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Chapter

Anthocyanins: Natural Sources and Traditional Therapeutic Uses

Yogini S. Jaiswal, Yifu Guan, Ki Hwan Moon and Leonard L. Williams

Abstract

Anthocyanins are water-soluble naturally occurring pigments that are therapeutically beneficial and that have gained considerable interests by researchers in the field of phytopharmaceuticals and pharmacology. The evidence based scientific reports on the potential and efficacy of anthocyanins has caused an upsurge in their testing in clinical trials and formulation of herbal drug supplements since the past few decades. Their structural attributes enable them to be absorbed and react with various biomolecules in the human body, to provide beneficial physiological benefits. The anthocyanins are 2-phenylbenzopyrylium derivatives of dietary phenolics and exhibit antioxidant, anti-inflammatory and protective effects against metabolic and cardiovascular conditions. The metabolism of anthocyanins and their stability *in-vivo* in human body and during post-harvest storage still needs extensive investigation to fully explore their benefits. In the present chapter, we discuss the chemistry, medicinal uses in folklore/traditional medicine and the natural sources of their occurrence. The pre-clinical, clinical and pharmaceutical applications are also discussed, to emphasize the consumer demands and medicinal value of anthocyanins.

Keywords: anthocyanins, bioavailability, stability, metabolic disorders, herbal supplements

1. Introduction

Since several decades, flavonoids have captured the attention of scientists worldwide. The popularity of flavonoids in the scientific world is due to their versatile applications, therapeutic uses and environmental significance. They are reported to possess several beneficial pharmacological effects. Based on published reports, flavonoids exist in eight different classes and they are more than 9000 in number. These classes include anthocyanins, anthocyanidins, lipophilic flavones and flavonols, flavone and flavonol glycosides, chalcones, dihydrochalcones and aurones, flavanones and dihydroflavonols [1, 2]. Anthocyanins occur in various parts of plants including flower petals, stems, leaves and fruits. They are polyphenolic pigments that range in colors from red to purple. Literature survey reveals the presence of more than 700 anthocyanin compounds [3, 4]. Anthocyanins have several phenyl groups in their structure and mostly occur in glycosylated form. When more than one sugar group is attached in the C-ring, they are classified as "anthocyanidins" [5]. The anthocyanidins are reported to be less stable than anthocyanins [5]. The structural diversity of anthocyanins provides advantage to the chemical modifications that can be carried out. The most reported structural modifications on anthocyanins include acylation. Some studies report the bioavailability of anthocyanins to be low, except for cyanidin-3-glucoside which exhibits a bioavailability of about 12% [6]. Routine consumption of anthocyanins is reported to be beneficial in preventing cardiovascular, neurological and metabolic disorders [7]. They are not essential constituents of diet but can be easily supplemented through intake of fruits and vegetables. There are no dietary intake reference levels established for anthocyanins till date. However, institutes worldwide recommend the use of anthocyanins for promoting good health. Publications such as *Dietary Guidelines for Americans* have been published to create awareness among consumers about their health benefits [8]. A report published on the dietary intake of anthocyanins states that, on an average the female population has a higher intake of anthocyanins compared to males. There is variation also observed among individuals of various races/ethnicities in consumptions of anthocyanins. A report indicates that the intake of anthocyanins was found to be higher in white population compared to Hispanic and non-Hispanic other populations in the USA [9]. Traditionally, fruits especially berries have been recommended as rich sources of anthocyanins. Despite their long use in traditional medicine, the use of anthocyanins in western medicine is still awaited. With their increasing popularity, the application of anthocyanins as a substitute to synthetic colors in food products is gaining acceptance. In the current chapter, the chemistry, pre-clinical, clinical and pharmaceutical uses are discussed in detail. The natural sources of anthocyanins and their traditional medicinal uses are also discussed in detail.

