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REVIEW

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Anthocyanins: Plant-based flavonoid pigments with diverse biological activities

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ABSTRACT

Anthocyanins are flavonoid containing polyphenolic phytochemicals. They are widely present in plants and accounts for different color shades displayed by the plant organs. A broad range of health-revitalizing effects is attributed to anthocyanins, constituting a vital part of the human diet. They are also accountable for ameliorating the detrimental effects of various lifestyle diseases, including cancer, cardiovascular disorders, neurological disorders, etc. These beneficial impacts highly depend on the bioavailability of anthocyanins, governed by their absorption and metabolism in the human body. The primary goal of this review is to summarize the latest anthocyanin knowledge while focusing on the chemistry, pharmacokinetics, and various biological advantages with anti-cancer, neuroprotective, antidiabetic, antioxidant, cardiovascular protective, vision improvement, antiviral, and antimicrobial effects.

1. Introduction

The term Anthocyan has been derived from the Greek word Anthos, which means flower, and kyanos means blue (Marquart, 1835). It was introduced by Ludwig Clamor Marquart, a German pharmacist, to distinguish the blue color pigments of various flowers. In the plant kingdom, most species contain anthocyanins (Richardson and Harborne, 1990). They exist in all tissues, including leaves, stems, fruits, flowers, and roots of the higher plants. Anthocyanins are found in the cell vacuole, which gives color shade to the plant tissue such as red, blue, and purple as per their essential structure organization. Fruit plants such as red raspberry, blackberry, bilberry, blueberry, grapes, zante currants, cherry, blood orange, red cabbage, red onion, purple sweet potato, red-skinned potato, fennel, eggplant, and radish can be found in these plants (Table 1).

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Anthocyanins play a shielding role in vegetables and plants, including monosaccharide transport vehicles, the absorbance of harmful radiations, and osmotic adjuster during frost or drought (Clifford, 2000). These also play a critical role in attracting livestock facilitating pollination and dispersal of seeds (Eder, 2000; Timberlake and Henry, 1988).

Recently, anthocyanins have been the primary focus of researchers for their pharmacological effects, biological properties, and high-water solubility. Certain nutritionists are progressively suggesting the utilization of foods containing anthocyanins. They are less active compared with related drugs but show physiological results of great importance when consumed in a regular diet. In traditional medicinal items, several red flowers (clove, hibiscus, pineapple sage, and rose), purple (passionflower, lavender, and purple sage), and blue (blue rosemary and cornflower) are used (Calderaro et al., 2020).

A few exceptional reports have delineated these natural dietary phytochemicals in terms of their intake (McGhie and Walton, 2007), metabolism (He and Giusti, 2010), pharmacokinetics (Kay, 2006), molecular mechanisms (Li et al., 2017), and bioavailability (Fernandes et al., 2014) over the past few years. In recent years, the enthusiasm for studying anthocyanins' health and medical benefits has increased rapidly. Vanamala (2019) has summarized the effect of red and purple anthocyanins on colon cancer stem cells. Khan et al. (2019) have checked out the neuroprotective effect of anthocyanins, whereas Krga and Milenkovic (2019) have described the impact of anthocyanins on cardiovascular diseases.

Table 1. Total anthocyanin content in common fruits and vegetables (Clifford, 2000; Eder, 2000; Timberlake and Henry, 1988)

Fruit or vegetable	Total anthocyanin content (mg/kg)
Cherry	3500-4500
Cranberry	460-2000
Strawberry	127-360
Grapes (blue)	80-3880
Orange	2000
Grapes (red)	300-7500
Plum	19-250
Cabbage (red)	250
Onion (red)	Up to 250
Bilberry	4600
Eggplant	7500
Elderberry	2000-15600
Radish (red)	110-600

This review describes the chemistry of anthocyanins and recent literature about various biological benefits of anthocyanins, such as anti-cancer activity, neuroprotective activity, anti-diabetic, antioxidant, cardiovascular protecting activity, vision improvement, antiviral and antimicrobial effects (Figure 1).

