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Investigating the Biological and Nutraceutical Potential of Anthocyanins: AReview

Tambe Suhas[1], Geetha Kannoth Mukundan[1], P. Sivakami Sundari[2,*]

[1]*Department of Pharmacology, College of Pharmaceutical Sciences, Dayananda Sagar University,*

ShavigeMalleshwara Hills, Kumaraswamy Layout, Bengaluru, Karnataka, 560078, India

[2]*Department of Pharmacognosy, College of Pharmaceutical Sciences, Dayananda Sagar University,*

ShavigeMalleshwara Hills, Kumaraswamy Layout, Bengaluru, Karnataka, 560078, India

*Correspondence: P. Sivakami Sundari

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Abstract

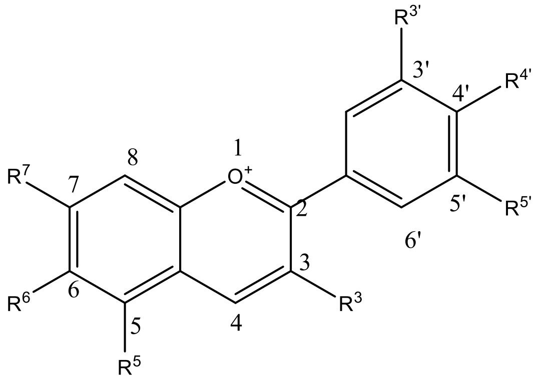
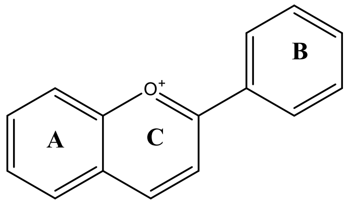
Anthocyanins are polyphenolic compounds responsible for the different colors observed in nature. It has a significant number of health benefits and has been used traditionally for different ailments. Anthocyanins, primarily owing to their capacity to lower free radicals, reactive species, COX and MAPK pathways, and pro-inflammatory indicators, can reduce oxidative stress, prevent the onset of inflammatory processes, and preserve human organs and cell components from harm, providing protection at several levels. Studies suggested the benefit of anthocyanins as an anticancer, antiobesity, cardiovascular disease, visual health, and prevention of neurogenerative disorders over the years. Therefore, this review intends to discuss the research progress of anthocyanins, their various pharmacological mechanisms of action, and an emphasis on their chemistry and dietary sources.

Keywords

Anthocyanins; Biological activity; Neutraceuticals; Plant pigments; Polyphenolic flavonoids

1. Introduction

Anthocyanin is a flavonoid polyphenolic pigment that is highly prevalent in flowering plants, and it imparts flowers, fruits, leaves, and storage organs with distinctive red to blue colors. These are secondary metabolites that accumulate in the tissues and organs at various stages of development and depending on the different environmental factors [1]. The general molecular structure of anthocyanin is given in Fig. 1. To date, seven hundred structurally different anthocyanin derivatives have been found in nature from twenty-seven aglycones, known as "anthocyanidins" [2]. Anthocyanins are rarely found as aglycons despite having numerous phenyl groups and present as glycosides of polyhydroxy and polymethoxy derivatives of 2-phenylbenzopyrylium or flavylium salts [3]. Depending on the number and position of hydroxyl and methoxyl groups substituted with sugar and the nature and number of aliphatic or aromatic acids bound to the sugar residues, the individual members of anthocyanins are differentiated [4].

	
Basic anthocyanin structure	Flavylium ion

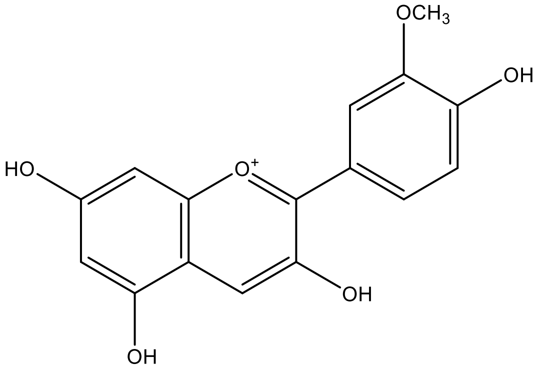
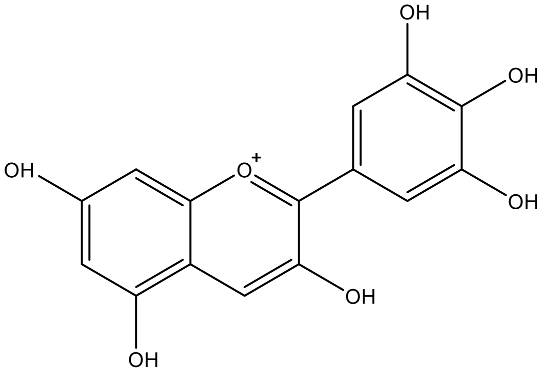
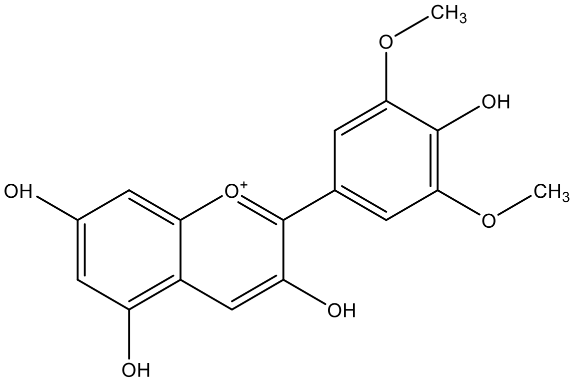
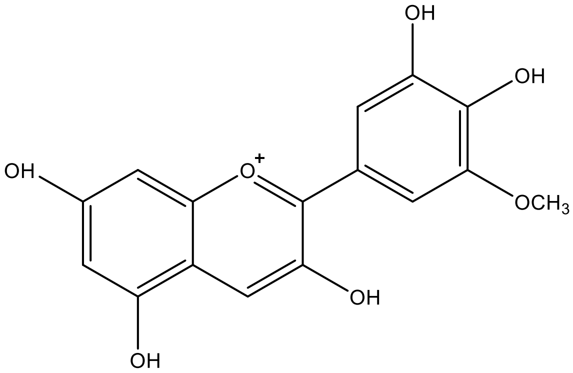
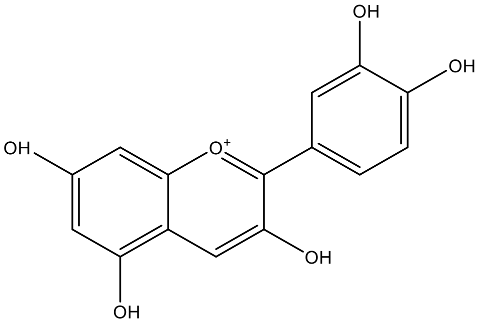
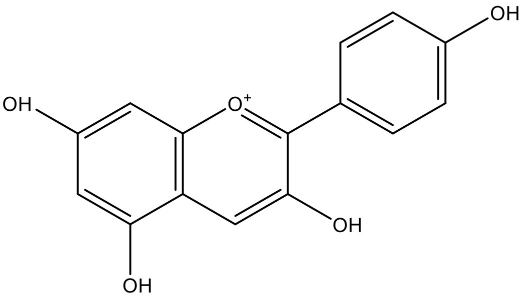
	
Peonidin	Delphinidin
	
Malvidin	Petunidin
	
Cyanidin	Pelargonidin

Fig. 1. Structures of some commonly found anthocyanins in plants

Anthocyanidin binds to one or more sugar moieties, conjugated to the C3 OH group in the C-ring, forming glycosides. Anthocyanins, except for 3-deoxyanthocyanidins, are almost exclusively present in glycosylated form; their anthocyanidin counterparts were generally unstable and rare in nature [5]. Six anthocyanidins are prevalent in nature, accounting for 90% of all anthocyanins discovered to date [6]. The widely distributed anthocyanidins in plants are delphinidin (Dp), malvidin (Mv), pelargonidin (Pg), petunidin (Pt), cyanidin (Cy), and peonidin (Pn) [7]. Cy 50%, Pg 12%, Pn 12%, Dp 12%, Pt 7%, and Mv 7% are the contents of these anthocyanidins in the edible portions of plants [8]. About 50% of anthocyanins discovered in nature are acylated. They are formed by the aliphatic or cinnamic acid esterification to one or more sugar substitutions, adding to their natural diversification.