2. Natural sources of anthocyanins

The natural sources of anthocyanins include fruits, flowers, leaves and roots of plants. The most widely consumed anthocyanin natural products include cherries, berries and cereals. Scientific reports reveal several anthocyanins and their derivatives isolated from natural sources. A comprehensive list of some sources with specific anthocyanins is provided in **Table 1**. Anthocyanins occurring in flowers are observed to be more stable than the anthocyanins found in grapes. Studies

Source (common names)	**Plant parts**	**Anthocyanins and derivatives**
Chica	Leaves	6,7,3′,4′-Tetrahydroxy-5-methoxyflavylium [10, 11]
Onion	Scales	5-CarboxypyranoCy 3-glucoside [12, 13]
Peruvian lily	Flowers	6-OH Cy 3-(6-malonylglucoside) [14]
Palm-leaf fern	Fronds	Luteolinidin 5-(3-glucosyl-2-acetylglucoside) [15]
Black currant	Seeds	Pyranocyanins C and D [16, 17]
Spanish marigold	Flowers	Dp 3-[2-(2-caffeoylglucosyl)-6-malonylgalactoside]-7-(6-caffeoylglucoside)-3′-glucuronide [18, 19] Cy 3-[2-(2-caffeoylglucosyl)-6-(2-tartarylmalonyl)galactoside]-7-(6-caffeoylglucoside)-3′-glucuronide [18, 19]
White water lily	Leaves	Cy 3-(6-acetylgalactoside) [20]
Thale cress	Leaves and stems	Cy 3-[2-(2-sinapoylxylosyl)-6-(4-glucosyl-p-coumaroyl)glucoside]-5-(6-malonylglucoside) [21, 22]

Source (common names)	Plant parts	Anthocyanins and derivatives
Asian pigeonwings	Flowers	Dp 3-(2-rhamnosyl-6-malonylglucoside) [23]
Blue poppy	Flowers	Cy 3-(2-xylosyl-6-malonylglucoside)-7-glucoside [24, 25]
Blue bugle	Flowers	Dp 3-[2-(6-feruloylglucosyl)-6-p-coumaroylglucoside]-5-(6-malonylglucoside) [26, 27]
Tea tree	Flowers and leaves	Dp 3-(6-p-coumaroylgalactoside) [28, 29]
Ginger-leaf morning-glory	Flowers	Cy 3-[2-(6-caffeoylglucosyl)-6-{4-(6-3,5-dihydroxycinnamoylglucosyl)}caffeoylglucoside]-5-glucoside [30]
Potatoes	Tubers and sprouts	Pn 3-[6-(4-caffeoylrhamnosyl)glucoside]-5-glucoside [31–33]
Grape hyacinth	Flowers	Dp 3-(6-p-coumaroylglucoside)-5-(4-rhamnosyl-6-malonylglucoside) (muscarinin A) [34]
Garden petunia	Flowers	Mv 3-[6-(4-{4-(6-feruloylglucosyl)-p-coumaroyl}rhamnosyl) glucoside]-5-glucoside [35–37]
Purple maize	Cob	Catechin-(4,8)-cyanidin 3,5-diglucoside, cyanidin 3-malonylglucoside, cyanidin 3-succinylglucoside, cyanidin 3-dimalonylglucoside [38]
Black-purple rice	Whole grain	Cyanidin 3,5-diglucoside, pelargonidin 3-glucoside,cyanidin 3-arabidoside [39]
Black rice	Bran, whole grain	Cyanidin 3-glucoside, cyanidin 3-rutinoside [40]
Blue wheat	Whole grain	Delphinidin 3-glucoside, cyanidin 3-glucoside [41]
Winter blue barley	Whole grain	Cyanidin 3-malonylglucoside [42]
Sorghum	Whole grain	Apigeninidin, 7-O-methyl apigeninidin [43]
Rye	Pericarp	Acylated peonidin 3-glucoside [44]

Table 1.
List of sources of anthocyanins found in flowering plants, fruits and cereals.