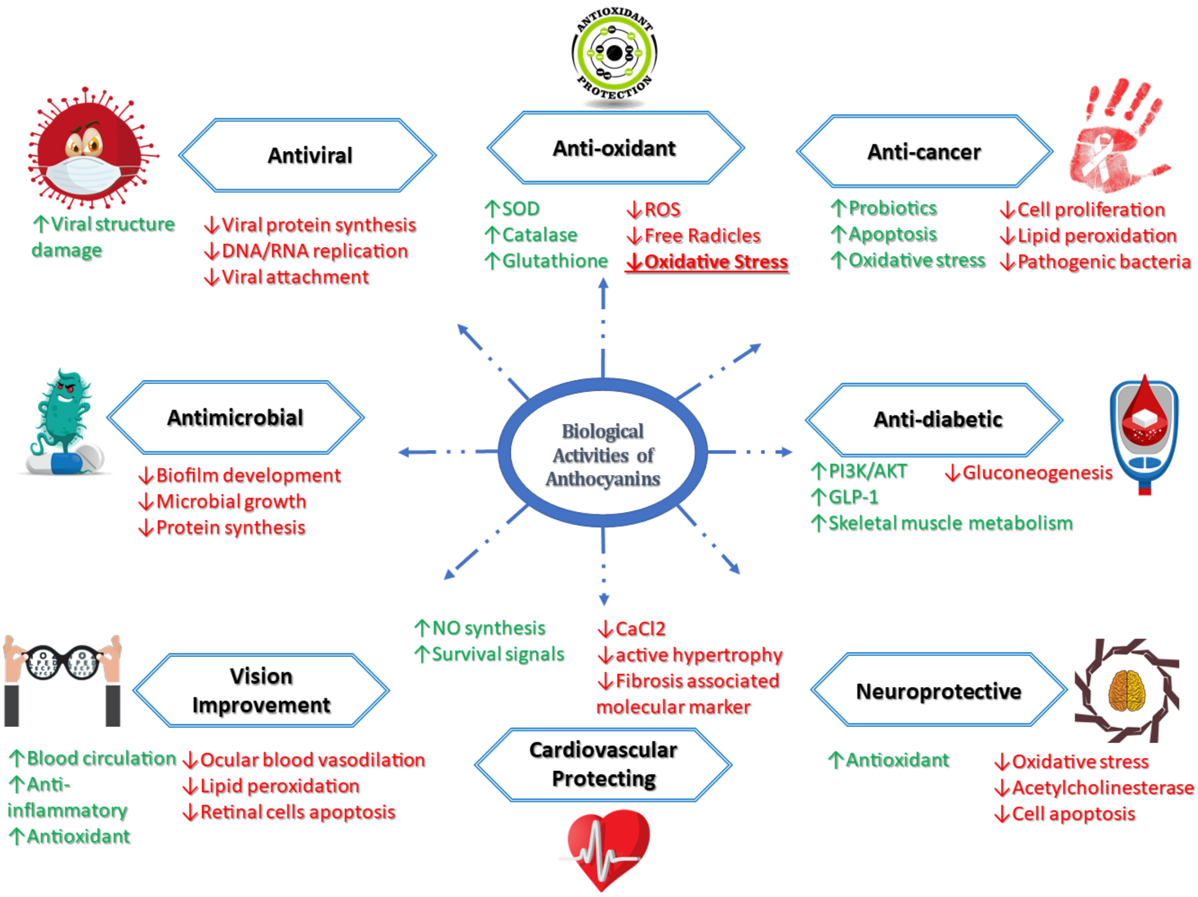
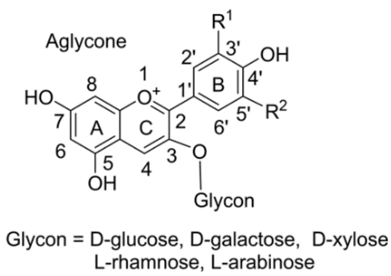


Figure 1. Biological benefits of anthocyanins

2. Chemistry of anthocyanins and anthocyanidins

Anthocyanins are anthocyanidin glycosides, have a distinctive carbon skeleton with 2 phenyl rings (A and B rings, Figure 2) and a heterocyclic pyran (C ring) fused with A ring (Castañeda-Ovando et al., 2009). Cytoplasmically-localized glycosyltransferases generally catalyze glycosylation, and the most common sugars are L-arabinose, L-rhamnose, D-galactose, D-glucose, and D-xylose. Sugars are usually bound to the 3-hydroxyl position of anthocyanidins or the 5- or 7- position of anthocyanidins (Pina et al., 2012). Anthocyanidins (aglycone) are chemically flavylium salts or (2-phenylchromenylium) ion compounds. With a molecular weight of 207.25, the molecular formula for the flavylium ion is $C_{15}H_{11}O^+$. The biosynthetic process of anthocyanins is initiated from the acetate and shikimate pathways. Anthocyanins are transported into the vacuole by 3 possible mechanisms after completion of their biosynthesis: (i) via vesicle-mediated mass transport; (ii) via glutathione S-transferase-like protein; and (iii) via flavonoid/H^+ antiporter (Zhang et al., 2006). In the vacuole, the anthocyanins occur as the equilibrium of four molecular species, are essentially flavylium cation (I), the quinoidal base (II), the carbinol pseudo base (III), and the chalcone pseudo base (IV) (called as secondary structures, Figure 3) (Prior and Wu, 2006).

Over 600 anthocyanins have been identified, and the number continues to increase exponentially (Kong et al., 2003). Anthocyanins can be distinguished based on (i) the number and location of the hydroxyl group, (ii) the degree of hydroxyl group methylation, (iii) the number and nature of sugar (glycon) molecules linked to the aglycone portion, and (iv) the acylation of the sugar (aliphatic or aromatic acid) molecules. Caffeoylated anthocyanin, malonylated anthocyanin, acrylated anthocyanin, and coumaroylated anthocyanin can be further categorized as the acylated form of anthocyanins. Both color and hue of anthocyanins are affected by hydroxylation, glycosylation, methylation, and acylation pattern of the phenyl constituent of the anthocyanidins, and the color varies from orange-red (cyanidin, pelargonidin) to purple and pink-magenta (petunidin, delphinidin, malvidin, and peonidin) (da Costa et al., 2000; Iversen, 1996; Keppler and Humpf, 2005; Khoo et al., 2017; Lo Piero, 2015).