Anthocyanins pose a challenge to plant biochemists because of their precise chemical variety and the intricacy of biosynthesis, metabolism, and control. The identification of leucoanthocyanidins (flavan-3,4-diols) as the direct precursors of flavylium cations was a significant breakthrough in understanding the biosynthetic pathway of anthocyanins. The structure of the gene encoding chalcone synthase in Antirrhinum was elucidated [9], while the C locus in *Zea mays*, which regulates anthocyanin synthesis, was established by transposon tagging [9,10].

Anthocyanins are significant natural compounds present in the Rosaceae (strawberry, raspberry, cherry, peach, apple, etc.) and Vitaceae (grape) families. Some other plant families where anthocyanin is found are Ericaceae (cranberry and blueberry), Saxifragaceae (red and black currants), Solanaceae (eggplant and pepper), and Cruciferae (red cabbage) [11]. Berries have long been known for their high anthocyanin pigment content, and as a result, they have been used as a source of healthy food or dietary supplements or as a medicine all over the world. Strawberries, grapes, black currants, mulberries, cherries, black raspberries, black beans, purple rice, purple maize, and sweet potatoes can also be used to extract anthocyanins [12,13]. Plant species, cultivation methods, and growth zones all influence the quantity and distribution of anthocyanins in berries.

Researchers have recently been interested in anthocyanins due to their possible preventive and therapeutic benefits on human health. Different in-vitro experimental systems and human studies using purified anthocyanins or anthocyanin-rich extracts have demonstrated the pigments' potential efficacy [14]. Anthocyanin bioavailability is estimated to be 1% in studies measuring the presence of anthocyanin in plasma and urine following food consumption. However, recently, in a 13 C-tracer research, the relative bioavailability of cyanidin-3-glucoside, the most prevalent anthocyanin found in nature, was determined to be 12.4 % ± 1.38 % [15]. The degree to which anthocyanins are absorbed into the bloodstream strongly depends on their structure [16]. The regular usage of anthocyanins and/or anthocyanin-rich foods has been linked to several health advantages, including cardiovascular protection, neuroprotection, eyesight improvement, antihyperglycemic and antiobesity characteristics, anti-inflammatory effects and cancer prevention [17,18].

2. Sources

Anthocyanins are abundantly found in higher plants, although a few have been discovered in lower plants, such as mosses and ferns [19,20]. Anthocyanins are plentiful in red-purple or red-to-blue-colored flowers, fruits, leaves, and roots, and also outside of these, they can be found in bulbs, legumes, cereals, roots, tubers, grasses, cole crops, and a variety of other crops. Anthocyanins are found in many fruits and vegetables in amounts ranging from 0.1 % to 1.0 % dry weight [19,21]. They are found to be uniformly distributed in the vacuolar solutions of plant epidermal cells. However, some are stored in vacuolar inclusions called anthocyanoplasts in a wide range of plant species. These inclusions are present in the cytoplasm as vesicles and are membrane-bound [22,23]. These intravacuolar structures discovered in the flower petals of various plants, including carnation and lisianthus, are known as anthocyanicvacuolar inclusions (AVIs) [24].

Table 1 represents the different types of anthocyanidin and anthocyanins distributed in several fruits and vegetables. Multiple internal and external factors, including genetic and agronomic characteristics, temperature, light intensity, processing, and storage, can cause anthocyanin content to vary from fruit to fruit of the same type [25]. For example, anthocyanin concentrations in red grapes can reach up to 250 mg/100 g. In contrast, concentrations in red wines vary depending on the grape varietals used, the technique of vinification, and, most importantly, aging. It is also worth noting that anthocyanins are employed in beverages, fruit fillings, snacks, and dairy goods as food additives [21].

The common anthocyanidins present in plants are cyanidin, delphinidin, pelargonidin, petunidin, peonidin, and malvidin (Fig. 1). In nature, the most abundant anthocyanidins, delphinidin, cyanidin, and pelargonidin represents 80%

of leaf pigments, 69% pigments in fruits and 50% in flowers. In most fruit, the cyanidin-3-glucoside is the most widespread anthocyanin [4]. Its abundance is high in plants due to its low pH [21]. However, in red grape and derived products (wine, juice, etc.), the most characteristic anthocyanins are malvidin glycosides [26]. Malvidin, petunidin, and peonidin are not found in berries. These pigments are often absent in red berries because the anthocyanidins are methylated. Furthermore, these anthocyanidins are commonly found in blue-colored fruits [27]. Petunidin is another anthocyanidin formed in most fruits.

3. Chemistry

Anthocyanins are essential colored pigments found in various plants such as fruits, flowers, or seeds, so color intensity, hue, and stability are all important qualities. Structure, pH, temperature, light, oxygen, metal ions, and various other variables impact these qualities [46]. These are polyphenolic compounds glycosylated to form anthocyanidins, depicted by the presence of one heterocyclic ring and two benzyl rings, A and B (Fig. 1). The A and B rings are linked with the C ring by a three-carbon bridge. The polyhydroxy and polymethoxy derivatives of 2-phenylbenzopyrylium salts are the most prevalent glycosides. Glycosylation of the hydroxyl group at the C3 position is most common, but some derivatives have 3,5-glycosylated and 3,7-glycosylated sugars, as well as 3′ and/or 5′ replacements, have also been identified [4]. The amount and location of sugars, the number and position of hydroxyl groups, and aromatic and aliphatic acids connected to the sugars may all contribute to many derivatives [47].

Anthocyanins undergo color changes in response to variations in pH, which is due to the ionic nature of the molecular structure [46]. The flavylium cation represents anthocyanins and is orange or crimson at a pH of 3 or below. At neutral pH, it changes to a purple hue and changes to blue with increasing pH. The hydration process of the flavylium cation and the proton transfer reactions associated with its acidic hydroxyl groups compete kinetically and thermodynamically as the pH rises [48]. The initial reaction shows a colorless carbinol pseudo-base, where the ring may open to form a yellow chalcone, whereas the further reactions produce quinonoidal bases. At a pH of 6-7, the quinonoidal base is deprotonated, resulting in the generation of purple-blue resonance-stabilized quinonoid anions [49,50].

