbiota aid in anthocyanin metabolism, anthocyanins can favorably reshape microbial communities by promoting beneficial taxa (e.g. Lactobacillus, Bifidobacterium) and suppressing pathogenic ones. This mutualistic relationship has additional cardiovascular implications, including reduced production of harmful metabolites such as TMAO and increased levels of SCFAs, which regulate blood pressure, lipid metabolism, and endothelial function (Grosso et al., 2022; Xin et al., 2024).

Metabolites: The true bioactive agents?

The growing consensus is that the biological efficacy of anthocyanins is primarily driven by their metabolites rather than the parent compounds. Metabolites such as PCA and VA have been shown to accumulate in plasma and exert diverse vascular effects (Garcia & Blesso, 2021; Woolf et al., 2023). These include upregulation of endothelial antioxidant defenses via Nrf2 signaling, suppression of monocyte adhesion via NF-κB inhibition, and improvement of endothelial NO production through the Akt-eNOS pathway. These pathways are critically involved in maintaining vascular homeostasis and preventing atherosclerotic progression (Festa et al., 2023).

Furthermore, the anti-inflammatory effects of anthocyanin metabolites extend to systemic modulation of cytokine expression and immune cell recruitment, central processes in the development of cardiovascular diseases. The timing of metabolite appearance in plasma (typically 2–30 hours post-ingestion) aligns with observed vascular improvements, further supporting the relevance of these metabolites in mediating anthocyanin effects.

Limitations and strengths

Several limitations should be considered when interpreting the findings of this systematic review. First, only 12 studies met the inclusion criteria, reflecting a limited evidence base. Additionally, heterogeneity across the included studies in terms of study design, populations, interventions, and outcome measures limited direct comparison of findings. Variability in the methodological quality of the included studies may also have influenced the overall interpretation of the results.

At the review level, the search was restricted to studies published in English and within the past five years, which may have led to the exclusion of relevant studies published earlier or in other languages. Furthermore, the review was limited to three electronic databases (Scopus, WoS, and GS), and grey literature was not comprehensively searched, increasing the potential for publication bias. Although the review process followed a systematic approach, the possibility of reviewer bias cannot be entirely excluded.

Despite these limitations, this systematic review has several methodological strengths. A comprehensive and transparent search strategy was applied across multiple major databases, and study selection was guided by clearly defined inclusion and exclusion criteria. Data extraction and quality assessment were conducted systematically, with the involvement of multiple reviewers, enhancing the reliability and validity of the findings. Additionally, the use of thematic analysis enabled an in-depth synthesis of evidence across heterogeneous studies, providing meaningful insights despite methodological diversity.

CONCLUSION AND FUTURE DIRECTIONS

Collectively, current evidence supports the multifaceted role of anthocyanins in cardiovascular protection. While their low bioavailability has traditionally been viewed as a limitation, it is now evident that their extensive transformation into active metabolites via host and microbial metabolism enables broad systemic effects. These effects are mediated by improvements in endothelial function, reduction in oxidative stress, and attenuation of inflammatory signalling, all of which are relevant to atherosclerosis and hypertension.

Future research should aim to identify the most potent anthocyanin-derived metabolites and uncover their specific mechanisms of action. Additionally, it is important to elucidate how individual microbiota profiles influence the metabolism and efficacy of anthocyanins. Investigating dietary and probiotic strategies to enhance the microbial bioconversion of anthocyanins could further optimize their therapeutic potential. Finally, translating preclinical findings into well-controlled human intervention studies with standardized anthocyanin dosing and precise tracking of resulting metabolites will be essential for confirming their clinical relevance and efficacy.

Ultimately, anthocyanins may be most accurately viewed as prodrugs whose cardiovascular benefits rely on a complex interplay between host metabolism and gut microbial activity. Recognizing this dynamic offers a new perspective on dietary polyphenols opening the door to personalized nutrition strategies aimed at enhancing vascular health.

AUTHOR CONTRIBUTION

The study was conceptualised and designed by Liyana Nursyahirah Johari and Wan Amir Nizam Wan Ahmad. Resource acquisition was carried out by Liyana Nursyahirah Johari and Wan Amir Nizam Wan Ahmad. The manuscript was reviewed by Liza Noordin and Wan Amir Nizam Wan Ahmad. Final approval of the manuscript was done by Wan Amir Nizam Wan Ahmad and Liza Noordin.

ETHIS APPROVAL

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest in this work.

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