S. No.	Anthocyanidin (or aglycone)	R^1	R^2	Distribution in fruits and vegetables (%)	Major metabolic degraded products
1	Cyanidin	OH	H	50	Protocatechuic acid
2	Delphinidin	OH	OH	12	Gallic acid
3	Pelargonidin	H	H	12	4-Hydroxybenzoic acid
4	Petunidin	OCH_3	OH	7	3-*O*-methylgallic acid
5	Lanvidin	OCH_3	OCH_3	7	Syringic acid
6	Peonidin	OCH_3	H	12	Vanillic acid

Figure 2. Anthocyanidins relevance to human diet - general structure, distribution, and metabolic products (Leong et al., 2018; Turturică et al., 2015)

It is currently thought that six anthocyanins are relevant to the human diet (Figure 2). Their distribution in fruits and vegetables are 50% cyanidin, 12% delphinidin, 12% pelargonidin, 12% peonidin, 7% malvidin, and 7% petunidin (Leong et al., 2018; Turturică et al., 2015).

Due to the presence of electron-deficient flavylium cation, anthocyanins are sensitive and highly reactive, and thus easier to be degraded (Felgines et al., 2007; Yang et al., 2011). Anthocyanin's stability is affected by its molecular structure. Due to the reactive -OH group; delphinidin and cyanidin are considered more stable than peonidin, malvidin, and petunidin. Different transformations at position 4 resulting in hetero-dimers, condensation, and cycloaddition products, make anthocyanins more durable. Glycosylation at position 3 makes it stable, whereas glycosylation at position 5 leads to instability. The stability of anthocyanins increases with acylation by intramolecular pigmentation and self-association reactions (Clifford, 2000).

Since the anthocyanins' molecular structure has an ionic nature, the solution's pH determines the anthocyanins' color (Fossen et al., 1998). In acidic solution (pH 1-3), some of the anthocyanins appear red due to flavium cation formation (I), whereas in neutral pH, they appear colorless due to carbinol pseudo base formation (III). At the same time, color changes from blue to purple as pH increases to 7-8 due to the quinoidal base formation (IV) (Figure 3) (Hribar and Poklar Ulrih, 2014). It is determined that the stability of anthocyanins is directly proportional to the density of their solutions, but intermolecular interaction within the formulation often improves balance by hindering water-based anthocyanin deterioration.

3. Absorption of anthocyanins

In recent years, the study of dietary intake and health-promoting effects of anthocyanins has been increased. The aiding and therapeutic benefits of anthocyanins directly depend on the pharmacokinetic properties (absorption, distribution, metabolism, and excretion) and consequently bioavailability of individuals. The absorption mainly relies on the chemical structure, nutrient components of food, gut microbiota, and individual genetic factors (Felgines et al., 2007; Yang et al., 2011). For instance, anthocyanins based on pelargonidin or 3'-hydroxyanthocyanins are more quickly absorbed than other anthocyanins with more B-ring substituents. Usually, non-acylated anthocyanins show more absorbance capacity as compared to acylated anthocyanins.

The absorption of anthocyanin occurs within the stomach and mainly occurs in the small intestine, although it is absent in the intestinal tract. Bilitranslocase, an organic anion membrane transporter located in the gastric mucosa, produces gastric absorption (Passamonti et al., 2002). Injection of red grape wine anthocyanins into the stomach of Wistar male rats, followed by the blood from the portal vein analysis, confirmed the existence of malvidin-3-*O*-glucoside in the heart (Passamonti et al., 2003). Similarly, hexose transporters expressed on intestinal epithelium are accountable for anthocyanins' active and passive transport (Han et al., 2019). Talavéra et al. (2004) used an *in situ* perfusion procedure to examine the absorption of anthocyanins in the small intestinal tract. The rate of anthocyanins absorption in the small intestine was determined by measuring the number of anthocyanins left in the effluent; the absorption rate for cyanidin-3-*O*-glucoside was found to be 22%, and for malvidin-3-glucoside, it was found to be 10-11%. He et al. (2009) determined that 7.5% of the black raspberry anthocyanins administered were absorbed into the small intestinal tissues of rats. In line with the above predictions, animal model studies also demonstrate that anthocyanins quickly appear in the systemic circulation (6-20 minutes) and reach a maximum blood level after 15-50 minutes (Pojer et al., 2013). However, few experimental studies demonstrate contradictory results, presenting that there is a minimal quantity of anthocyanins (i.e., < 1% of the consumed amount) in systemic blood circulation or the plasma (Prior, 2004).