The color generated is also influenced by the hydroxyl and methoxyl moieties present in each anthocyanin, which might be understood by examining the six most prevalent anthocyanidin compounds. The hydroxyl group at C-3, which is usually glycosylated, is extremely important because it causes anthocyanins to change color from yellow-orange to red [51]. Above pH 8, malvidin 3-glucosides, pelargonidin, and peonidin maintain bluish hues with intensity and stability. However, beyond pH 8, delphinidin, cyanidin, and petunidin show a change from blue to reddish pigmentation. Petunidin and delphinidin compounds were extremely unstable in primary conditions, although cyanidin has shown stability at high pH [52]. Except for cyanidin stability, pelargonidin, peonidin, and malvidin 3-glucosides, aglycons with one free -OH group on the B ring were found to provide more blue hues and be more stable in basic conditions than petunidin and delphinidin aglycons. At different pH, the effects of glucosidic substitutions in alkaline solutions, the 3-glucoside and 5-glucoside anthocyanins, have bluer colors and have low color persistence. The increased electrophilicity of the flavylium cation due to the electron-withdrawing action caused by the sugar moiety is one of the explanations for the color loss that occurs after glucosidic substitution [53].

Anthocyanins may differ in acylating groups of the sugar replacements indicated above, in addition to the number of sugars and attachment location. Acylated anthocyanins are less sensitive to pH variations. As pH increases, the proportion of flavylium cations of acylated anthocyanins also increases and maintains a consistent redness of anthocyanins [33]. However, acylated anthocyanins have better color persistence in neutral and alkaline conditions than glucosidic anthocyanins. Because acylated anthocyanins are more resistant to flavylium ion hydration, the equilibrium is shifted towards more quinonoidal base forms, as shown in Fig. 2 [48,54].

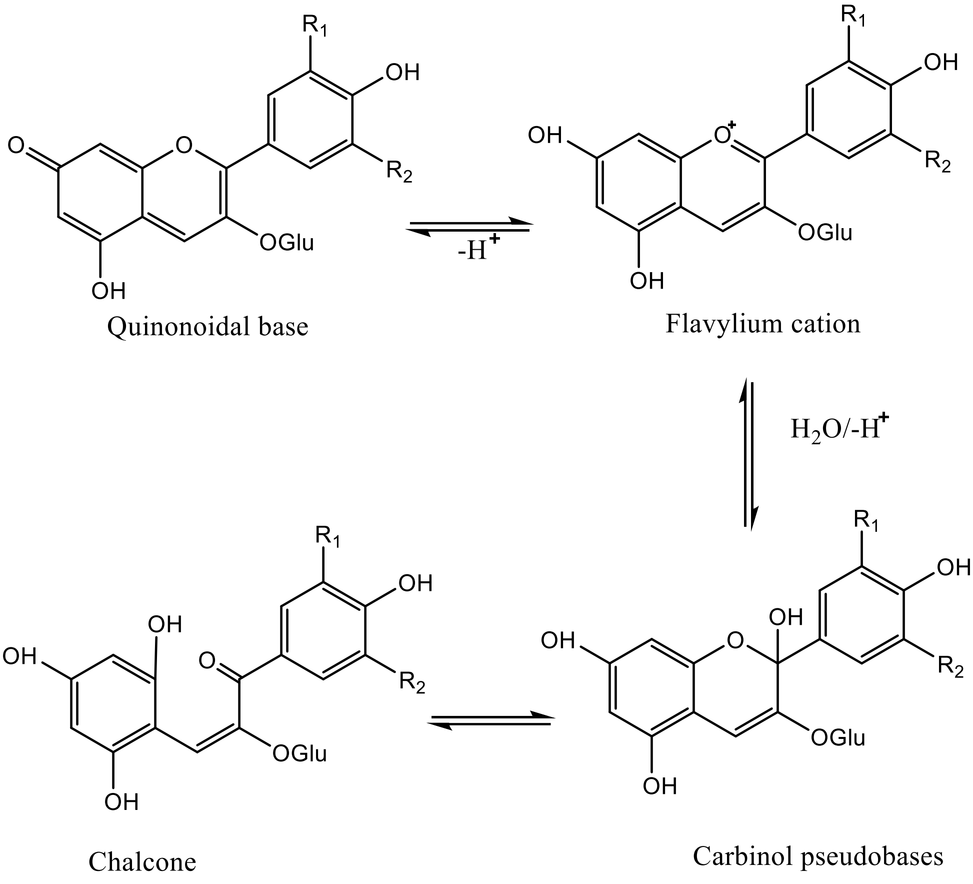


Fig. 2. Chemical transformation of anthocyanins

Anthocyanins are unstable and readily oxidized. Apart from pH, they are sensitive to various conditions that can impact their color and stability, including temperature and UV radiation. Anthocyanins are known to be broken down by light and temperature. They are also influenced by the presence of sulphur dioxide, ascorbic acid, or metal ions in the medium, as well as other food components and additives [55]. The bleaching impact of sulphur dioxide on anthocyanins has implications for their storage and preservation. While SO_2 is commonly used to limit microbial development in fruits and vegetables, it also functions as a nucleophile, attacking the anthocyanin's flavylium ion and efficiently bleaching the pigment as it proceeds to the colorless hemiacetal form [56,57]. Oxidative reactions, including the enzyme polyphenol oxidase (PPO), also destroy anthocyanins. PPO is present in blueberries, strawberries, grapes, and cherries, and it aids in the browning of fruits' juices. Polyphenol oxidase, on the other hand, cannot breakdown anthocyanins in the absence of another substrate, like chlorogenic acid, caffeic acid, or gallic acid, as these acids are o-diphenolic chemicals present in fruits and are engaged in polyphenolic oxidation initial phase [58-60]. Ascorbic acid acts as a hydrogen donor, preventing color loss by reverting the quinone to its acid state. In the presence of polyphenol oxidase, the anthocyanins are maintained as far as ascorbic acid is present in the reaction mixture. However, ascorbic acid (vitamin C) exerts a degradative impact on anthocyanins on its own. In the presence of ascorbic acid in an anthocyanin solution, oxygen causes both molecules to be destroyed. The flavylium ion is oxidatively cleaved by ascorbic acid like SO2 [61].

Co-pigmentation's influence on the color and intensity of solutions changes with anthocyanin structure and different pH environments. A co-pigment is a colorless molecule that, when combined with anthocyanins, interacts with anthocyanin and stabilizes the color of the leaves, fruits, and flowers of the plant [62]. Intermolecular co-pigmentation occurs when anthocyanins interact with co-factors like metal ions, other polyphenolics, or organic acids to form weaker bonds with improved chemical and physical properties. The two compounds are bound together by hydrophobic stacking (vertically) of the aromatic nucleus when polyphenol chemicals function as co-factors for anthocyanins. Flavylium cation interacts with the co-pigment that stabilizes it, preventing hydration and the formation of the colorless carbinol pseudo-base. Instead, the solution contains more flavylium ions, resulting in strong red hues [63,64]. Catechin, epicatechin, procyanidin B2, caffeic acid, p-coumaric acid, chlorogenic acid, myricitrin, and quercetin are some of the most common organic co-pigments

[65]. Co-pigmentation also boosts color intensity at pH levels ranging from 2 to neutral. This suggests that a co-pigment stabilizes both the flavylium ion and the quinonoidal base at neutral pH, resulting in stronger red colors in acidic conditions and brighter blue hues at neutral pH [66]. Metal ion complexation is another type of co-pigmentation observed in blue flowers. These metalloanthocyanins are formed from a supramolecular metal-complex pigment made up of simple anthocyanins, flavone co-factors, and metal ions present in other flowers. Fe^{3+}, Al^{3+}, Mg^{2+}, and Ca^{2+} are among the metals required for the blue coloring of flower petals. The anthocyanins and flavone co-factors in all known metalloanthocyanin complexes are stacked in a chiral molecular stacking, which separates these pigments from other assemblies of chemicals [67-69].

