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Potential health benefits of anthocyanins in oxidative stress related disorders

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Abstract Anthocyanins are naturally occurring water-soluble plant pigments belonging to the flavonoids chemical class. The red, blue and purple colours of leaves, flowers and fruits of plants confirm that they are rich sources of anthocyanins. Many in vivo and in vitro studies reveal that anthocyanins have different health beneficial effects such as antioxidant, antidiabetic, anti-inflammatory, anti-obesity, antihypertensive and anticancer properties. Major benefits of anthocyanin administration are owing to their potent anti-inflammatory and antioxidant activities. Recent investigations have revealed that anti-inflammatory activities of anthocyanins follow the inhibitory pathways of NF-κB-mediated decline of inflammatory cytokines production. Inhibition of the anti-inflammatory pathways also influences the modulation of arteriolar disorders and cardiovascular complications due to anthocyanin administration. Moreover, anthocyanins improve diabetes, obesity and cancer pathology by inhibiting NF-κB-mediated inflammatory pathways. However, considerable variations in activities do exist among structurally diverse anthocyanins. This review appraises the recent literature regarding the health benefits of anthocyanins and their molecular mechanisms in various oxidative stress related pathophysiological conditions.

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Introduction

The healthy human body always maintains a good balance between free radical production and antioxidant systems. Free-radicals are species that exist independently, having one or more unpaired free electrons and may react with other molecules in cells by taking or supplying electrons. The imbalanced production of reactive oxygen species (ROS) or reactive nitrogen species (RNS) and their limited degradation through compromised enzymatic defence may turn into oxidative stress (García-Sánchez et al. 2020), playing an important in the initiation, development and progression of several non-communicable diseases such as obesity, diabetes (Pang et al. 2020; Yaribeygi et al. 2020), cardiovascular disease, neurodegenerative diseases (Bhatt et al. 2020), as well as the modulation of gut bacterial environment (Hu et al. 2020a, b), and bone metabolism (Bernatoniene and Kopustinskiene 2018). Researchers also suggest that oxidative stress and free-radical generated reactions are prime contributors to degenerative processes like aging (Speer et al. 2020; Lobo et al. 2010; Kattoor et al. 2017). Major ROS/RNS species include superoxide anion radical ($O_2^{\bullet -}$), hydroxyl radical ($HO^{\bullet}$), nitric oxide radical ($NO^{\bullet}$) and other molecular species such as hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), peroxynitrite ($ONOO^-$) etc. are generated endogenously in cells and tissues (Valko et al. 2007). Several other oxygen species such as singlet oxygen ($^1O_2$), lipid radicals ($R^{\bullet}$, $RO^{\bullet}$, $ROO^{\bullet}$), and hydroperoxyl radical ($HOO^{\bullet}$) are also contributing to the oxidative stress in biological system which may produce on later part and are linked to ROS/RNS mediated reactions (Phaniendra et al. 2015). The species $O_2^{\bullet -}$, H_2O_2, and $HO^{\bullet}$ are generated from molecular oxygen by one-, two-, and three-electron reduction of molecular oxygen primarily from the mitochondrial electron transport chain (Phaniendra et al. 2015). Other sources of ROS/RNS species are the nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) in phagocytes, myeloperoxidase in neutrophil, xanthin oxidase system, nitric oxide synthase system and cytochrome p450 phase II metabolizing enzyme system etc. (Di Meo et al. 2016).

Endogenous enzymatic antioxidants such as superoxide dismutase (SOD) (removes $O_2^{\bullet -}$), catalase (decomposes H_2O_2) and glutathione peroxidase (GPX) may serve as the primary defence against oxidative stress and related disorders (Ighodaro and Akinloye, 2018; Kurutas, 2016). Several other non-enzymatic antioxidants such as glutathione, lipoic acid, albumin, uric acid, and bilirubin, are also some contributing agents against the free radical mediated oxidative stress (Kuciel-Lewandowska et al. 2020). Exogenous antioxidants are also available from dietary sources such as ascorbic acid, retinol, α-tocoferol, carotenoids, polyphenolic compounds (flavonoids and phenolic acids), and trace elements such as zinc, manganese, selenium, and chromium (Bouayed and Bohn, 2010; Singh et al. 2010). Deficiency of these antioxidants in diet may also lead to degenerative diseases in human (Bouayed and Bohn 2010).

Anthocyanins, natural dietary antioxidants that provide protective effects against harmful effect of oxidative stress (Ullah et al. 2019), have become one of the key topics for research linking to diabetes, obesity, inflammation, cancer and degenerative neurological disorders (Fallah et al. 2020; Pandey and Rizvi 2009). These polyphenolic compounds are capable of trapping free-radicals in the human body. Plants are rich sources of natural antioxidants such as phenolic acids, flavonoids and anthocyanins. Anthocyanins are an important group of pigments that are water-soluble and belong to the flavonoids family. They give the distinctive red, purple and blue pigments in most fruits and vegetables (Fallah et al. 2020; Passeri et al. 2016). Anthocyanins display numerous potential health benefits and they have been investigated recently for their use as possible clinical treatments for many human disorders (Bakuradze et al. 2019). They have both anti-inflammatory and antioxidant properties, which have proven effectiveness in in vivo and in vitro models of various chronic disease conditions such as cardiovascular disease, ophthalmic disorders, obesity, type II diabetes and atherosclerosis (Toufektsian et al. 2008; Seymour et al. 2009; Basu et al. 2010; Kalt et al. 2010; Mauray et al. 2012; Blesso, 2019).

This review appraises recent studies on the health benefits of anthocyanins that include their roles in cardiovascular diseases, neurodegenerative diseases, visual acuity, cancer, diabetes and several other health-related issues.

Methodology

In order to assess the current data on anthocyanin, a comprehensive search of the scientific literature was conducted using Google Scholar, PubMed, Web of Knowledge and Science Directory with the key words or phrases ‘anthocyanin’, ‘anthocyanin in diabetes’, ‘anthocyanin in inflammation’, ‘anthocyanin in cardiovascular diseases’, ‘anthocyanin in cancer’ and ‘anthocyanin in neurological disorder’. Furthermore, the reference lists of the selected literatures have also carefully analysed to clarify information. Our exploration indicated that the most of the research done in the last decade was focused on the effect of dietary anthocyanins in minimizing health risks linked to various diseases. This information was then tabulated and discussed critically to evaluate the mechanism of anthocyanins in various cellular processes. A further prospective research goal related to anthocyanin molecules was also warranted.