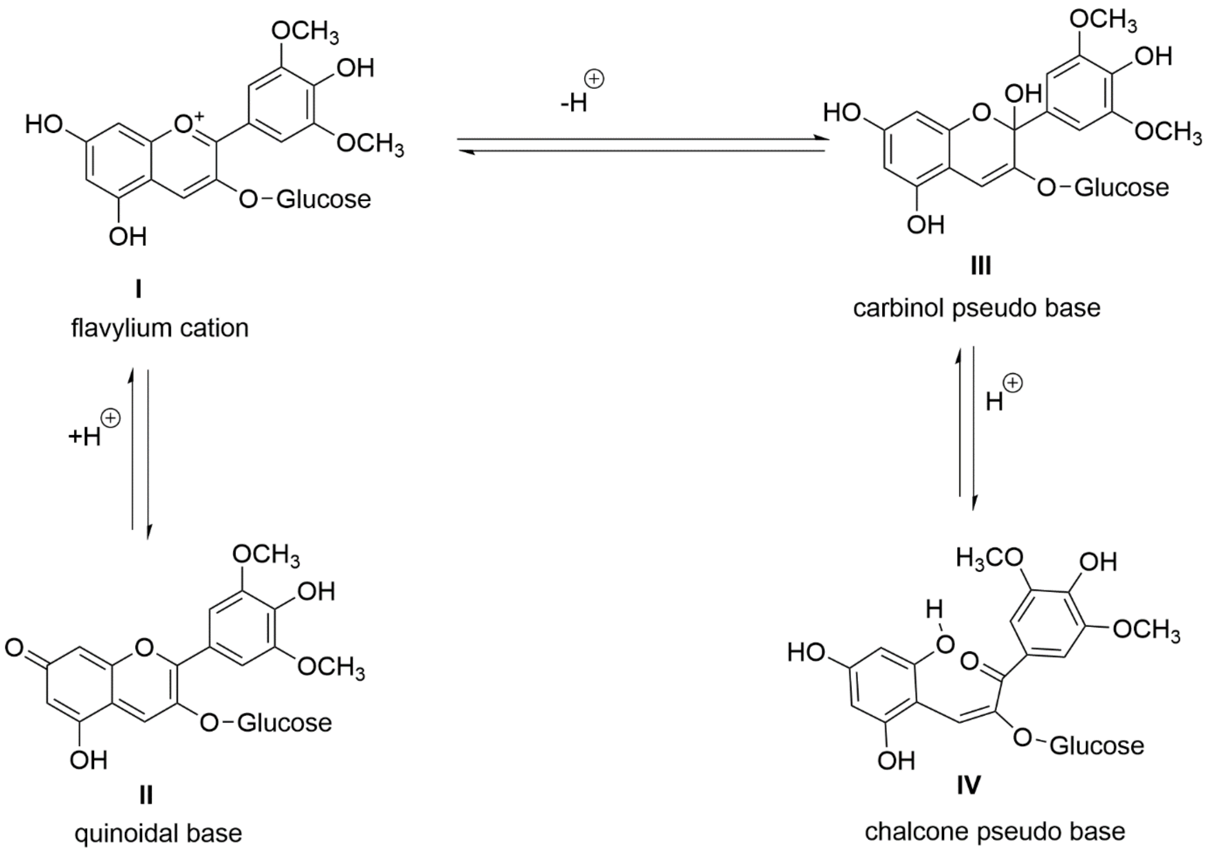


Figure 3. Anthocyanins equilibria (Prior and Wu, 2006)

Temperature, intestinal pH, and the microbes influence the digestion of anthocyanins in the human intestinal tract (Hidalgo et al., 2012). Breaking the glycosidic linkage among the sugar and aglycone moieties is activated by intestinal microflora and releases aglycone. The microbes responsible for the metabolism include *Clostridium*, *Bacteroides*, *Eggertheilla*, *Ruminococcus*, and *Eubacterium* (Blaut and Clavel, 2007; De Ferrars et al., 2014; Jang and Kim, 1996). The basic conditions and microbiota further convert aglycons into phenolic aldehydes and acids (Hanske et al., 2013). When cyanidin-3-glucoside was incubated with the intestinal bacteria, a critical aggregation of metabolic degradation products including 2,4,6-trihydroxy benzaldehyde and protocatechuic acid was brought about. The reported primary metabolites from anthocyanins relevant to the human diet are protocatechuic acid, 3-*O*-methyl gallic acid, 3,5-dihydroxybenzoic acid, vanillic acid, and syringic acid contingent upon the parent anthocyanin structure (Figure 2) (Muñoz-González et al., 2013; Nurmi et al., 2009). The usual chemical transformations such as demethylation, hydrogenation, hydroxylation, demethoxylation, decarboxylation, hydrolysis, and dehydroxylation occur during the degradation of anthocyanins and their metabolites (Forester and Waterhouse, 2008; Stalmach et al., 2013).