4. Biosynthesis

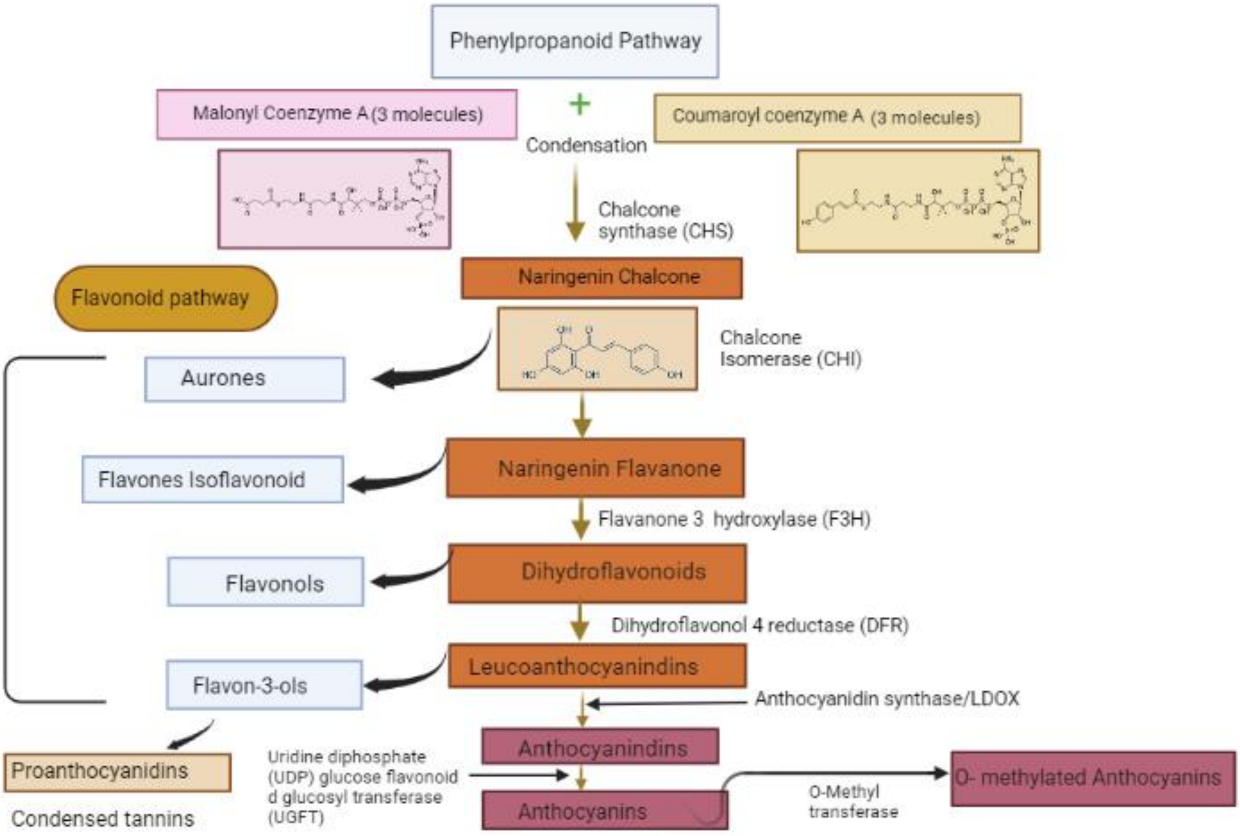


Fig. 3. Biosynthesis of anthocyanins through Phenylpropanoid pathway

Anthocyanins are a sub-class of phenolic compounds flavonoids [70]. Anthocyanins are responsible for the mirage of color that we observe in our surrounding nature. The biosynthetic pathway of anthocyanins is one of the widely studied pathways of secondary metabolites, and it has led to the identification of many genes and enzymes responsible for the biosynthesis of anthocyanins [71]. Anthocyanins are synthesized from the phenylpropanoid pathway, which is a flavonoid synthetic pathway that begins with the condensation process involving three molecules of malonyl-CoA and one molecule of 4-coumaroyl coenzyme A (as shown in Fig. 3). The condensation reaction is carried out in the presence of chalcone synthase enzyme. Leucoanthocyanins are formed from Dihydroflavonoids with the help of the enzyme dihydro-flavonol-4-reductase (DFR). They further converted into anthocyanidin like cyanidin and delphinidin, with the help of the enzyme anthocyanidin synthase or leucoanthocyanidin dioxygenase (LDOX), followed by glycosylation reaction caused by uridine diphosphate (UDP)-glucose: flavonoid-O-glycosyltransferase (UGFT) that forms anthocyanins. Ortho-methyl transferase (OMTs) further catalyzes the conversion of anthocyanins to ortho-methylated anthocyanins like peonidin, malvidin, and petunidin [72]. The enzymes involved in the catalytic process are found in the cytosol, impacting the overall biosynthetic process. Heterologous expression, overexpression, or silencing of single enzyme genes causes substantial changes in the composition of flavonoids [73].

Naringenin chalcone is a yellow-coloredtetrahydroxychalcone [71]. Chalcone provides the precursor for the formation of different classes of flavonoids: flavones, flavan-diols, proanthocyanidins (condensed tannins), isoflavonoids, and anthocyanins [74]. This tetrahydroxychalcone undergoes stereospecific isomerization by the chalcone isomerase (CHI) to form colorless naringenin flavanone. The isomerization can occur freely without CHI but at a low rate. Flavanones (like naringenin) provide a central branch point as a substrate of enzymes in the flavonoid pathway before the pathway diverges into side branches, leading to different classes of flavonoids [72]. Flavanone 3-hydroxylase (F3H) catalyzes hydroxylation at position 3 of the C ring of naringenin to form a dihydro flavanol (dihydro kaempferol). Dihydro kaempferol on hydroxylation in B ring at 3' position by flavanone 3'-hydroxylase (F3'H) produces dihydroquercetin, and at 3' and 5' position catalyzed by flavanone 3',5'-hydroxylase(F3'5'H) give dihydromyricetin. F3'5'H is also able to convert dihydroquercetin to dihydromyricetin [75].

The unpigmented dihydro flavanols are reduced by dihydro flavanol 4-reductase (DFR) to still colorless leucoanthocyanidins (leucopelargonidin, leucocyanidin, and leucodelphinidin) [73]. These leucoanthocyanidins are then converted to corresponding colored anthocyanidins (brick-red pelargonidin, red cyanidin, blue delphinidin) by the action of ANS/LDOX and further glycosylated by flavonoid 3-*O*-glucosyltransferase (3-GT) [76]. Anthocyanidin 3-glucosides may be modified further by glycosylation, methylation, and acylation to give different flavonoids [77]. These modifications provide flavonoids with unique properties. After the biosynthesis of anthocyanins is completed, the final product is transported to vacuoles for storage [78]. Due to the acidic vacuolar condition, the pseudo-base anthocyanin is converted to its colored flavylium ion form. Fig. 4 represents the synthesis of different anthocyanins from the phenylpropanoid pathway.