Chemistry of anthocyanins

Anthocyanin structurally belongs to the flavonoid class of natural products (Nahar and Sarker, 2019). Free anthocyanins are rare in fruits and vegetables and generally, they form glycosides, with several carbohydrates such as arabinose, galactose, glucose, rhamnose or xylose, which are attached to an aglycone anthocyanin nucleus (Harborne and Grayer 1988; Mazza and Francis 1995; Khoo et al. 2017; Salehi et al. 2020). Anthocyanins have a unique ability to form flavylium cations that distinguish them from other flavonoids (Ullah et al. 2019). Unlike other flavonoids, the positive charge makes anthocyanins more stable in acidic environments, such as in the stomach (Mazza and Francis 1995). The anthocyanidins are the aglycone or de-glycosylated forms of anthocyanins, including cyanidin, delphinidin, malvidin, pelargonidin, petunidin and peonidin (Fig. 1, Table 1). The glycosides of the three non-methylated anthocyanidins (cyanidin, delphinidin and pelargonidin) (Fig. 1, Table 1) are widespread in nature, being 80, 69 and 50% abundant in pigmented fruits and flowers, respectively. The most plentiful anthocyanins in edible parts of plants are cyanidin, followed by pelargonidin, peonidin, delphinidin, petunidin and malvidin (Kang et al. 2003; Su et al. 2019). The sugar parts of anthocyanins are usually attached to the anthocyanidin skeleton through the C_3 hydroxyl group. Numerous anthocyanins vary in the basic anthocyanidin skeleton, and the extent and position by which the glycosides attach to the skeleton (Table 2) (Harborne and Grayer 1988). Structural diversities among anthocyanins render significant differences in their physicochemical characters implicating their various pathways of absorption (Prior and Wu 2006; Bonesi et al. 2020).

The intensity of colour of anthocyanins depend on pH and the presence of chelating metal ions, mainly occurring as blue, purple or red colour (Ibrahim et al. 2011). Flavylium cation is red at pH 1–3, at pH 5 the resultant carbinol *pseudo* base is colourless, while at pH 7–8 (Fig. 2), the blue to purple quinoidal is formed (Harborne and Williams 2001). The cationic and polyphenolic nature of anthocyanins and their metabolites initiate various cellular responses among which the polyphenolic nature is mainly responsible for their strong free-radical scavenging and antioxidant activities, and thus produce their pharmacological effect.

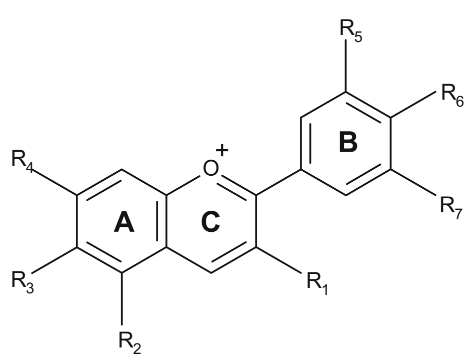

Fig. 1 Basic structure of anthocyanidin. It has two benzoyl rings (**A** and **B**) which are connected by a heterocyclic (**C**) ring. Glycosides are attached through the R_1 hydroxyl group

Pharmacokinetics and bioavailability

Recent studies on the bioavailability of anthocyanins suggest that they are rapidly absorbed from the small intestine and the stomach (Mcghie and Walton 2019). Anthocyanins are quickly metabolized resulting in low concentrations of the parent compounds being present in plasma within a few hours of ingestion (Woodward et al. 2009; Azzini et al. 2010). In general, anthocyanins are absorbed intact as glycosides with their absorption and elimination being relatively quick. The absorption and subsequent metabolism of black raspberry (*R. occidentalis*) anthocyanins were investigated in humans, where high doses of anthocyanins were taken (2.69 g/day) (Stoner et al. 2005). Four anthocyanins from the raspberries were observed in plasma within 2 h of oral berry administration and their elimination was found to follow first-order kinetics. They were excreted, both as intact anthocyanins and as methylated derivatives. Similar results were recorded in bilberry (*V. myrtillus*) studies conducted in rodents (He et al. 2006). Maximum concentrations of anthocyanins were found in plasma

Table 1 Various groups present in anthocyanidin ring structure

	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Colour
*Common Anthocyanidins**								
Cyanidin	–OH	–OH	–H	–OH	–OH	–OH	–H	Orange-red
Delphinidin	–OH	–OH	–H	–OH	–OH	–OH	–OH	Bluish-red
Pelargonidin	–OH	–OH	–H	–OH	–H	–OH	–H	Orange
Peonidin	–OH	–OH	–H	–OH	$–OCH_3$	–OH	–H	Orange-red
Petunidin	–OH	–OH	–H	–OH	–OH	–OH	$–OCH_3$	Bluish-red
Malvidin	–OH	–OH	–H	–OH	$–OCH_3$	–OH	$–OCH_3$	Bluish-red
6-Hydroxylated Anthocyanidins								
6-Hydroxycyanidin	–OH	–OH	–OH	–OH	–OH	–OH	–H	Red
6-Hydroxydelphinidin	–OH	–OH	–OH	–OH	–OH	–OH	–OH	Bluish-red
6-Hydroxypelargonidin (aurantinidin)	–OH	–OH	–OH	–OH	–H	–OH	–H	Orange
Methylated Anthocyanidins								
5-Methylcyanidin	–OH	$–OCH_3$	–H	–OH	–OH	–OH	–H	Orange-red
5-Methyldelphinidin (pulchellidin)	–OH	$–OCH_3$	–H	–OH	–OH	–OH	–OH	Bluish-red
7-Methylmalvidin (hirsutidin)	–OH	–OH	–H	$–OCH_3$	$–OCH_3$	–OH	$–OCH_3$	Bluish-red
5-Methylmalvidin (capensinidin)	–OH	$–OCH_3$	–H	–OH	$–OCH_3$	–OH	$–OCH_3$	Bluish-red
7-Methylpeonidin (rosinidin)	–OH	–OH	–H	$–OCH_3$	$–OCH_3$	–OH	–H	Red
5-Methylpetunidin (europinidin)	–OH	$–OCH_3$	–H	–OH	$–OCH_3$	–OH	–OH	Bluish-red
Others								
Apigeninidin	–H	–OH	–H	–OH	–H	–OH	–H	Orange
Luteolinidin	–H	–OH	–H	–OH	–OH	–OH	–H	Orange
Tricetinidin	–H	–OH	–H	–OH	–OH	–OH	–OH	Red

*Common anthocyanidins present in naturally occurring important foods

within 1 to 2 h, and maximum quantities in urine appeared in 4 h. Overall, less than 1% of these compounds were absorbed and excreted in urine.

The biological activities of anthocyanins are closely correlated to their absorption and metabolism (Tian et al. 2019). Acylation and glycosylation patterns decrease the anthocyanin bioavailability; however, glycosidases present in the gastrointestinal tract may hydrolyze anthocyanins into anthocyanidins, thereby enhances their biological potential but reduces their stability. The presence of a glucose substituent compared to an arabinose or galactose on the cyanidin and peonidin anthocyanidins present in cranberry (*V. macrocarpon*) juice appeared to increase their bioavailability as a percentage of the administered dose (Milbury et al. 2010).