4. Biological activities of anthocyanins

4.1. Antioxidant effects

Compounds that are easier to oxidize are often termed antioxidants. They can also be described as molecules, giving free hydrogen or electron atom to react with free radicals. Several therapeutic activities of anthocyanins are mainly contributed by their antioxidant property (Joshi et al., 2017; Lucioli, 2012). Anthocyanins' free radical scavenging property confers a superior antioxidant activity. The antioxidant activity of anthocyanins relay upon its structure, and the properties are influenced by (i) the B ring catechol moiety; (ii) the number of –OH group; (iii) the hydroxylation and methylation pattern; (iv) acylation; (v) glycosylation; and (vi) the oxonium ion present in the C ring. Glycosylation of anthocyanins lessens the antioxidant properties due to the inability of anthocyanin radicals to delocalize its electron. Acylation of anthocyanins with phenolic acids shows a prominent result of increased antioxidant activities. Diacylation of anthocyanins also shows increased antioxidant activity, whereas 5-glycosylation minimizes its activity. When comparing anthocyanins with oligomeric proanthocyanidins and other flavonoids, anthocyanins' antioxidant strength and hydrogen-donating effect are greatly affected by the positive charged O_2 atom in the scaffold (Shaik et al., 2018; Smeriglio et al., 2016). There may be two mechanisms by which anthocyanins impose their antioxidant effect, i.e., direct and indirect pathways. These exhibit direct free radical scavenging behavior due to the hydrogen (electron) donating potential of the flavonoid molecules, which can form a bond with reactive oxygen species (ROS) such as singlet oxygen ($^1O_2$), superoxide (O_2^-), hydroxyl radical species ($\cdot OH$), and hydrogen peroxide (H_2O_2) (Borkowski et al., 2005; Janeiro and Brett, 2007; Tsuda et al., 1996). On the other hand, anthocyanins increase the antioxidant property through various mechanisms such as: (i) increasing or restoring the superoxide dismutase (SOD), glutathione peroxidase, and the antioxidant enzymes, consequently elevating glutathione content; (ii) decreased production of DNA oxidative adducts, decreased production of endogenous ROS by obstructing xanthine oxidase and NADPH oxidase, or by altering the arachidonic metabolism and respiration of mitochondria; and (iii) activation of genes that code for the above antioxidant enzymes.

Anthocyanins-rich food mostly contains cyanidin, malvidin, peonidin, and these all play a crucial role in scavenging radicals and protecting them from DNA damage. For example, eggplant shows antioxidant activity by scavenging the oxygen-free radical with > 65% scavenging activity achieved in 2,2-diphenylpicrylhydrazyl (DPPH) assay (Li et al., 2012). Similarly, sweet cherry (*Prunus avium* L.) anthocyanins demonstrate antioxidant properties with above 70% activity on the DPPH (Sonmez et al., 2022). Likewise, blackberries exhibit the scavenging action against superoxide radicals, and the anthocyanins present in red cabbage protect it from oxidative stress (Igarashi et al., 2000; Murapa et al., 2012; Wang and Jiao, 2000; Zafra-Stone et al., 2007). Delphinidin-3-glucoside (IC_{50} values: 1.6 and 0.7 µM) and delphinidin (IC_{50} values: 2.6 and 0.9 µM) shows maximum inhibitory effect against $^1O_2$ scavenging activity and lipid peroxidation, respectively, whereas pelargonidin has the greatest inhibitory effect on the -OH radical scavenging activity with IC_{50} value of 8.5 µM (Tsuda et al., 1996). The presence of 3-OH groups on the B ring advances the antioxidant properties of delphinidin. However, oxidation of the hydroxyl group can be achieved by donating one electron (semiquinone form) or two-electron (quinone form).

4.2. Anti-cancer activity

Anthocyanins' chemopreventive effects are largely due to their anti-inflammatory and antioxidant activities. The consumption of anthocyanin-rich foods and vegetables leads to anti-cancer effects through different mechanisms like (i) anti-angiogenesis and inducing apoptosis, (ii) prohibiting oxidative DNA damage, (iii) inhibiting COX-2 enzymes (iv) inhibition of cell proliferation. 2.5-100 µM extracts from anthocyanin-containing berries of different types and eggplant and black rice tend to inhibit the invasion of cancer cell types in Matrigel (Wang and Stoner, 2008). Strong anti-proliferative activity was shown by the hydrolyzed pulp of Jamun with an IC_{50} value of 59 ± 4 µg/ml. Anthocyanins extracted from berries, especially black raspberries, help lower the epigenetic factors involved in cancer. Histone modification and DNA methylation are part of this epigenetic regulation of gene expression. They are involved in the demethylation of tumor suppressor genes and the suppression of DNA methyl transferase and thus help prevent cancer (El-Ella and Bishayee, 2019). Studies of anthocyanin extracts *in vivo* and *in vitro* (cancer cells) have shown anti-carcinogenic effects on breast cancer (Singletary et al., 2007), prostate and liver cancer (El-Ella and Bishayee, 2019; Lin et al., 2017), colon cancer (Jaganathan et al., 2014) and lung cancer. Anthocyanin rich extract of *Syzygium cumini* (Aqil et al., 2012), purple-fleshed sweet potato (clone P40) (Lim et al., 2013), raspberries, strawberry (Giampieri et al., 2018; Zhang et al., 2008), sorghum, black lentil, and red grapes exhibited anti-proliferative action on the cancer cells (Grimes et al., 2018; Mazewski et al., 2018). Anthocyanidins seem to inhibit different kinase pathways and show better antiproliferative activity than anthocyanins (Zhang et al., 2005). Delphinidin-3-glucoside and cyanidine-3-glucoside inhibit the development of colon cancer HT-29 cells (Grimes et al., 2018). Delphinidin has the best inhibitory characteristics as it possesses a hydroxyl group in its structure, which seems to show its effect by halting the MAPK pathway (Hou, 2003). Anthocyanins, gallic acid, 3-*O*-methyl gallic acid, and 2,4,6-trihydroxybenzaldehyde metabolites reduce cell viability and apoptosis of colon cells in Caco-2 cells (Forester et al., 2014). A recent study shows that the petal anthocyanins from *Crocus sativus* (saffron) have a beneficial effect on the mouse model with polycystic ovary syndrome. Saffron petal anthocyanins hinder the polycystic ovary syndrome by improving antioxidant enzymes, steroidogenic dysregulation of ovarian steroids, and inflammatory markers (Moshfegh et al., 2022). Likewise, it was found that the total anthocyanins extracted from sweet cherry (*Prunus avium* L.) inhibit human carbonic anhydrase I and II enzyme activities and thus show the anticancer effect (Sonmez et al., 2022).