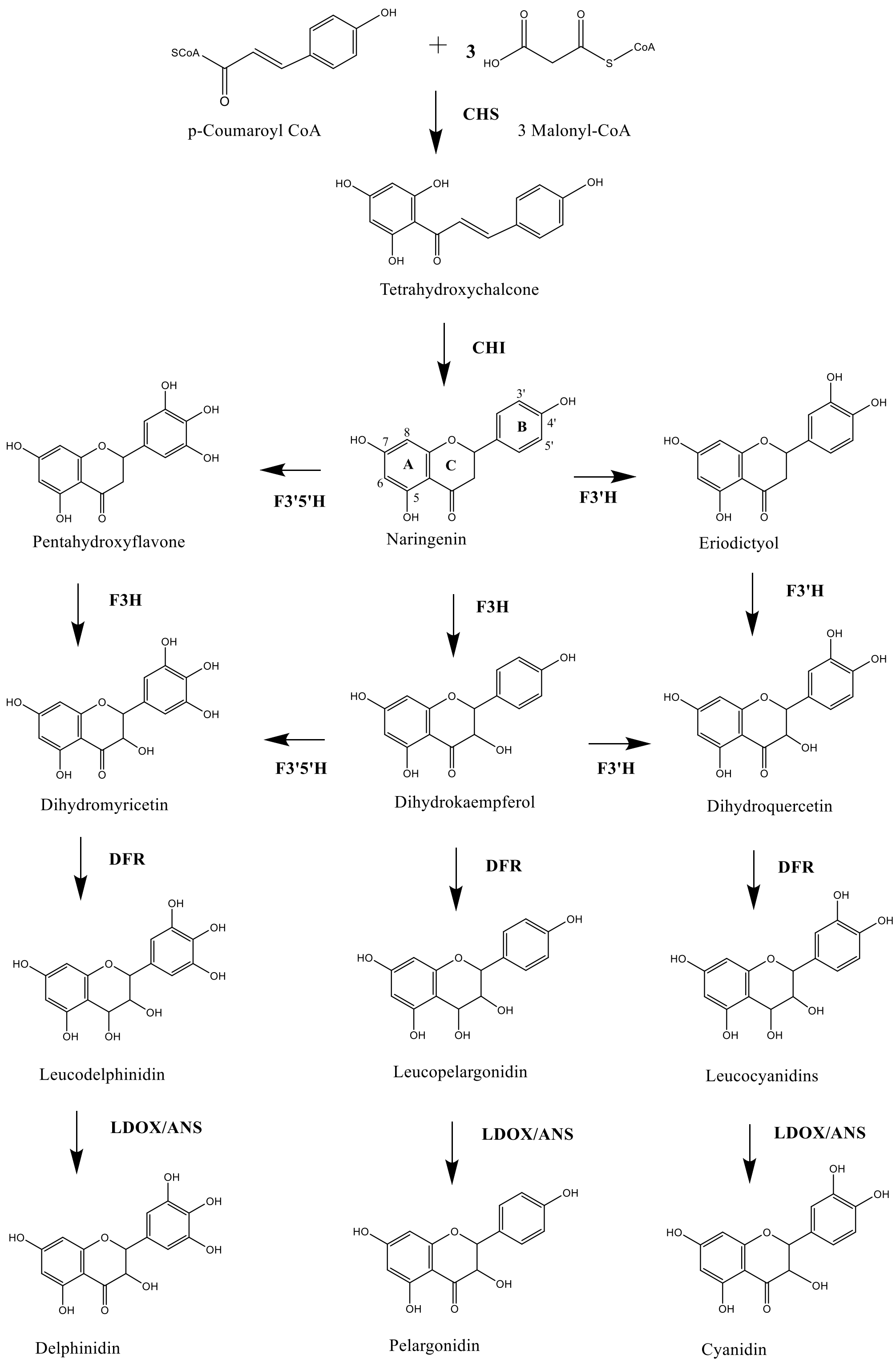


Fig. 4. Schematic presentation of the synthesis of different types of anthocyanins.

Abbreviations: CHS, chalcone synthase; CHI, chalcone isomerase; F3'5'H, flavonoid-3',5'-hydroxylase; F3H, flavonoid-3-hydroxylase; F3'H, flavonoid-3'- hydroxylase; DFR, dihydroflavonol-4- reductase; LDOX/ANS, leucoanthocyanidin dioxygenase/anthocyanidin synthase.

5. Nutraceutical and Biological Activities of Anthocyanins

Anthocyanin has been used for centuries as an appetite stimulant, phytopharmaceutical agent, and treatment for various ailments. Among many different bioactive components, anthocyanin is used as nutraceuticals and traditionally for ages. Recently, many potential health benefits have been reported based on different *in-vivo* and *in-vitro* studies. The health benefits of anthocyanins include antioxidative effects, anti-inflammatory, prevention of CVD, antidiabetic, antiobesity, anticarcinogenic, improved visual health, antimicrobial, and neuroprotection (as shown in Fig. 5). Here we have summarized the effects of anthocyanins on various conditions and their role as natural medicines for the treatment and prevention of diseases [79].

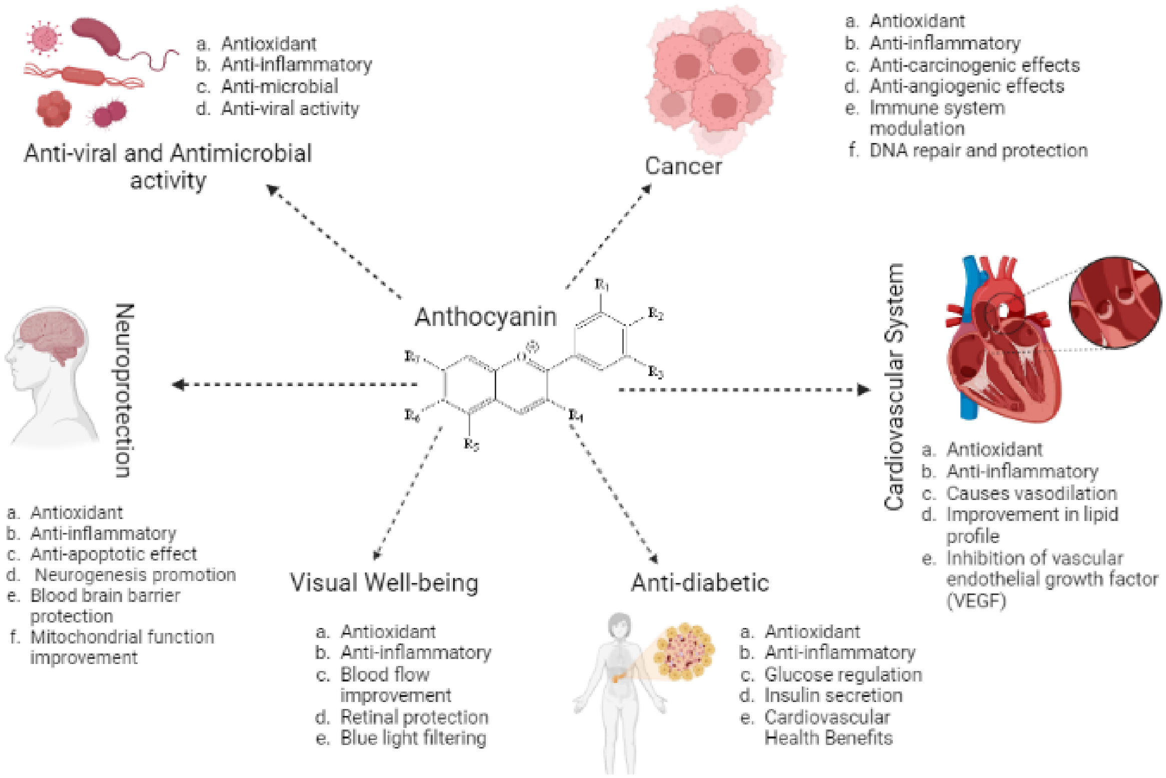


Fig. 5. Nutraceutical and Biological Activities of Anthocyanins

5.1 Antioxidant activity

The ROS are naturally produced in the body and are important in cell signaling, immunity, and various other functions. However, when produced in excess, it imbalances the body's oxidative state, leading to cellular damage, and is the cause of many degenerative diseases like inflammation, aging, cardiovascular disease, cancer, and metabolic disorders [80]. However, it must be emphasized that antioxidants have no evidence of therapeutic benefits [81,82]. As reported in the literature [83], it is from the chemical structure of anthocyanin chalcones and quinoidal bases with a double bond conjugated to the keto group that are efficient antioxidants in scavenging free radicals. The antioxidant activity of anthocyanins is superior to other conventional antioxidants like α-tocopherol, trolox, and catechin [84]. This is due to the molecules' chemical structure, the oxonium ion in the C ring, hydroxylation and methoxylation patterns, and glycosylated B-ring structure of anthocyanin contribute to the high antioxidant activity [85,86].