Anthocyanins exist in the blood circulation and in urine in various forms such as intact, methylated, glucuronide derivatives and/or sulphate conjugated forms (Mazza et al. 2002; Felgines et al. 2003; Kay et al. 2005, 2007), reaching peak plasma concentrations 1–3 h after consumption. This depends on the individual compound along with the food matrix. The metabolites may remain in urine for up to 24 h and can retain their basic anthocyanin structure (Kay et al. 2005, 2007). Pharmacokinetic evidence indicated that parent glycosides and glucuronide derivatives were conspicuous in the bloodstream for 0–5 h after ingestion but became increasingly methylated after 6–24 h, which suggested that the bioactivity of anthocyanins was likely altered from metabolic transformation (Kay and Mazza, 2008). Various in vivo studies have suggested that the food matrix had a

Table 2 Anthocyanins and their derivatives in natural food sources

Source	Anthocyanins and their derivatives		Acyl	Origin	References
	Aglycones	Glycoside types			
Acai berry	Cyn, Mav, Plg, Pen	3-*O*-glucoside		Fruit pulp	(Poulose et al. 2012)
(*Euterpe oleracea*)	Cyn, Mav, Plg, Pen				
Bilberry	Cyn	3-*O*-arabinoside, 3-*O*-galactoside, 3-*O*-glucoside		Fruit	(Madhavi et al. 1998; Cooke et al. 2006)
(*Vaccinium myrtillus*)					
Blackberry	Cyn	3-*O*-arabinoside, 3-*O*-rutinoside		Fruit	(Skrovankov
(*Rubus fruticosus*)	Cyn, Plg, Pen	3-*O*-glucoside			a et al. 2015)
Black carrot (*Daucus carota*)	Cyn, Pen	3-*O*-xylosylgalactoside, 3-*O*-xylosyl (feruloylglucosyl) galactoside		Root	(Montilla et al. 2011)
	Cyn, Pen, Plg	3-*O*-xylosyl (sinapoylglucosyl) galactoside			
	Cyn, Pen				
Black currant (*Ribes nigrum*)	Cyn, Del	3-*O*-rutinoside		Fruit	(Abo El-Ella and Bishayee 2019)
Black raspberry (*Rubus occidentalis*)	Cyn	3-*O*-sambubioside, 3-*O*-glucoside, 3-*O*-(xylosyl) rutinoside,		Fruit	(Overall et al. 2017)
	Cyn, Plg	3-*O*-rutinoside			
Blueberry (*Vaccinium corymbosum*)	Cyn, Del, Mal	3-*O*-arabinoside, 3-*O*-galactoside, 3-*O*-glucoside, 3-*O*-arabinoside, 3-*O*-galactoside	3-*O*-acetylglucoside	Fruit	(Nile and Park 2014; Skrovankova et al. 2015)
	Pen, Pet				
Cabbage (*Brassica oleracea*)	Del, Plg, Pen, Pet	3-*O*-diglucoside-5-*O*-glucoside		Flower	(Ahmadiani et al. 2019; Burton-Freeman et al. 2019)
	Cyn				
Cherry sweet (*Prunus avium*) and sour (*Prunus cerasus*)	Cyn, Del, Plg, Pen, Pet	3-*O*-glucoside, 3-*O*-rutinoside, *O*- 3-*O*-glucosylrutinoside, 3-*O*-sophoroside		Fruit	(Mulabagal et al. 2009; Burton-Freeman et al. 2019)
	Cyn, Plg, pen				
	Cyn				
Chokeberry (*Aronia melanocarpa*)	Cyn, Plg	3-*O*-arabinoside, 3-*O*-glucoside, 3-*O*-galactoside, 3-*O*-xyloside		Fruit	(Kulling and Rawel 2008)
	Cyn				
Concord grape (*Vitis labrusca*)	Cyn, Del, Pet, Pen	3-*O*-glucoside, 3-*O*-(coumaroyl) glucoside, 3,5-*O*-(coumaroyl) diglucoside,	3-*O*-acetyl and coumaroyl	Fruit	(Overall et al. 2017)
	Cyn, Del				

Table 2 continued

Source	Anthocyanins and their derivatives		Acyl	Origin	References
	Aglycones	Glycoside types			
Cranberry (*Vaccinium macrocarpon*)	Cyn, Pen, Plg, Mal, Del Cyn, Pen, Pet	3-*O*-arabinoside, 3-*O*-galactoside, 3-*O*-glucoside 3-*O*-galactoside		Fruit	(Skrovankova et al. 2015; Abo El-Ella and Bishayee 2019;)
Eggplant (*Solanum melongena*)	Del	3-*O*-glucoside, 3-*O*-rutinoside, 3-*O*-rutinoside 5-*O*-glucoside		Fruit	(Sadilova et al. 2006)
Elderberry (*Sambucus nigra*)	Cyn	3-*O*-glucoside, 3-*O*-sambubioside, 3-*O*-sambubioside-5-*O*-glucoside		Fruit	(da Silva et al. 2019)
Grapes (*Vitis vinifera*)	Cyn, Del, Mal, Pen Pet	3-*O*-glucoside, 3,5-*O*-diglucoside		Fruit	(Mazza and Francis 1995; Grimes et al. 2018)
Jamun berry (*Syzygium cumini*)	Cyn, Del, Mal, Pen, Pet	-		Fruit	(Aqil et al. 2012)
Lingonberry (*Vaccinium vitis-idaea*)	Cyn	3-*O*-arabinoside, 3-*O*-galactoside, 3-*O*-glucoside		Fruit	(Isaak et al. 2017)
Pigmented rice (black and brown) (*Oryza sativa*)	Cyn, Pen	3-*O*-glucoside		Seed	(Yawadio et al. 2007)
Pigmented wheat (blue and purple) (*Triticum aestivum*, *Triticum durum*)	Cyn, Del, Pen, Mal	3-*O*-glucoside		Seed	(Zhu 2018)
Pomegranate (*Punica granatum*)	Cyn, Del, Pen Cyn, Del	3-*O*-glucoside 3,5-*O*-diglucoside		Fruit	(Sharma et al. 2017)
Purple cauliflower (*Brassica oleracea* var. botrytis)	Cyn	3-*O*-sophoroside-5-*O*-glucoside, 3-*O*-sophoroside-5-(malonyl) glucoside, glucoside-5-malonyl) glucoside, 3-*O*-(coumaryl)sophoroside-5-*O*-glucoside	3-*O*-(coumaryl-caffeyl)	Flower	(Chiu et al. 2010)
Purple corn (*Zea mays*)	Cyn, Plg, Pen	3-*O*-glucoside, 3–6-*O*-malonyl-glucoside		Seed	(Aoki et al. 2002)
Purple-fleshed sweet patato (*Ipomoea batatas*)	Cyn, Pen, Cyn	3-*O*-sophoroside-5-*O*-glucoside, 3-*O*-(6,6-dicaffeoyl sophoroside)-5-*O*-glucoside *p*-hydroxybenzoylated-3-sophoreside-5- glucoside), Caffeoylated-3-*O*- sophoroside-5-*O*-glucoside		Root	(Su et al. 2019)
Radish (*Raphanus sativus*)	Cyn, Cyn, Pet	3-*O*-glucoside, 3-*O*-rutinoside-5-glucoside, 3,5-*O*-diglucoside		Root	(Zhang et al. 2019b)