that investigated the chemistry behind intensification and stability of grape wine color upon storage reveal that a cycloaddition reaction leads to the formation of 4-substituted anthocyanins. These anthocyanins are suggested to be the possible reason for stability of wine color upon maturation. The grape varieties that contain 3,5-diglycosides produce wine of an inferior quality compared with the varieties that contain high levels of 3-monoglycosides [45, 46]. The cycloaddition reaction leading to formation of 4-substituted anthocyanins was also observed in seeds of red currant [1]. Cereals form an important part of human diet and they are available in various colors ranging from red, yellow, purple and black. These colored cereals are a rich source of anthocyanins and include common cereals such as wheat, barley, sorghum, rice, maize, rye, oats, etc. [38, 44, 47–50]. Structures of some representative anthocyanins found in cereals, and fruits and flowers are represented in **Figures 1** and **2**, respectively.

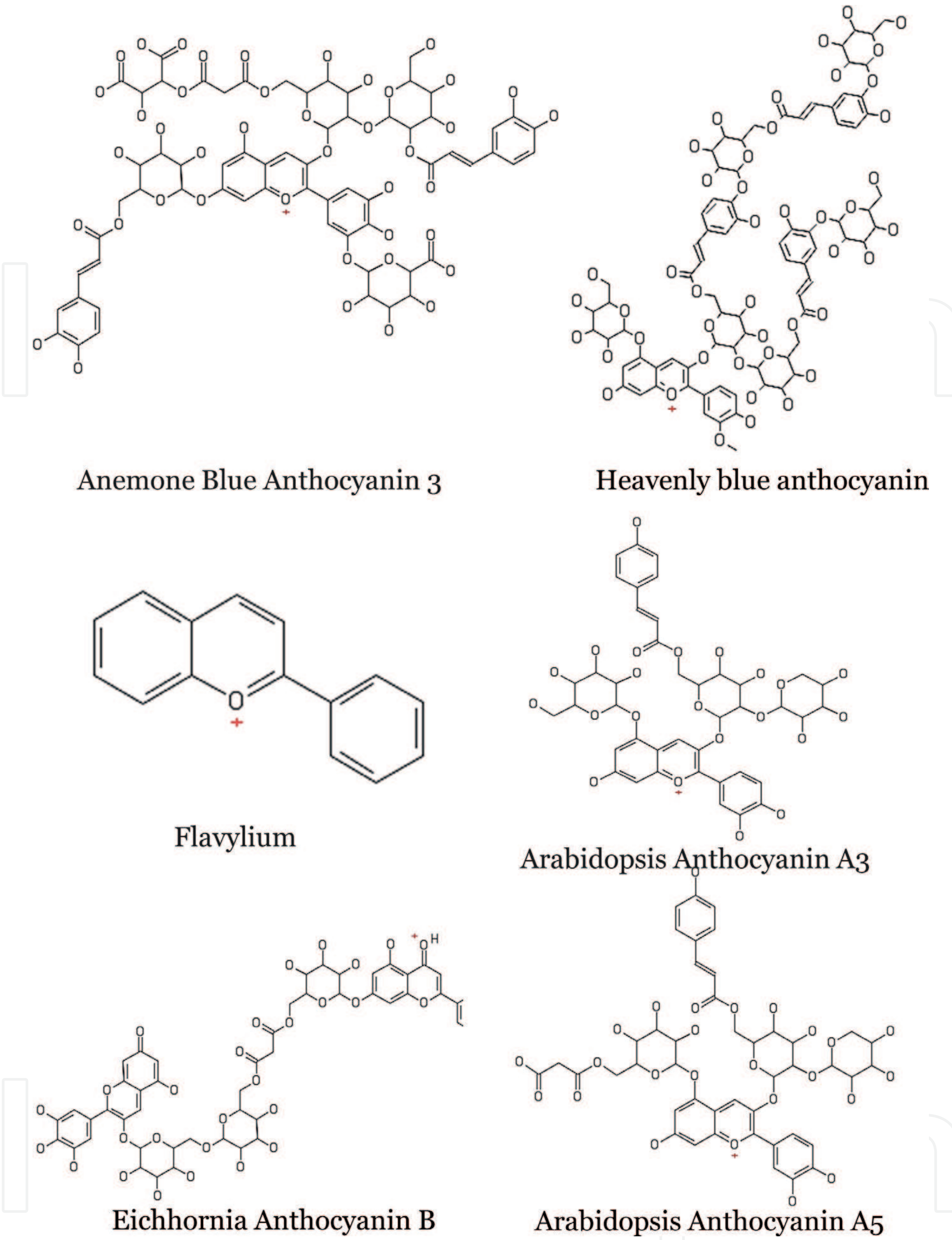

Figure 1.
Structures of representative anthocyanins and their derivatives found in cereals.

3. Chemistry

Anthocyanins are naturally occurring pigments. They are phenolic compounds that are mostly hydroxy derivatives of flavylium salts or glycosides of methoxy derivatives. Anthocyanins vary in forms based on the attachment of acids and hydroxyl groups to the sugar moieties within their structure. The anthocyanins found in plants include: cyanidin, delphinidin, pelargonidin, malvidin, peonidin and petunidin. Of these, cyanidin 3-glucoside is the most widely found anthocyanin [51]. The anthocyanins have an ionic structure and thus their color in solution is pH dependent [52]. They possess colors in shades of blue as the solutions

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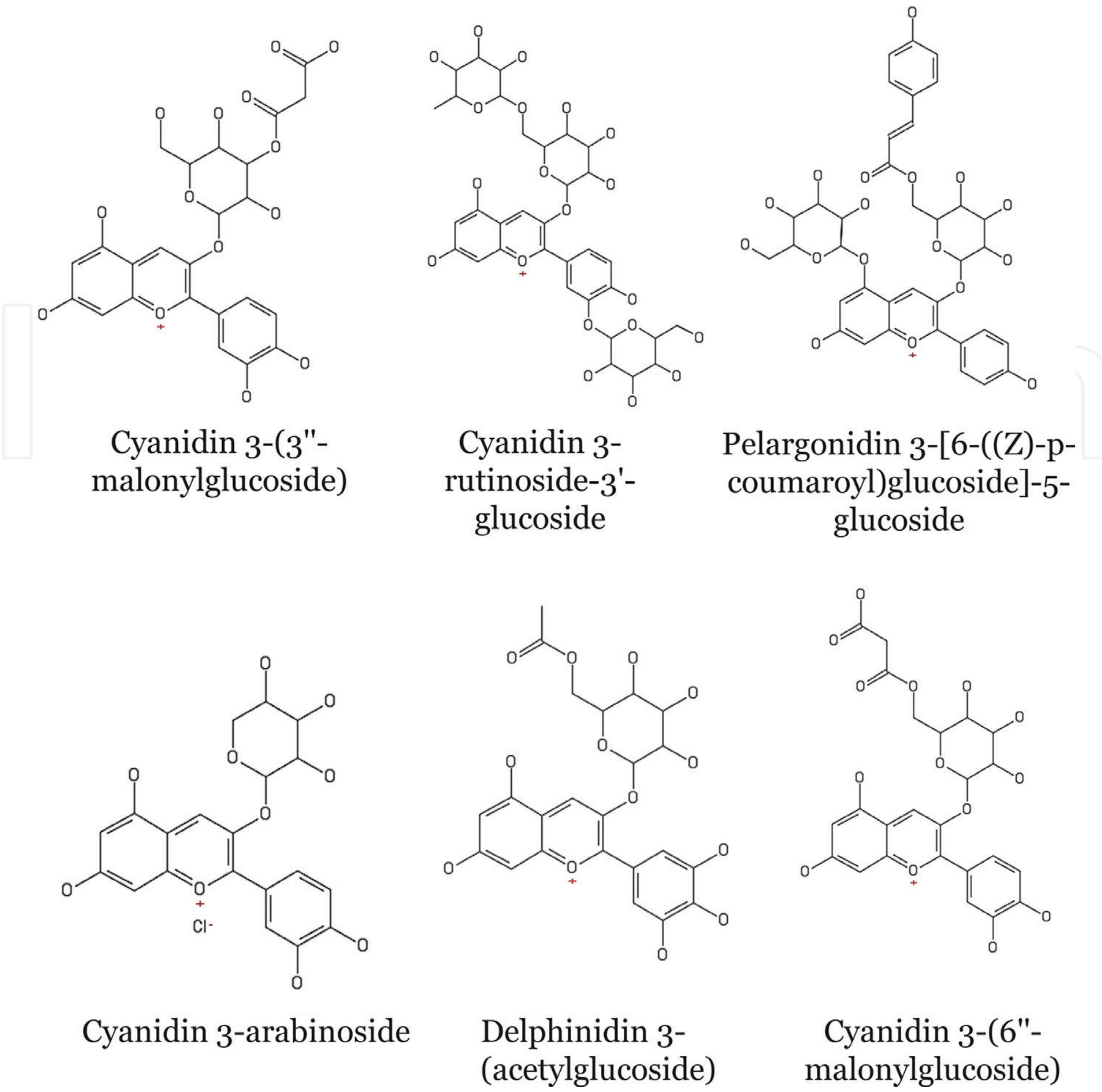