5.2 Cardioprotective activity

Several survey-based studies have discovered links between cardiovascular diseases (CVDs) and anthocyanins and a link between total consumption of anthocyanin and the risk of acquiring these illnesses. They act on various cells implicated in atherosclerosis development, one of the most common causes of CVDs. The chemokine monocyte chemotactic protein 1 (MCP-1) plays a significant role in the mobilization of macrophages to sites of infection or inflammation, and it has been linked to atherogenesis. In primary human endothelial cells, anthocyanins have been demonstrated to protect against TNF-a-induced MCP-1 production [57]. The pro-angiogenic and pro-atherosclerotic factor of vascular endothelial growth factor (VEGF) is inhibited by anthocyanins in vascular smooth muscle cells [87]. Physiologic angiogenesis disorders have been linked to various human disorders, including CVD, diabetes, and cancer [88]. The delicate balance of angiogenic (FGF2-fibroblast growth factor, VEGF, TGF-transforming growth factor, and angiopoietin) and antiangiogenic (thrombospondins, angiostatin, and endostatin) factors are required for normal angiogenesis [89]. Several investigations have found that anthocyanins have an antiangiogenic impact. Several investigations have found that anthocyanins have an antiangiogenic impact. In HaCaT cells (human keratinocytes), anthocyanin-rich extracts of many berries (wild blueberry, bilberry, cranberry, elderberry, and strawberry) substantially decrease hydrogen peroxide and TNF-induced VEGF production [90]. In a co-culture of human umbilical vein endothelial cells and fibroblasts, bilberry anthocyanidins (delphinidin, cyanidin, and malvidin) have similarly been shown to prevent VEGF-induced tube formation [91].

5.3 Antidiabetic activity

Anthocyanins from plants have been examined extensively for their antidiabetic properties. It is reported that anthocyanins have mechanisms that can reduce insulin resistance and hyperglycemia, inhibit gluconeogenesis and actions of carbohydrate hydrolyzing enzymes α-glucosidase and α-amylase, and as such, restore glucose levels, promote insulin secretion and pancreatic β-cell proliferation [92-94]. Pelargonidin and pelargonidin-3-galactoside generated a 1.4-fold increase in insulin secretion in humans at a 4 mM glucose concentration, indicative of normal glucose levels [95]. Pelargonidin-3-galactoside, cyanidin-3-glucoside, and delphinidin-3-glucoside are the anthocyanins that can trigger insulin secretion in that order. This discovery shows that the number of hydroxyl groups on their B-ring influences anthocyanins' capacity to produce insulin. Despite this, cyanidin, delphinidin, pelargonidin, malvidin, and petunidin do not increase insulin secretion much [33]. The molecular structure of anthocyanins plays a role in the inhibitory effect on α-glucosidase. Anthocyanin glycosides were found to be very weak enzyme inhibitors [96,97], whereas acylated anthocyanins were found to have the best inhibitory activity [98,99], owing to the caffeoyl sophorose component of the acylated anthocyanin molecule, rather than the anthocyanidin itself [100].

Cornus fruits, high in anthocyanins, are used in traditional Chinese prescription medications to treat diabetes [101]. The glycosides of cyanidin, delphinidin, and pelargonidin have been recognized as the primary bioactive components in *Cornuskousa*. It has been reported that among the anthocyanins and anthocyanidins investigated, cyanidin-3-glucoside and delphinidin-3-glucoside efficiently improved insulin production from rat pancreatic-cells (INS-1 832/ 13) [102]. Anthocyanins obstruct glucose absorption, but they also protect pancreatic cells. The simultaneous and daily administration of anthocyanins from red wine to rats, together with streptozotocin, a diabetogenic substance with beta-cytotoxic effects, has been found to lower glucose levels in urine and serum [4]. The adenosine monophosphate-activated protein kinase pathways were activated by consuming bilberry extract in white adipose tissue and skeletal muscle. Thereby, glucose transporter 4 is upregulated in muscle, resulting in increased glucose absorption by tissues [103].

5.4 Antiobesity activity

Antiobesity effects are found in anthocyanidin and anthocyanin pigments. Adipocyte dysfunction is significantly linked to obesity. Preadipocyte division and differentiation lead to a rise in the number of adipocytes, which leads to obesity. Through this mechanism, anthocyanins have a potential anti-effect [104]. As a result, blocking adipocyte differentiation and adipogenesis is an efficient strategy to combat obesity. Obese mice fed a diet high in cyanidin-3-glucoside from purple maize for 12 weeks lost weight and had lower white and brown adipose tissue weights, according to a prior study. The study shows that when obese rats are fed a purple corn diet, hyperinsulinemia, hyperglycemia, hyperleptinemia, and elevation in tumor necrosis factor (TNF-a) mRNA levels are corrected [105]. Anthocyanins from *Vitis coignetiae* can efficiently increase AMPK activation while inhibiting the expression of adipocyte-specific genes such as adipocyte fatty acid-binding leptin, protein, and fatty acid synthase [106]. Purple corn significantly reduced sterol regulatory element-binding protein-1 mRNA levels in white adipose tissue and suppressed mRNA levels of enzymes involved in fatty acid and triacylglycerol production. Low triacylglycerol accumulation in white adipose tissue may be attributed to these downregulations [33]. A study with overweight and obese people who had high blood lipids found that drinking tart cherry juice for four weeks reduced very-low-density-lipoprotein (VLDL) and the triglycerides/high-density lipoprotein (TG/HDL) ratio [107].

5.5 Ocular and retinoprotective activity

Anthocyanin pigments are essential nutraceuticals for clear eyesight. Anthocyanin-rich berries have long been related to eye health and are frequently associated with night vision. Anthocyanins due to their ability to boost blood circulation in retina capillaries and the production of retinal pigments, which improve night vision and protect eyes from oxidative damage, diabetic retinopathy, and macular degeneration in vivo and in vitro studies [108,109].

The majority of the berries are substantial in anthocyanins. The treatment of bilberry extract (which contains around 39% anthocyanins) in six-week-old C57BL/6 mice prevented photoreceptor cell function deterioration during retinal inflammation [110]. Moreover, bilberry anthocyanins have also been discovered to aid night vision by interacting with rhodopsin or phosphodiesterase [17]. It is observed that blackcurrant anthocyanins at oral doses in the range of 12.5-50 mg in a dose-dependent manner were able to lower the threshold of dark adaptation [111]. In healthy participants and patients with normal-tension glaucoma, oral black currant anthocyanins (BCACs) treatment has been shown to lower intraocular pressure [112]. Long-term oral treatment of black currant anthocyanins can prevent visual field degeneration and alleviate glaucoma in open-angle glaucoma patients, potentially via acting on ETB receptors and normalizing serum endothelin-1 levels and improving ocular blood flow [113]. Anthocyanins from black soybean seeds can protect the retinal nerve from N-methyl-N-nitrosourea damage, and they can be employed as therapeutic agents to prevent and treat retinal degeneration [114]. *Ribes nigrum* anthocyanins relax the ciliary smooth muscle, which relieves and prevents myopia [115]. This is because the delphinidin-3-rutinoside major component can suppress endothelin-1-induced ciliary muscle contraction [116].