Table 2 continued

Source	Anthocyanins and their derivatives		Acyl	Origin	References
	Aglycones	Glycoside types			
Raspberry (*Rubus idaeus*)	Cyn	3-*O*-arabinose, 3-*O*-rutinoside, 3-*O*-sophoroside		Fruit	(Probst 2015; Skrovankova et al. 2015)
Red onion (*Allium cepa*)	Cyn,	3-*O*-glucoside, 3-*O*-laminaribioside, 3-*O*-(6-malonyl-glucoside), 3-*O*-(6-malonyl-laminaribioside)		Root	(Fossen and Andersen 2003; Frond et al. 2019)
Sweet potato (*Ipomoea batatas*)	Pen	3-*O*-glucoside		Root	(Lim et al. 2013)
	Cyn, Pen, Plg	3-*O*-sophoroside-5-*O*-glucoside			
	Cyn, Pen	3-*p*-hydroxybenzoylsophoroside-5-*O*-glucoside			
Strawberry (*Fragaria* × *ananassa*)	Plg	3-*O*-arabinoside, 3-*O*-malonylglucoside, malylglucoside, dissacharide (hexose + pentose) acylated with acetic acid		Fruit	(Giampieri et al. 2012; Skrovankova et al. 2015)
	Cyn, Plg,	3-*O*-glucoside, 3-*O*-galactoside, 3-*O*-rutinoside			
	Pen	3-*O*-glucoside			
Violet pepper or capsicum (*Capsicum annuum*)	Del	3-*O*-glucoside, 5-*O*-glucoside, 3-*O*-rhamnoside, 3-*O*-rutinoside, 3-*O*-caffeoyl rutinoside	3-*O*-coumaroyl-hexoside	Fruit	(Sadilova et al. 2006)

Cyn, Cyanidin; Plg, Pelargonidin; Mal, Malvidin; Pen, Peonidin; Pet, Petunidin; Del, Delphinidin; and ‘_’, No glycoside

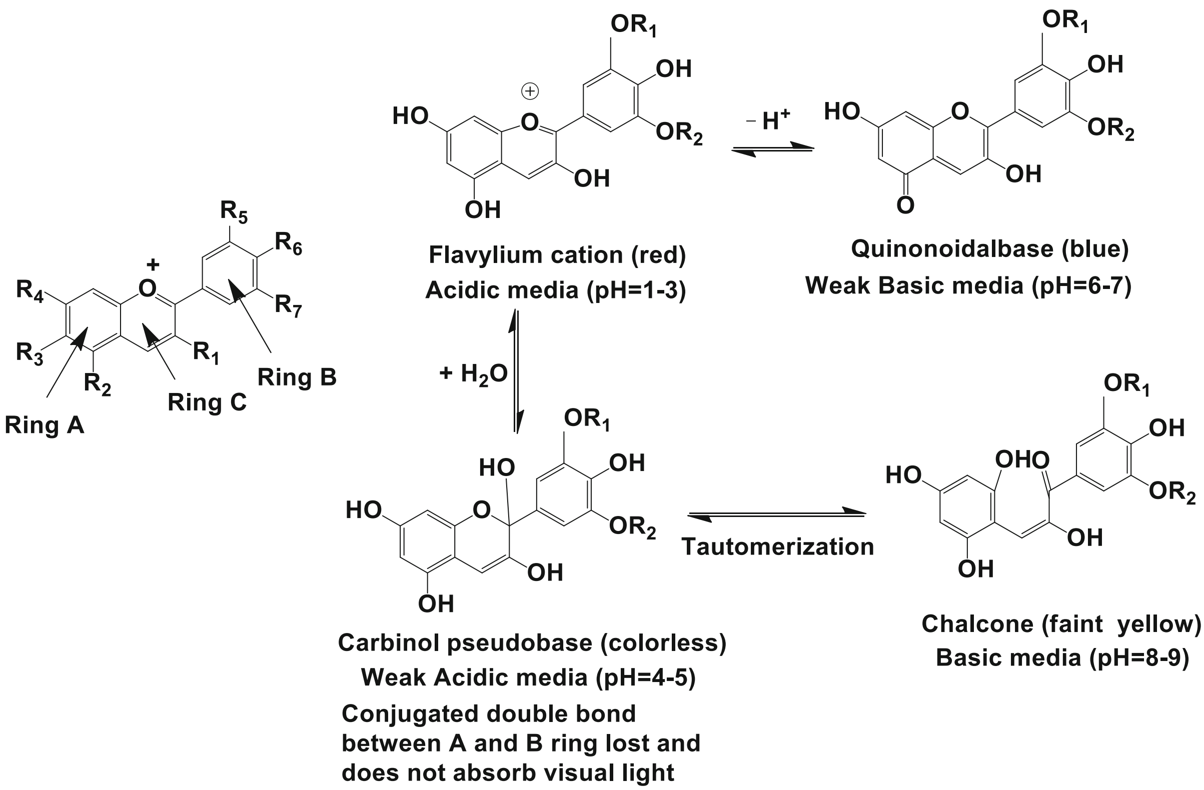

Fig. 2 Different forms of anthocyanins vs. pH values. Adopted and modified from previously reported articles (Borkowski et al. 2005; Marco et al. 2011)

significant effect on the absorption and metabolism of anthocyanins. The bioavailability of an individual anthocyanin may vary in xenobiotic metabolism in the liver, GIT and other tissues. Human polymorphisms have been reported in the genes for catechol-*O*-methyltransferase, glucuronosyl transferase and glutathione *S*-transferases (Lampe and Chang 2007). The variation of human gut microflora may also have an important role in anthocyanin bioavailability (Zhu et al. 2018; Tian et al. 2019). Anthocyanins may be metabolized by microbiota occurring in the GIT and produce smaller, and more bioavailable end-products (Zhu et al. 2018).