Figure 2.
Structures of representative anthocyanins obtained from fruits and flowers.

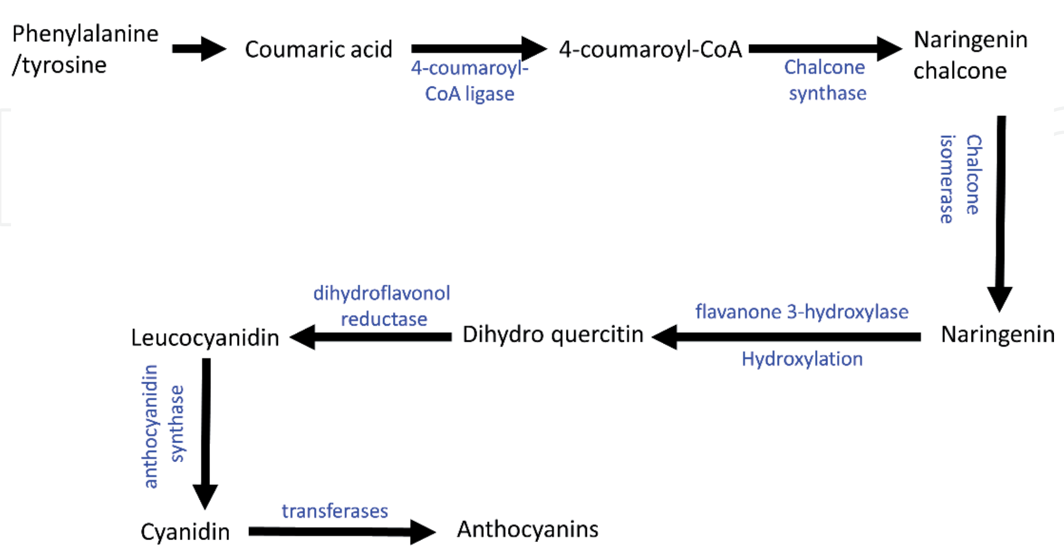

Figure 3.
Biosynthesis of anthocyanins in plants.

approach a neutral pH and a red color shade as the solutions are made acidic. Lower pH values provide higher stability to anthocyanins. The flavylium cations increases the solubility of colored pigments in water at low pH. With increase in protonation caused due to increase in pH, the concentration and stability of pigments reduces. Polymerization reactions are also reported to increase their color stability. Purple-colored stable quinonoid anions are formed at neutral pH [53].

Plants synthesize anthocyanins and store them in vacuoles. The colors of anthocyanins in the vacuoles will vary depending on the existing pH conditions. A general flavonoid pathway is used by plants for their synthesis. 4-coumaroyl-CoA is formed from phenylalanine or tyrosine and further condensed with malonyl-CoA to produce naringenin chalcone. Chalcone isomerases convert naringenin chalcone to naringenin [54]. Naringenin then undergoes several hydroxylation steps to form anthocyanins. A schematic representation of the anthocyanin formation pathway is provided in **Figure 3**.