5.6 Anticancer activity

Based on *in vitro*, cell culture study, and *in vivo* animal study data, anthocyanins have been widely explored for their anticancer and antiangiogenesis activities. Angiogenesis is a crucial phase in the shift of tumors from a benign to a malignant state, and it is essential for cancer growth. Antiangiogenesis prevents the new blood vessel generation that delivers oxygen to cancerous cells in cancer prevention. Antiangiogenic agents include flavonoids and anthocyanins, among other phytochemicals. Anthocyanins have been collected and purified from various plant sources to investigate their anticancer properties in malignancies of the esophagus, colon, breast, liver, hematological, and prostate [33].

Anthocyanins from black raspberries have been reported to prevent tumor formation by blocking angiogenesis [117]. The anthocyanin-rich fraction of red wines has been found to inhibit the proliferation of HCT-15 human colon cancer cells and gastric adenocarcinoma (AGS) cells [118,119]. The anthocyanidins, delphinidin, cyanidin, petunidin, pelargonidin, peonidin, and malvidin have been shown to decrease cell growth in human vulva cancer cells (A431) and human colon carcinoma cells(HT29) [120]. Furthermore, the authors demonstrated that anthocyanidins could intervene with multiple signaling pathways involved in cell growth regulation based on B-ring substitution. Cyanidin-3-glucoside and other anthocyanin-rich extracts have been demonstrated to cause apoptosis in various human leukemia cell lines [121]. In liver hepatoma cells treated [122], the same effect was observed. The mutagenesis of direct-acting mutagen methyl methane sulfonate and the metabolically activated carcinogen benzo(a)pyrene were considerably suppressed by juices from anthocyanin-rich fruits like strawberry, blueberry, and raspberry [123]. Another research found that black rice anthocyanins inhibit breast cancer cell metastasis by inhibiting the mitogen-activated protein kinase pathway [124]. In a previous study, 5 % whole freeze-dried black raspberries and the anthocyanin-rich fraction supplemented to N-nitroso-methyl benzylamine-induced F344 rats showed chemopreventive potential, inhibiting cell proliferation, inflammation, angiogenesis, and inducing apoptosis in both preneoplastic and papillomatous esophageal tissues [125]. As a result, anthocyanins have chemopreventive properties.

5.7 Neuroprotective Activity

Anthocyanin-rich diets have been shown to protect against cognitive decline and age-related neurodegeneration via modulating neuronal functioning [126,127]. Different food-derived anthocyanins were studied in animal models under specific investigations [128]. Shukitt-Hale et al. [129] found that anthocyanin extracts from blackberries and plums could delay the onset of neural function deterioration and improve cognitive and motor function by reducing neuro-inflammation and modulating neural signaling. Furthermore, by utilizing transgenic mice as a model for Alzheimer's disease, researchers learned that blueberry extracts have been shown to improve the outcome of this neurodegenerative condition [130].

In vitro research found that cyanidin-3-glucoside and its aglycone protect human brain cells from hydrogen peroxide-induced oxidative damage (SH-SY5Y) [131]. The results showed that pretreatment of SH-SY5Y cells with 100 M cyanidin and cyanidin-3-glucoside causes a rise in the total antioxidant activity in the membrane and cytosolic fractions of the cells; cyanidin also increases mitochondrial functioning and inhibits hydrogen peroxide-induced DNA fragmentation. Kim et al. [132] showed that three main anthocyanins extracted from black soybean (a combination of cyanidin-3-glucoside, delphinidin-3-glucoside, and petunidin-3-glucoside) protect cells against cell death caused by hydrogen peroxide. They report that the purified anthocyanin combination (1–25 g/ml) significantly lowers intracellular ROS levels in human neuroblastoma SK-N-SH cells in a dose-dependent manner. The anthocyanins also suppressed ROS-dependent stimulation of the apoptotic signal-regulating kinase 1 (ASK1)–JNK/p38 pathways, increased the expression of heme oxygenase 1 and increased the expression of sialidase 1 (also known as Neu1). Anthocyanins derived from plants have a neuroprotective impact, according to this study.

5.8 Antimicrobial and Antiviral Activity

Polyphenolic chemicals, such as anthocyanins, have antibacterial action against a variety of microorganisms and are particularly effective in inhibiting the growth of food-borne diseases [133]. Anthocyanins have antibacterial action through various mechanisms, including cell wall, membrane, and intercellular matrix destruction [17].

Furthermore, they discovered that blackcurrant extracts enhanced the growth of *Lactobacillus rhamnosus* and *Lactobacillus paracasei* strains but hindered the growth of *Escherichia coli* strains. Blackcurrant concentrates have been shown to suppress the growth of various strains of *Staphylococcus aureus*, *Escherichia coli*, and *Enterococcus faecium* while stimulating the growth of Saccharomyces cerevisiae in recent research [134]. Blueberry, raspberry, blackcurrant, and strawberry extracts contain anthocyanins that have an inhibitory effect on gram-negative bacterial growth but have no effect on gram-positive bacteria [135]. This difference might be related to the differences in cell wall architectures between Gram-negative and Gram-positive bacteria, with Gram-negative bacteria's outer membrane acting as a preventative barrier against hydrophobic substances but not hydrophilic molecules [136]. These antimicrobial properties of anthocyanin-containing extracts may be attributed to the many processes and synergistic actions of diverse phytochemicals in the extracts, such as anthocyanins, weak organic acids, phenolic acids, and their combinations of chemical forms [137]. Different cyanidin glycosides found in *Ribes nigrum* L. extracts have proved to possess antiviral activity against influenza A and B viruses, as well as the herpes-1 virus [138,139]. Anthocyanins, found in purple, red, and blue fruits and vegetables, are also the key bioactive in preventing microbial and viral infection through various processes.

Table 1.Anthocyanin and anthocyanidin determined in various fruits and vegetables

Common	Scientific Name	Part of	Phytoconstituents	Reference

Name		**plant**		
Acai berry	*Euterpe oleracea* Martius	Whole fruit	Cya-3-glu, cyan-3-rut, Del-3-gal, del-3-glu, del-3-rut, peo-3-glu	[28]
Berry	*Berberis lyceum*Royle	Whole fruit	Cya-3,5-dihex, cya-3-gal, Cya-3-glu, cya-3-lat, cya-3-rut, del-3-glu, mal-3,5-dihex, pel-3,5-diglu, pel-3-pentoxilhex, pel-3-rut, pel-hex, peo-3-rut	[29]
Bilberry	*Vaccinium myrtillus* L.	whole fruit	cy-3-ara, cya-3-gal, cya-3-glu, del-3-ara, del-3-glu, del-3-gal, mal-3-ara, mal-3-gal, mal-3-glu, peo-3-ara, peo-3-gal, peo-3-glu, pet-3-ara, pet-3-gal, pet-3-glu	[30]
Blackberry	*Rubusfruticosus* L.	Whole fruit	cya-3-glu, cya-3-rutl del, mal, pel, pel-3-glu, peo	[31, 32]
Blackcurrant	*Ribes nigrum* L.	Whole fruit	cya-3-glu, cya-3-rut, del-3-glu, del-3-rut	[32]
Blueberry	*V. corymbosum* L.	Whole fruit	cya-3-ara, cya-3-gal, cya-3-glu, del-3-ara, del-3-gal, del-3-glu, mal-3-ara, mal-3-gal, mal-3-glu, peo-3-gal, peo-3-glu, pet-3-ara, pet-3-gal, pet-3-glu	[32]