Gut microflora are able to metabolize anthocyanins Chen et al. 2018; Zhu et al. 2018; (Li et al. 2019; Tian et al. 2019). By the use of a bacterial preparation imitating the normal human microbiota population, Williamson et al. (2009) were able to demonstrate the conversion of larger polyphenols to phenolic acids, which had similar anti-inflammatory effects as the parent compounds. In addition, smaller phenolic acids and other anthocyanin metabolites possessed greater chemical and microbial stability, suggesting that they may have an important role in the antioxidant activity and physiological effects observed in many studies (Keppler and Humpf 2005).

Health benefits of anthocyanins

The chemical nature of anthocyanins reveals that they have beneficial roles in the control of many diseases. Their beneficial roles have been found significant in various pathological conditions such as heart disease, neurodegenerative diseases, in improving visual acuity, cancer, diabetes and obesity etc. Some of the health benefits of anthocyanins are discussed below.

Antioxidant properties of anthocyanins

The beneficial effect of anthocyanins primarily relies on their antioxidants and free-radical scavenging properties. Antioxidant activity of anthocyanins were tested in various assay systems such as ferric reducing antioxidant potential (FRAP), trolox equivalent antioxidant capacity (TEAC), oxygen radical absorbance capacity (ORAC), peroxynitrite ($^{\bullet}ONOO^{-}$) scavenging activity, lipid peroxidation inhibition, ability to bind heavy metals such as copper, iron and zinc and the free-radical scavenging activity of 2,2-diphenyl-1-picrylhydrazyl (DPPH) (Kahkonen and Heinonen 2003; Yang and Zhai 2010; Ge and Ma 2013). However, antioxidant activities of anthocyanin derivatives are greatly dependent on anthocyanin chemical structure. Thus, various anthocyanin derivatives possess different capacities for scavenging diverse radioactive oxygen species (ROS) and radioactive nitrogen species (RNS). Moreover, induction of antioxidant enzymes such as glutathione-*S*-transferase (GST), glutathione reductase (GR), glutathione peroxidises (GPx) and superoxide dismutases were also observed due to anthocyanins (Turner et al. 2009, Huang et al. 2016b).

Cyanidin 3-*O*-glycosides (arabinoside, galactoside, glucoside and rutinoside) and delphinidin 3-*O*-rutinoside were purified from various berries and in vitro investigation was performed to evaluate their effect on lipid peroxidation induced either by UV irradiation, Fe(II) ions or scavenging of 2,2′-azobis (2-amidinopropane) dihydrochloride peroxyl radicals at the concentrations of 15–20 μM (Gabrielska and Oszmiański 2005). Delphinidin-3-rutinoside produced a higher antioxidant activity against Fe(II)-induced liposome oxidation than cyanidin-3-rutinoside (Gabrielska and Oszmiański 2005). However, in terms of Fe(II)-induced liposome oxidation the antioxidant activity of the anthocyanins was higher than that of trolox (Gabrielska and Oszmiański 2005). Huang et al. (2016b) investigated malvidin and its two glycosides on cell lines to evaluate the effects on the ROS, heme oxygenase-1 (HO-1), superoxide dismutase (SOD) and xanthine oxidase-1 (XO-1). Malvidin glycosides displayed a greater inhibitory effect than malvidin in inhibiting xanthine oxidase activity; however, malvidin glycosides showed synergistic effects in HO-1 production in the cells (Huang et al. 2016b). Gabrielska and Oszmiański (2005), Huang et al. (2016b) found the antioxidant activity in anthocyanin glycosides though they performed different antioxidant methods and at different concentrations. The peonidin-based anthocyanin components in purple sweet potato (*Ipomoea batatas*) were investigated in 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals and superoxide anions scavenging assay system (Sun et al. 2018). Significant increase of DPPH radicals and superoxide anions scavenging activity were observed with an increase in anthocyanin concentration (Sun et al. 2018). Moreover, these anthocyanin components also showed good potential in reducing Fe^{2+} chelating ability and total power activity (Sun et al. 2018).

Anti-inflammatory properties of anthocyanins

Anthocyanins also possess anti-inflammatory properties. Inflammation is an integral part of tissue regeneration and wound healing due to infection. However, several pathways are considered responsible for inflammation such as nuclear factor-kappa B (NF-κB)-mediated cytokines production, cyclooxygenase mediated pathway, mitogen activated protein kinase activity, inducible nitric oxide synthase (iNOS) expressed signalling, LPS-induced macrophage activation, endothelial adhesion molecules expression (Chen et al. 2017; Liu et al. 2017). Various reports suggest that anthocyanins have shown promising results in inhibiting most of the inflammatory signalling cascade and limiting inflammation mediated tissue damage (Pereira et al. 2017; Huang et al. 2018; Valenza et al. 2018). Anthocyanin, or anthocyanin-extract, inhibited NF-κB through down-regulation of mitogen activated protein kinase (MAPK) pathways and reduced the expression of some pro-inflammatory cytokines in vitro (Pergola et al. 2006; Vendrame and Klimis-Zacas 2015). Malvidin and its glycosides inhibited high glucose-induced expression of intercellular adhesion molecule-1 (ICAM-1) and NF-κB in human retinal capillary endothelial cells and significantly increased cell viability (Huang et al. 2018). The anthocyanin-rich fraction of Portuguese blueberries (*V. corymbosum*) showed down regulation of cyclooxygenase-2 (COX-2) and iNOS in colon tissue homogenates (Pereira et al. 2017). The strong inhibition of COX-2 expression in colon tissue appears to be a key anti-inflammatory mechanism (Pereira et al. 2017).

Several anthocyanins such as delphinidin-3-*O*-glucoside, cyaniding-3-*O*-glucoside and petunidin-3-*O*-glucoside showed decreased NF-κB activities via mitogen activated MAPK pathways (Afaq et al. 2005b; Jeong et al. 2013). Mulberry (*Morus australis*) anthocyanins such as cyanidin and pelargonidin showed decreased tumour necrosis factor alpha (TNF-α) and Interleukin 6 (IL-6) levels in animals fed a high fat diet (Wu et al. 2013). Joo et al. (2018) found that cyanidin collected from red Chinese cabbage (*Brassica rapa*) also inhibited TNF-α-induced NF-κB. Black soybean (*Glycine max*) extract, rich in delphinine and petunidin, decreased the TNF-α and IL-6 level in high fat diet fed animals (Kim et al. 2015).