4. Traditional and pharmaceutical uses of anthocyanins

Traditionally anthocyanins from plants have been used for treatment of hepatobiliary issues such as hyperbilirubinemia, obstructed bile ducts and treatment of lack of appetite [55]. In this section several therapeutic uses of anthocyanins reported in literature are discussed. A list of the effect of anthocyanin treatment in disease conditions and the tested pathological markers is provided in **Table 2**.

4.1 Antioxidant effects

Anthocyanins act as good free radical scavengers due to the keto group with a conjugated double bond. The high reactivity and instability of aglycones in their structure provides an advantage for anthocyanins in acting as antioxidant agents [61]. Glycosylation reactions reduce and diacylation reactions increase their free radical scavenging activity. Anthocyanins have been investigated in various systems and models for their antioxidant effect. In a study investigating the formation of malondialdehyde after UVB irradiation, delphinidin-3-glucoside and pelargonidin-3-glucoside exhibited significant antioxidant effects [62]. Pelargonidin acts as an excellent hydroxyl radical scavenger, and delphinidin acts as a good oxygen radical scavenger. Studies also report cyanidin and cyanidin-3-glucoside to possess inhibitory effects against oxidation of low-density lipoproteins (LDL) [63].

4.2 Effects on angiogenesis

Angiogenesis is the process of development of new blood vessels with the help of endothelial cells. Chemical mediators within the body (angiogenic and anti-angiogenic factors) maintain the environment required for normal angiogenesis. Angiogenic factors include growth factors such as vascular endothelial growth

Pathological condition	Effect(s) of treatment with anthocyanin extracts
Inflammation	Anti-inflammatory effect and reduction in muscular pain [56, 57]
Hyperglycemia	Reduction in glycated hemoglobin levels. Reduction in triglyceride and very low density lipids (VLDL) contents [58]
Cardiovascular diseases	Reduction in plasminogen activator inhibitor-type-1 and regulation of blood pressure [59]
Brain disorders	Antianxiety effect. Improvement of memory and cognition [60]

Table 2.
Effect of anthocyanin treatment in disease conditions and the tested pathological markers.

factor (VEGF), angiopoietin and fibroblast growth factor. Antiangiogenic factors include factors such as thrombospondins. Disruption in the balance between these factors can lead to complications in disorders such as diabetes and cancer.

Reports published on evaluation of expression of VEGF reveal that colored berries due to their anthocyanin contents, reduce expression of VEGF and VEGF induced tube formation in *ex-vivo* models of human cell lines, under oxidative stress [64]. When high glucose concentrations were induced in human endothelial cells, anthocyanins from purple corn were found to inhibit expression of angiogenic factors [65].

4.3 Antitumor activity

Angiogenesis play a very critical role in proliferation of cancer cells. Reports suggest that anthocyanins extracted from berries have antiangiogenic effects in various cancer cell lines. Blue berry, bilberry and black rice anthocyanins are reported to exhibit anti-invasive properties in breast cancer cells and in *in-vivo* animal models by reducing the expression of cyclooxygenase-2 gene [65]. Other mechanisms of action reported for anticancer effect of black rice include suppression of activation of mitogen-activated protein kinase (MEK), and decreased expression of matrix metalloproteinase 2 (MMP2) and matrix metalloproteinase 9 (MMP9) [66]. A study of purple potato anthocyanins in CF-1 mice model reports the antitumor effect of its extracts in colon cancer by induction of cell-cycle arrest [66].