4.3. Anti-diabetic activity

Diabetes (Type-2) mainly emerges because of continuous stress on the pancreas, β-cells degeneration, decreased insulin level, and expanded insulin resistance. In hyperglycemic and hyperlipidemic states, there is high oxidative stress upon pancreatic β-cells, which may lead to the execution of these cells. Consumption of anthocyanins can reduce free radicals' excessive production, which prevents the β-cells from oxidative damage (Al-Awwadi et al., 2005; Cao et al., 2019; Hossain et al., 2016). Anthocyanins inhibit alpha-glucosidase, an enzyme responsible for the hydrolysis of small intestinal carbohydrates that helps control diabetes (Zhang et al., 2019). Similarly, the anti-inflammatory effects of anthocyanins manifested by decreasing monocyte chemotactic protein-1 (MCP-1), tumor necrosis factor-alpha (TNF-alpha), interleukin-6 (IL-6) expression help in the recovery of insulin resistance and type 2 diabetes (Khanra et al., 2015; Zhu et al., 2012). Infusion of pelargonidin on streptozotocin (STZ)-induced diabetes rats brought about an increased serum level of superoxide dismutase and lowered the level of malondialdehyde and fructosamine (Roy et al., 2008). Cyanidin, a major anthocyanidin present in plants, vegetables, and fruits, helps in inciting insulin secretion by raising the level of intracellular calcium in pancreatic β-cells (Pesce and Menini, 2019). Zhu et al. (2012) examined the effect of cyanidin-3-glucoside on HepG2 cells and was found to increase the expression of glutamate-cysteine ligase, which reduces the level of ROS. Black soybean seed coat extract contains peonidin-3-*O*-glucoside, delphinidin-3-O-glucoside, and cyanidin-3-*O*-glucoside, showing protection against obesity and diabetes, reducing oxidative stress, inflammation, level of α-amylase, and lipid aggregation in adipocytes in HepG2 cells. Fasting blood glucose (FBG) and oral glucose tolerance test (OGTT) results obtained in diabetic mice showed black soybean seed coat extract (BSSCE) to exhibit the hypoglycemic effect. BSSCE could alleviate FBG levels and cause a significant decrease ($p < 0.05$) in the AUC value concerned with OGTT at a concentration of 400 and 200 mg/kg, respectively, which was comparable to positive control drug rosiglitazone (Chen et al., 2018).

4.4. Neuroprotective effects

Studies show that anthocyanins defend against several neurodegenerative diseases, including Parkinson's disease, Alzheimer's disease, ischemia, and other neuronal injuries (Airoldi et al., 2018; Jung and Kim, 2018). The glycosylated forms of anthocyanins could cross the blood-brain barrier and reach the CNS to convey their natural and biological impacts. Collective evidence suggests that the transfer of anthocyanin takes place through a bilitranslocase transporter, mainly into the vascular endothelium and thus into the target tissue (Aqil et al., 2014; Maestro et al., 2010). The polyphenolic cationic structure of anthocyanins allows scavenging free radicals, reducing ROS formation, giving an impression of being profoundly viable in neurodegenerative diseases. Anthocyanins help boost the PI3K/Akt/GSK3 pathway and control the endogenous antioxidant Nrf2/HO-1 pathway in Alzheimer's disease. Anthocyanin (12mg/kg *i.p.* for 30 days) significantly improved memory function in APP/PS1 transgenic AD mice (Ali et al., 2018). The arrangement of soluble amyloid-β 25-35 oligomers and their neurotoxicity in the human neuronal cell line SH-SY5YY could be prevented by cyanidin-3-*O*-glucoside (Tarozzi et al., 2010). Furthermore, if malvidin-3-*O*-glucoside is tested with amyloid-β neuronal cells, it shows inhibition of the cell cycle interruption caused by the amyloid-β (Shih et al., 2011). An *in silico* study found that anthocyanins could cause conformational modifications that trigger FKPB52, a potential protein known for restricting tau accumulation (Cao and Konsolaki, 2011).