Anthocyanins in cardiovascular diseases

The development of cardiac and vascular dysfunction are attributed to the generation of free radicals from various sources such as mitochondrial electron transport chain, angiotensin II (ANG-II) mediated NADPH oxidase system, xanthin oxidase and inducible nitric oxide synthase (Münzel et al. 2017). Free radicals and reactive oxygen species may contribute to the cardiomyocyte loss in the heart and destroy the endothelial cells in the blood vessel as well as leading to cellular signalling for hypertrophic responses. Previous reports suggest that antioxidant treatment may ameliorate oxidative stress and cardiac remodelling in oxidative stress (Alam, 2019; Ulla et al. 2017). A strong relationship has been found between oxidative stress protection and the role of anthocyanins in cardiovascular diseases. Key findings of anthocyanin and its derivatives for cardiovascular benefits are summarized in Table 3. In one study, four anthocyanins were isolated from elderberries and incorporated into the cytosol and plasmalemma of endothelial cells to examine any protective roles, as endothelial dysfunction is part of the initiation and development of vascular disease (Youdim et al. 2000). The test result revealed that anthocyanin could be incorporated into endothelial cells and that significant protection was evident against oxidative stress. Endothelium-dependent vasorelaxation was provided by delphinidin in the rat aorta, giving a pharmacological benefit that can be compared with the polyphenolics of red wine from Cabernet-Sauvignon grape variety (Andriambeloson et al. 1998). Feeding of purified anthocyanins or anthocyanin rich extracts from black currant (*R. nigrum*) or elderberry (*S. nigra*) showed little influence on the fatty acid patterns or cholesterol levels in the liver of a rat model, but the pigments were able to spare vitamin E (Frank et al. 2002). Capillary permeability has been found to be reduced by administration of crude bilberry (*V. myrtillus*) anthocyanin extracts, both orally and via intravenous injection (Kong et al. 2003). Prevention of heart attacks through administration of red grape juice or wine have been found to be strongly linked to the roles of these anthocyanin rich preparation in enhancing the capillary strength and permeability, enhancing the nitric oxide (NO) release, reducing inflammation and inhibiting the platelet aggregate formation (Folts 1998). In addition, administration of black currant (*R. nigrum*) extract containing high concentration of anthocyanins, resulted in endothelial-dependent vasorelaxation in rings of rat aorta in vitro (Nakamura et al. 2002). Also, when rats were pre-treated to be more susceptible to oxidative damage and fed with anthocyanin-rich extracts, a significant reduction in lipid peroxidation indices and decreased DNA damage were observed (Ramirez-Tortosa et al. 2001). Anthocyanins of blueberries (*V. corymbosum*) such as malvidin and its glycosides (malvidin-3-galactoside and malvidin 3-*O*-glucoside) increased the levels of HO-1 and SOD in endothelial cells followed by a decrease in ROS and XO-1 (Huang et al. 2016b). The effects of cyanidin 3-*O*-glucoside, delphinidin 3-*O*-glucoside, and pelargonidin 3-*O*-glucoside were investigated on mitochondrial respiratory chain complex I activity in rat hearts, subjected to ischemia for 45 min, which provides evidence that anthocyanins may regulate energy metabolism in ischemia-induced inhibition of ATP production after ischemia (Skemiene et al. 2015).

Postmenopausal women who participated in an Iowa Women's Health study showed significant reduction in mortality from the cardiovascular diseases (CVD) after being treated with strawberry (*Fragaria x ananassa*) extracts for a 16 year follow up period (Mink et al. 2007). Blueberries-enriched diet also produced a significant decrease in coronary heart diseases related mortality in a study model adjusted for age and energy (Ahmet et al. 2009). Red wine intake has been shown to reduce CVD mortality in several studies (Rimm et al. 1991; Klatsky 2001). A consistent dose-responsive cardio-preventive effect has been suggested in an analysis of wine consumption relative to CVD risk (Di Castelnuovo et al. 2002). Red wine has proven to have greater beneficial effects on lipid metabolism than white wine, probably due to its increased phytochemical content (van Velden et al.

Table 3 Function of anthocyanin rich natural extracts and anthocyanins in the prevention of cardiovascular complications and diseases

Food extracts containing anthocyanins	Model	Dose	Experimental Outcomes	Reference
Anthocyanins	Human aortic culture cardiomyocytes	1 mg/mL used for cell cultured experiments	Endothelium-dependent vasorelaxant activity	(Youdim et al. 2000)
			Reduces the degree of apoptotic and necrotic cell death and also the infarct size after ischemia mediated by the inhibition of signal transducers and activators of transcriptional factors	
Anthocyanin rich extract of purple barley grain (pigmented genotypes of *Hordeum vulgare*)	In vitro ACE inhibition	IC_{50} 8.77 mg/mL	Have antioxidant activity and potent angiotensin I-converting enzyme inhibitory capacity	(Lee et al. 2013)
Anthocyanins and colonic metabolites	Endothelioma cell line	50 to 250 µg/mL	Inhibits CD40-induced pro-inflammatory signaling,	(Atalay et al. 2003)
			Protect against production of adhesion molecule induced by activated platelets	
Extracts of elderberry (*Sambucus nigra*), bilberry (*Vaccinium myrtillus*), and chokeberry (*Aronia melanocarpa*)	64 porcine coronary arteries were isolated and performed in vitro study	0.005–5 mg total anthocyanins/L	Prevent loss of endothelium-dependent and NO mediated relaxation	(Bell and Gochenaur 2006)
Blackcurrant extract	Human endothelial cells and 10 female Sprague–Dawley ovariectomized rats	Orally intake 3% (with or without) blackcurrant extract for 3 months	Up-regulated eNOS mRNA levels and NO synthesis both in vitro human endothelial cells and in vivo ovariectomized rats	(Horie et al. 2019)
Blueberries	Pulmonary arterial hypertension in rats. Forty-eight male Wistar rats in 7 groups	50, 100, and 200 mg/kg via oral gavage for 5 weeks	Increased the Early/Late ratio of blood flow across the tricuspid valve and tricuspid annular phase systolic excursion	(Turck et al. 2020)
			Decreased total reactive species concentration and lipid oxidation, reduced activity of nicotinamide adenine dinucleotide phosphate oxidase and expression of xanthine oxidase	
			Increased the activity of superoxide dismutase and restored sulfhydryl content	
Blueberry anthocyanin-enriched extract	Transverse aortic constriction (TAC)-induced myocardial dysfunction in 30 male mice	0.5 g/kg of blueberry anthocyanin enriched extract was administered daily by oral gavage for 6 consecutive weeks	Treatment markedly reduced asymmetric dimethylarginine (ADMA) concentration	(Hu et al. 2020a, b)
			Significantly ameliorated heart weight, left ventricular weight, myocardial dysfunction, left ventricular hypertrophy and fibrosis	