4.4 Antidiabetic effects

Anthocyanins from Cornus fruits are reported to induce insulin secretion in *ex-vivo* rodent beta cells. Cornus fruits are used in Traditional Chinese Medicine as antidiabetic agents. It is reported that the property of inducing insulin secretion in anthocyanins may be due to the hydroxyl groups in their B-ring [67]. Anthocyanins reported to induce insulin secretion include delphinidin-3-glucoside and pelargonidin-3-galactoside. Seoritae extract is reported to inhibit diabetic nephropathy by suppressing renal lipid deposition [68]. Anthocyanins from Bilberries act as antihyperglycemic agents by stimulating the adenosine monophosphate-activated protein kinase (AMPK). Bilberry extracts are also reported to improve visual function in patients suffering from diabetic neuropathy and glaucoma [69].

4.5 Neuroprotection

Neuroprotection is achieved by reduction in toxic effects and injuries caused to neurons due to oxidative reactions. Cyanidin glucosides are reported to inhibit DNA fragmentation and oxidative stress caused due to hydrogen peroxide formed *in-vivo* in human neuronal cells [70]. Tart cherry anthocyanins, when tested for neuroprotective activity in mice brain under oxidative stress inhibited generation of apoptosis-inducing factor [71]. Cyanidin-3-O-β-ᴅ-glucopyranoside and petunidin-3-glucoside isolated from mulberry and black soybeans, are reported to exhibit neuroprotective activity in *ex-vivo* models. They inhibit cerebral ischemia and cell death caused due to hydrogen peroxide induced oxidative stress [72, 73].

5. Anthocyanins in food products and pharmaceuticals

Incorporation of anthocyanins as an ingredient in foods and pharmaceutical has undergone several challenges. The prime issue with their use, is their stability and hence their effectiveness as a beneficial component in food and pharmaceutical. Anthocyanins are used as colorants in pharmaceuticals and food products as a substitute to synthetic colors. Studies have compared the stability of anthocyanins as colors with synthetic colors and have found that the synthetic colors have better stability than anthocyanins. In a study, stability of synthetic colors such as Carmoisine, Allura red and Ponceau were compared with natural anthocyanin colors, viz. enocyanin, dark carrot and cochineal. The results of the study indicate that at higher temperatures and higher pH conditions the stability of natural anthocyanins was much lower that the synthetic colors [74]. However, the beneficial effects of anthocyanins cannot be ignored due to their stability issue.

In another study, the stability of freeze-dried powder of anthocyanin extract of wild blueberry was compared at various temperature values over a storage period of more than a month. It was observed that the total anthocyanin content and the content of individual anthocyanins was most retained at 25°C and reduced significantly at higher temperatures [75]. A combination of ascorbic acid with anthocyanins from plant extracts was evaluated for stability under varying humidity, temperature and pH conditions in both freeze dried and solution form. It was observed that in solution form the stability of the combination reduced with increase in pH and temperature. In freeze dried form the stability of the combination decreased with increase in humidity [76]. Commercially several yoghurt variants are available with a variety of fruits. Some studies carried out on extracts of blackcurrant and wine grape extracts in yoghurt indicate that the fermentation process and addition of some probiotics reduce the stability of anthocyanins [77–79].

Microencapsulation is another technique tested for anthocyanin release and stability. In a cell line study carried out microencapsulated glycons and aglycons of some anthocyanins, glycons of anthocyanins were found to be more stable than the aglycon counterparts [80]. The conventional extraction methods are cost intensive and employ application of heat for extraction. Ground breaking research has been carried out in metabolic engineering of microbes for production of anthocyanins. Cyanidin 3-O-glucoside has been successfully produced by *E. coli*. However, its production at commercial scale poses challenges due to imbalances in the expression of other genes and lack of optimized transporters for extracellular secretion [81]. The merger of metabolic engineering with plant chemistry holds a promising future for anthocyanins and their application in food and drug industry.

6. Conclusions

The evidences provided through scientific studies till date, demonstrate the therapeutic benefits of anthocyanins. The anthocyanins are excellent natural sources of bioactive compounds that can help in treatment and prevention of many disease conditions. With the multidisciplinary research carried out in the last few years, anthocyanins have a promising future for their commercialization and application in the pharmaceutical and health foods sector.

Conflict of interest

The authors declare that they have no conflict of interests.

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