Cranberry	*V. oxycoccos*L.	Whole fruit	cya-3-ara, cya-3-gal, peo-3-ara, peo-3-gal	[32]
Dabai	*Canariumodonthophyllum* Miq.	Whole fruit	cya-3-glu, cya-3-gal, cya-3-ara, cya-3-sop, cya-3-rut, del-3-glu, del-3-gal, mal-3,5-diglu	[33]
Maqui berry	*Aristoteliachilensis*(Mol.) Stuntz	Whole fruit	cya-3-glu, cya-3-sam, cya-diglu, cya-sam-glu, del-3-glu, del-3,5-diglu, del-3-sam, del-3-sam-5-glu	[34]
Nitratia	*Nitrariatangutorun*Bobr.	Seed	cya-3-O-(caffeoyl)-diglu, cya-3-O-(cis-p-coumaroyl)-diglu, cya-3-O-(trans-p-coumaroyl)-diglu, cya-3-diglu, del-3-O-(p-coumaroyl)-hexose, del-3-O-(caffeoyl)- diglu, pel-3-O-(p-coumaroyl)-diglu, pel-3-O-diglu	[35]
Oregon grape	*Mahoniaaquifolium*(Pursh) Nutt	whole fruit	cya-3-glu, cya-3-rut, del-3-glu, del-3-rut, mal-3-glu , pel-3-glu, peo-3-glu	[36]
Pomegranate	*Punica granatum* cv. Mollar de Elche	edible flesh	cya-3,5-diglu, cya-3-glu, cya-pen, del-3,5-di-glu, del-3-glu, pel-3,5-di-glu, pel-3-glu	[37]
Raspberry	*(Rubusidaeus L.)*	whole fruit	cya-3-glu, cya-3-rut, cya-3-sop	[32]
Red grape	*Vitis vinifera* L. from	whole	cya-3-O-glu, del-3-O-glu,	[38[

	different Cultivars	fruit	mal-3-O-acetylglu, mal-3-O-glu, mal-3-p-coumarylglu, peo-3-O-acetylglu, peo-3-O-glu, peo-3-p-coumarylglu, pet-3-O-glu	
Black carrots	*Daucus carota ssp. sativus var. atrorubens*Alef.	Vegetable	cya-3-xylosyl-glucosyl-gal, cya-3-xylosyl-gal, cya-3-xylosyl-glucosyl-gal-coumaric acid, cya-3-xylosyl-glucosyl-gal-ferulic acid, cya-3-xylosyl-glucosyl-galsinapic acid	[39]
Black soybean	*Glycine max* (L.)Merrill		cya-3-gal, cya-3-glu, del-3-glu, peo-3-glu.	[40]
Purple corn	*Zea mays* L.	Grain	cya-3-(6″-malonylglu), cya-3,5-diglu, cya-3-dimalonylglu, cya-3-glu, cya-3-malonylglu, cya-3-malonylglu, cya-3-succinylglu, pel-3-(6″-maolonylglu), pel-3- dimalonylglu, pel-3-glu, peo-3-(6″-malonylglu), peo-3-dimalonylglu, peo-3-glu	[41]
Purple sweet potato	*Ipomoea batatas* L.	Vegetable	cya-3-(caffeoyl sop)-5-glu, cya-3-(caffeoyl-feruloyl sop)-5-glu, cya-3-(caffeoyl-p-hydroxybenzoylsop)-5-glu, cya-3-(dicaffeoylsop)-5-glu, cya-3-(feruloyl	[42]

			sop)- 5-glu, cya-3-(p-hydroxybenzoylsop)-5-glu, cya-3-sop-5-glu, pel-3-(caffeoyl-feruloyl sop)-5-glu, peo-3-(caffeoyl sop)-5-glu, peo-3-(caffeoyl-feruloyl sop)-5- glu, peo-3-(caffeoyl-p-coumaroyl sop)-5-glu, peo-3-(caffeoyl-p-hydroxybenzoylsop)-5-glu, peo-3-(dicaffeoylsop)-5-glu, peo-3-(feruloyl sop)-5-glu, peo-3- (feruloyl-p-coumaroyl sop)-5-glu, peo-3-(feruloyl-p-hydroxybenzoylsop)-5-glu, peo-3-(p-hydroxybenzoylsop)-5-glu, peo-3-sop-5-glu	
Red cabbage	*Brassica oleracea* L. *var. capitata* L.	Vegetable	cya-3-glu, cya-3-rut, del-3-glu, del-3-rut, cya-3-diglu-5-glu, cya-3-(caffeoyl)(p-coumaroyl) diglu-5-glu, cya-3-(sinapoyl) diglu-5-glu, cya-3-(caffeoyl-sinapoyl) diglu-5-glu, cya-3-(p-coumaroyl)(sinapoyl) triglu-5-glu, cya-3-(feruloyl)(sinapoyl) triglu-5-glu, cya-3-(p-coumaroyl) diglu-5-glu,	[43]

			cya-3-(sinapoyl) diglu-5- glu, cya-3-(p-coumaroyl)(sinapoyl) diglu-5-glu, cya-3-(feruloyl)(sinapoyl) diglu-5-glu, cya-3 (sinapoyl)(sinapoyl) diglu-5-glu, cya-3-(sinapoyl) diglu-5- (sinapoyl) glu	
Rice	*Oryza sativa* L. *cv. Heugjinju*	Grain	cya, cya-3-glu, peo-3-glu	[44]
Transgenic purple tomato	*Solanum lycopersicum*L. cv. Del/Ros1	Vegetable	del-3-(caffeoyl)-rut-5-glu, del-3-(feruloyl)-rut-5-glu, del-3-(trans-coumaroyl)-rut-5-glu, mal-3-(feruloyl)-rut-5-glu, mal-3-(p-coumaroyl)-rut-5-glu, pet-3-(feruloyl)-rut-5-glu, pet-3-(trans-coumaroyl)-rut-5-glu	[45]

*ara: arabinoside, cya: cyanidin, del: delphinidin, mal: malvidin, pel: pelargonidin, pen: pentoside, peo: peonidin, pet: petunidin, gal: galatoside, glu: glucoside, hex: hexoside, lat: lathyroside, rut: rutinoside, sam: sambubioside, sop: sophoroside

6. Conclusions

Anthocyanins are colored chemicals found mainly in plants and possess health benefits for humans. They have different colors, red in acidic conditions and blue in alkaline pH. Anthocyanins, primarily owing to their capacity to lower ROS levels, COX and MAPK pathways, and pro-inflammatory indicators, can reduce oxidative stress, prevent the onset of inflammation, and preserve human cell components from harm, providing protection at several levels. Thus, the structure, biochemistry, and dietary sources of anthocyanins have been thoroughly investigated to improve their usage, stability, and, as a result, bioavailability and activity. Till now, and while more preclinical and clinical studies are required, many research evidence suggests that these plant pigments are found to be a promising candidate for the engineering of novel pharmaceutical drugs and can be used as an adjuvant therapy to prevent or reduce the occurrence of a variety of diseases, including cancer, diabetes, glaucoma, cardiovascular, and neurological pathologies.

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