Table 3 continued

Food extracts containing anthocyanins	Model	Dose	Experimental Outcomes	Reference
Blueberry (Rabbiteye blueberries *Vaccinium ashei*) supplement	80 diet induced obese C57BL/6 mice were divided into eight groups (n = 10)	Orally intake 6.4 g/kg body weight/day of blueberries for 8 weeks	Reduced diastolic and systolic blood pressure in diet-induced obese mice	(Shi et al. 2019)
			Prevention of heart attacks by reducing inflammation, enhancing capillary permeability and strength, inhibiting formation of platelets and enhancing release of NO	
Black currant (*Ribes nigrum*) extract	Male Sprague–Dawley rats	The thoracic aorta was removed from the rats and induced 10–30 µg/mL of black currant extract	Endothelial-dependent vasorelaxation	(Nakamura et al. 2002)
Black mulberry (*Morus nigra*) fruit extract	50 male Sprague–Dawley rats divided into 5 groups (n = 10)	25 and 50 mg/kg/day via intraperitoneal route for 6 weeks	Significantly reduced total cholesterol, low-density lipoprotein-cholesterol and triglyceride levels and reduced atherosclerotic lesions	(Jiang et al. 2017)
Cyanidin 3-*O*-glucoside	Spontaneously hypertensive rats (SHRs)	10 mg/kg/day gavage for 15 weeks	Reduced blood pressure and cardiac hypertrophy	(Aloud et al. 2018)
Chokeberry (*A. melanocarpa*) and purple maize (*Z. mays*)	72 male Wistar rats divided 6 groups each contained 12 rats	Orally approx. 0.8 mg/kg/day for 16 weeks	Improved cardiovascular structure and function reduced systolic blood pressure, decreased plasma triglycerides and total cholesterol compared to high-fat diet rats	(Bhaswant et al. 2017)
Commercial grape juice	47 Adult mongrel dogs of either sex	Ranges from 2 to 10 mL/kg intravenous infusion	Inhibit platelet; activity and experimental coronary thrombosis in vivo	(Demrow et al. 1995)
Hibiscus sabdariffa aqueous extract	Two-kidney-one-clip (2K1C) model of hypertension in 42 rats seven groups (n = 6/group)	15, 30, or 60 mg/200 g body weight; orally for 2 weeks	Serum ACE activity and plasma angiotensin II level were significantly reduced	(Nurfaradilla et al. 2019)
			Reduced blood pressure	
Maize (*Z. mays*)	62 male Wistar rats divided into 2 groups	Special diet containing 20% anthocyanins rich or anthocyanins free diet taken orally for 8 weeks	Reduced vulnerability of myocardium to ischemia reperfusion injury in both ex vivo and in vivo studies	(Toufektsian et al. 2008)
Pure delphinidin	64 male Sprague–Dawley rat's left coronary artery isolated	Ventricular myocytes isolated from the rats and applied 10 µM pure sample to cultured myocytes 2 h prior to the hypoxic injury and during reoxygenation	Protection from heart treatment was linked with reduced NF-kB expression	(Scarabelli et al. 2008)
Red Chinese cabbage (*B. rapa*)	40 male ApoE$^{-/-}$ mice subdivided into 5 groups each consisted of 8 mice	150 or 300 mg/kg/day (27 or 54 mg cyanidin/kg/day) were fed by gavage for 12 weeks	Reduced: (i) plaque formation, (ii) infiltration of leukocytes, (iii) concentrations of blood inflammatory cytokines which lowered the risk of vascular inflammatory diseases	(Joo et al. 2018)

Table 3 continued

Food extracts containing anthocyanins	Model	Dose	Experimental Outcomes	Reference
Anthocyanidins (blueberries, strawberries, red wine)	34,489 Postmenopausal women	1%, 4% and 1% of total consumption of food one time/week for 16 years follow up	Reduction in CVD mortality	(Mink et al. 2007)
Anthocyanin-rich blueberry	A double-blind, parallel RCT, 138 eligible aged adults	2 dietary achievable blueberry oral intakes equivalent to 1/2 and 1 cup/day (75/150 g) for 6 months	Improved endothelial function, systemic arterial stiffness, and attenuated cyclic guanosine monophosphate concentrations	(Curtis et al. 2019)
Blueberries anthocyanins	63 healthy male volunteers randomized, double-blind, parallel controlled trial	300 mg anthocyanins, equivalent to 200 g of fresh blueberries for 1 month	Dose-dependent improvement of endothelial function in healthy humans measured by flow-mediated dilation	(Rodriguez-Mateos et al. 2019)
Blue honeysuckle, cyanidin-3-*O*-glucoside	A double-blind, counterbalanced, crossover intervention study carried in 20 older adults, aged 62–81 years	Oral drink containing 100 mg, 200 mg, and 400 mg anthocyanins for 1 week	The 400 mg dose elicited significantly lower diastolic blood pressure and heart rate	(Bell and Williams 2019)
Commercial red wine	Human	25 g (approximately 2 standard drinks)/day	Reduction in CVD mortality	(Klatsky 2001)
Concord grape juice supplementation (*Vitis vinifera*) juice or wine	40 men with mild hypertension	Orally intake 5.5 ml/kg body weight/day split over two servings per day, for 8 weeks	Decreased systolic blood pressure both in SHRs and in hypertensive humans and also improved aortic elasticity in stroke-prone SHRs	(Dohadwala and Vita 2009)
Freeze-dried bilberry (*V. myrtillus*) as a dietary supplement	50 ST-segment elevation myocardial infarction patients	Orally 40 g/day, equivalent to 480 g fresh bilberries for 8 weeks	A significant improvement was found in walk test and blood lipid profiles were altered within the bilberry group that could potentially translate the reduction of CVD	(Arevstrom et al. 2019)
New Zealand blackcurrant extract	Ten adult healthy male	Orally 1.87 mg total anthocyanins/kg bodyweight for 1 week	Acute ingestion of a single dose of blackcurrant extract maintained forearm blood flow and forearm vascular resistance during an extended period of sitting	(Barnes et al. 2020)
New Zealand blackcurrant extract	14 older adults, randomized, double-blind, placebo-controlled, cross-over design	600 mg/day for 1 week	Decrease in systolic and diastolic blood pressure	(Cook et al. 2020)
V. arctostaphylos, berry hydro-alcoholic extract	Randomized placebo-controlled trial in overweight/obese 50 hypertensive patients	3-month intake of 400 mg extract capsule three times daily	Systolic blood pressure and diastolic blood pressure decreased significantly	(Kianbakht and Hashem-Dabaghian 2019)

2002). There have been significant reductions in blood pressure, inflammatory status, ischemia, and lipid levels in patients with clinically diagnosed vascular diseases when given relatively low-dose anthocyanin therapy (Aviram et al. 2004; Sumner et al. 2005; Gorinstein et al. 2006; Naruszewicz et al. 2007). Commercially available grape juice (10 mL/kg) can markedly inhibit platelet activity and experimental coronary thrombosis in vivo (Demrow et al. 1995). Corn-derived anthocyanins resulted in the myocardium being less vulnerable to ischemia reperfusion injury, in both in vivo and ex vivo studies, as compared with the anthocyanin-free control (Toufektsian et al. 2008). A previous report suggests that anthocyanins containing purple barley extracts (pigmented genotypes of *Hordeum vulgare*) inhibited angiotensin converting enzyme (ACE) significantly, which is a crucial enzyme for hypertension and oxidative stress development in the heart (Lee et al. 2013). Delphinidin and cyanin showed interruption of the renin-angiotensin system mediated signalling pathway by inhibiting the ACE activity and decreasing production of mRNA (Parichatikanond et al. 2012). Anthocyanins from *Hibiscus sabdariffa* (delphinidin- and cyanidin 3-*O*-sambubiosides) inhibited ACE enzyme activity by competing with the substrate for the active site (Ojeda et al. 2010).