Likewise, anthocyanins inhibit inflammatory biomarker interleukin-8 and other pro-inflammatory cytokines, which may help curb neuronal apoptosis associated with the disease (Rasheed et al., 2009). When anthocyanins-rich extract of blueberry are treated with microglial cells, it reduces the expression of iNOX and COX genes, which are involved in the inflammatory process (Bensalem et al., 2015). Anthocyanins inhibit extracellular signal-regulated kinase (ERK), mitogen-activated protein kinases (MAPKs), and c-Jun N-terminal kinase (JNK), which are essential for the expression of pro-inflammatory cytokines (Bensalem et al., 2015; Pan et al., 2018; Rasheed et al., 2009; Shah et al., 2016).

4.5. Cardiovascular protecting effects

Cardiovascular disease is the leading cause of mortality globally and is the type of disease affecting the cardiovascular system. Several physiological regulations lead to cardiovascular disorder, including high plasma LDL cholesterol, hypertension, endothelium dysfunction, and platelet aggregation. Apart from all these, oxidative stress is one of the major risk factors for cardiovascular disorders. Anthocyanins play a vital role in protection against oxidative stress (Bell and Gochenaur, 2006). Delphinidin, which is present abundantly in red wine, shows a vasodilatory effect upon consumption. However, in terms of preventing atherosclerosis and improving lipid and antioxidant parameters, the juice of red grapes was more efficacious than red wine (Andriambeloson et al., 1998). Literature suggests that during a heart attack, ingestion of grape juice, which is rich in anthocyanins, could exhibit potent antioxidant activity by increasing capillary permeability and strength. This action also leads to inhibition of platelet formation and speed-up the nitric oxide (NO) production, which results in vasodilation (Andriambeloson et al., 1998; Erlund et al., 2008). Similarly, chokeberry extracts also possess vasorelaxation properties (Bell and Gochenaur, 2006; Bertuglia et al., 1995). Clinical trial studies have shown that in healthy participants, eating anthocyanin-rich strawberry for more than a month improves the lipid profile and platelet function (Alvarez-Suarez et al., 2014). Hyperlipidemia is known to be an important cardiovascular disease risk factor. The literature study shows that black currant, rich in anthocyanin, can act against the fatty acids to reduce its levels (Frank et al., 2002). Anthocyanins can carry out their cardiovascular protective action through their anti-inflammatory properties; they inhibit inflammation caused by TNF-α in the human endothelium via monocyte chemoattractant protein-1 (Garcia-Alonso et al., 2009). Free radicals are formed during ischemia-reperfusion injury, which leads to adhesion of WBC in the wall of the micro-capillary; thus, it reduces blood flow and causes capillary damage. The anthocyanins can scavenge these free radicals and prevents capillary damage (Bell and Gochenaur, 2006; Toufektsian et al., 2008).

4.6. Anthocyanins in vision improvement

Anthocyanin pigments maintain good eyes' health and are often associated with improving night vision (Kramer and Canter, 2004). Anthocyanin containing berries are beneficial for vision improvement in several ways, which includes (i) circulation increase within the retinal capillaries; (ii) improving night vision by the generation of retinal pigment; (iii) decreasing diabetic retinopathy and molecular degeneration; and (iv) preventing glaucoma, cataracts, and retinitis pigmentosa (Camire, 2000). Animal model studies show that anthocyanin-rich black currant and maqui berry have been used to improve eyesight (Matsumoto et al., 2006). Anthocyanins can be distributed through the blood-retinal and blood-aqueous barriers in ocular tissues. In 19 patients with open-angle glaucoma, anthocyanin-rich black current (50 mg/day) supplementation improved ocular blood flow for 24 months (Ohguro et al., 2012). Some literature studies indicate that anthocyanin intake may positively impact macular degeneration associated with age and diabetic retinopathy (Nabavi et al., 2015; Yang et al., 2022). These results suggest that berries rich in anthocyanins could be used as a conventional treatment for patients suffering from open-angle glaucoma and other ophthalmic disorders.

4.7. Antimicrobial activity

Polyphenol compounds like anthocyanins show antimicrobial activity against several microorganisms, especially in inhibiting food-borne pathogens. Via different mechanisms, they exhibit antimicrobial activity, such as morphological damage to the bacterial cell or degradation of the structural integrity of the cell membrane, cell wall, and intracellular matrix (Burdulis et al., 2009). Anthocyanins, such as cyanidin, pelargonidin, and delphinidin, have been effective gram-negative inhibitors of *Escherichia coli* strain CM 871. However, these results were not reported in the case of wild variety gram-positive bacteria and *E. coli* (Nohynek et al., 2006). In addition to this, anthocyanins are responsible for plasma membrane permeabilization, extracellular microbial enzyme inhibition, and cytoplasmic membrane destabilization. Cranberries may inhibit various bacteria, including both gram-positive and gram-negative bacteria (Wu et al., 2008). Similarly, extract of blackcurrant inhibits the growth of *Enterococcus faecium* and *Staphylococcus aureus* strains, whereas it shows favorable results in the case of *Saccharomyces cerevisiae* and *E. coli* (Werlein et al., 2005). Likewise, carboxypyranocyanidin-3-*O*-glucoside from the anthocyanin family inhibits the biofilm production by *S. aureus* and *Pseudomonas aeruginosa* strains in chronic wounds (Correia et al., 2021). Despite all the evidence of anthocyanins showing antimicrobial activity, it has been shown that anthocyanins positively modulate the intestinal bacterial population by enhancing the growth of *Lactobacillus enterococcus* and *Bifidobacterium* spp., so the findings seem questionable in attributing the antimicrobial effects of the anthocyanin compounds observed (Hidalgo et al., 2012).

4.8. Antiviral activity

Anthocyanins have the potential to treat viral diseases. The structure of anthocyanin plays a vital role in restricting various viral infections. Blackberry extracts play a virucidal role against *Herpes simplex* due to a large number of anthocyanins. Due to the presence of anthocyanins in the red grape pomace extract, it reduces plaque infectivity and shows antiviral activity against H5N1 (Santhi et al., 2021). Similarly, Kannan and Kolandaivel (2018) concluded that the nature-derived cyanidin-3-sabubiocide could potentially treat the H1N1 subtype influenza virus. Likewise, red-fleshed potato contains Pg-type anthocyanins, which inactivates influenza viruses A and B (Hayashi et al., 2003). Study shows that anthocyanin-enriched elderberry fruit (*Sambucus nigra* L.) extract can demonstrate activity against modified vaccinia virus Ankara. It acts by declining the secretion of cytokinin IFN-γ and TNF-α, which promotes the Th2-Helper cell response (Schön et al., 2021). Anthocyanins from small red beans (*Vigna angularis*) can be used as a novel agent in the early stage of rabies virus infection (Kawai and Fujita, 2007). Anthocyanins have been recently explored as an alternative therapeutic agent targeting COVID-19. The ongoing COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has turned out a global health concern. It has affected millions of lives to date, and researchers are still hunting for its effective treatment. Anthocyanin compounds like cyanidin-3-*O*-β-glucoside (chrysanthemin) showed antiviral effects by binding to the naphthalene inhibitor binding site and inhibiting PLpro, though only to a limited extent. Similarly, pelargonidin, an anthocyanin, interact at a fatty acid-binding pocket on the spike RBD and inhibits spike-ACE2 interaction, lowering SARS-CoV-2 spike-ACE2 interaction and viral multiplication in Vero cells (Kaul et al., 2021). Furthermore, elderberry anthocyanins have the antiviral potential for SARS CoV-2 by limiting virus multiplication via budding from the virus's host cell (Salamon, 2020). A molecular docking simulation also suggests that berry anthocyanin could be employed as a potential SARS-CoV-2 therapy. The lowest binding energy, which was shown by cyanidin-3-arabinoside, was found in the pocket through a sufficient number of hydrogen bonds with the major protease virus. Pelargonidin-3-glucoside and pelargonidin 3-rhamnoside, on the other hand, have greater binding energy with SARS-spike CoV-2's glycoprotein (Messaoudi et al., 2021).

4.9. Other uses of anthocyanins

In food industries, color plays a major role, and the acceptability of food mostly depends upon its appearance. So many industries use synthetic color for improving elegance, neglecting its side effect. But the natural colorants derived from anthocyanins shows many beneficial effects without any adverse effect. Cyanidin, delphinidin, and pelargonidin are the anthocyanins responsible for various pigmentations (Mazza and Miniati, 2018). Anthocyanin extracts from bilberry and elderberry are accountable for producing mucus in the stomach and protecting it from ulcers (Veberic et al., 2009). A recent clinical trial demonstrated that the mixture of blue butterfly pea petals, extracts of purple waxy corn, and anthocyanin complex niosomes has a beneficial effect on oral wound healing (Damrongrungruang et al., 2021). Another study shows that cyanidin-3-glucoside from purple maize, fed to an obese mouse for 12 weeks, reduced body weight and reduced brown and white adipose tissue (Tsuda et al., 2003). The ability of anthocyanins to inhibit metalloproteases like MMP-1 and MMP-9 makes it suitable for topical application as they can protect the animal skin from ultraviolet radiation (Veberic et al., 2009). Additionally, anthocyanins from red cabbage possess hepatoprotective, nephroprotective, hypocholesterolemic, and anti-obesity activity. These red cabbage anthocyanins also contain medicinal benefits against headaches, peptic ulcers, and gout (Ghareaghajlou et al., 2021). Apart from the above, much literature shows the beneficial effect of anthocyanins against diarrhea, hypertension, dysentery as analgesic and antifungal agents.

5. Conclusions

This review explains the current literature about anthocyanins' chemistry, absorption, and health benefits to give the reader a broad and updated scheme. It is believed that due to various pharmacological and beneficial activities, anthocyanins can be used as natural dietary sources in multiple diseases. Furthermore, the medical advantages of dietary anthocyanins have been shown in numerous *in vitro* and *in vivo* studies. Notably, it is evident from the above literature review that anthocyanins have been mainly explored in their extract form even with such medicinal properties. Therefore, it is time now that future studies should extensively focus on isolation and synthesis with the accurate and careful characterization of diverse anthocyanins as a sole chemical entity. This approach will allow the researchers to explore different mechanistic pathways about their biological effects and further intervene in their target-specific aspects

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Conflict of interest

The authors confirm that there are no known conflicts of interest.

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Supplementary File

None.

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