Anthocyanins may be effective in improving endothelial function through the adjustment of NO levels. Bilberry (*V. myrtillus*) and chokeberry (*A. melanocarpa*) and other anthocyanin-rich extracts can prevent loss of endothelium-dependent and NO mediated relaxation in porcine arteries in vitro (Bell and Gochenaur 2006). Another report suggests that delphinidin enhances NO release and endothelial nitric oxide synthase (eNOS) phosphorylation (Martin et al. 2003). A recent investigation showed that cyanidin 3-*O*-glucoside prevented a rise of blood pressure in spontaneously hypertensive rats (Aloud et al. 2018). Cyanidin 3-*O*-glucoside affects the interaction between soluble guanylyl cyclase and eNOS, thus increasing production of cyclic guanosine monophosphate (cGMP) by regulating phosphorylation of eNOS and protein kinase B (Akt) (Xu et al. 2004). Moreover, anthocyanin rich extract of purple barley grain showed potent in vitro inhibitory activity of angiotensin converting enzymes (Lee et al. 2013). A cross-sectional study reported that a higher intake of anthocyanins is associated with lower arterial stiffness (Jennings et al. 2012). *A. melanocarpa* extract rich in anthocyanins showed significant decreases in blood pressure in patients suffering from metabolic syndrome (Broncel et al. 2010).

Grape products associated with other foods containing polyphenols protect the heart from oxidative stress and inflammation, and activating novel proteins, e.g. Sirtuin 1 that prevent cellular senescence (Dohadwala and Vita 2009). Malvidin 3-*O*-glucoside inhibits NF-κB in bovine arterial endothelial cells which was also involved in suppression of pro-inflammatory mediators (Paixao et al. 2012). Malvidin also inhibited the ICAM-1, monocyte chemo-attractant protein-1(MCP-1) and vascular cell adhesion molecule-1 (VCAM-1) expression that was induced in endothelial cells by TNF-α (Huang et al. 2014). Human umbilical vein endothelial cells, when treated with anthocyanins, resulted in the regulation of cholesterol distribution by interfering with recruitment of TNF receptor-associated factors-2 in lipid rafts, thus inhibiting glycoprotein CD40-induced pro-inflammatory signalling (Atalay et al. 2003). Delphinidin can reduce the degree of necrotic and apoptotic cell death in cultured cardiomyocytes and also the infarct size after ischemia in rats. The process was mediated by inhibition of activators and signal transducers of transcription-1 (Cines et al. 1998). In this study, purple rice (*O. sativa*) extract prevented the rise of toll-like receptor-4, NF-κB and transforming growth factor-β (TGF-β) expression in heart as well as reduced activation of phospho extracellular signal regulated kinases-1/2, basic fibroblast growth factor and urokinase plasminogen activator in the heart of a diabetic group (Chen et al. 2016).

Anthocyanins may also protect against the production of adhesion molecules induced by activated platelets. An investigation involving optimal platelet function revealed that anthocyanins and their colonic metabolites inhibited thrombin peptide–induced, receptor-activating platelet aggregation but had no influence on the reactivity of platelets when strong agonists such as ADP and collagen were present (Liang et al. 2006). The beneficial effect of polyphenols on the suppression of platelet-mediated thrombosis was reported previously. Fractions from purple grapes (*V. vinifera*) containing delphinidin inhibited whole-blood aggregation, indicating a possible mechanism for the improvement of CVD (Freedman et al. 2001).

Increased levels of C-reactive protein (CRP) due to low-grade chronic inflammation can be considered an independent risk factor for CVD (Ellulu et al. 2017). Among adults in the United States, a significant inverse association between anthocyanin intakes and serum CRP was found upon analysis of the national health and nutrition examination survey data (Chun et al. 2008). Data from the United States department of agriculture flavonoid databases also indicated that anthocyanidin intakes were inversely linked with serum CRP concentration (Chun et al. 2008). By using sweet cherries (*Prunus auiun*) that were anthocyanin-rich, a recent clinical study showed a decrease in serum CRP level after four weeks of intervention (Carluccio Maria et al. 2003). Based on this discussion a possible mechanism for anthocyanin mediated prevention of inflammation, hypertrophy and fibrosis signal in the heart has been proposed in Figs. 3 and 4.

Anthocyanins in diabetes and obesity

Many recent studies suggest that eating fruits and vegetables, especially those rich in polyphenols, reduce the occurrence of type-2 diabetes, a condition associated with insulin resistance (Anderson and Polansky 2002; Landrault et al. 2003; Anderson et al. 2004; Lachin and Reza 2012; Putta et al. 2018). Our previous report also showed that antioxidant compounds prevented the oxidative stress and associated complications in insulin resistance and obesity (Alam et al. 2016). In this part, we discussed that anthocyanins and natural fruits and vegetables rich in anthocyanins may influence and modulate the diabetes condition by improving insulin resistance, improved glucose absorption in cellular level, prevented glucose absorption by inhibiting key enzymes such as alpha amylase and beta glucosidase, decreased cholesterol level by increasing lipid metabolism and lowered inflammatory states in the adipose tissues. Table 5 summarizes the beneficial effects of anthocyanins in diabetes and obesity. Insulin resistance is a disorder, where there is inadequate stimulation of glucose transport in skeletal fat and muscle by insulin, and it also enhances hepatic glucose production. Anthocyanins and anthocyanidins were found to protect pancreatic β-cells from glucose-induced oxidative stress in several studies (Al-Awwadi et al. 2005; Jayaprakasam et al. 2005). The glycoside and dimethoxy ether of leucopelargonidin, isolated from the bark of the Indian banyan tree (*Ficus bengalensis*), have shown significant hypolipidemic, hypoglycaemic and serum insulin-raising effects in moderately diabetic rats, being comparable with the effects of glibenclamide (Cherian et al. 1992; Augusti et al. 1994; Daniel et al. 2003). In addition, *Cornus* fruits which are a rich source of anthocyanins have been reported to possess anti-diabetic activity (Yamahara et al. 1981; Seeram et al. 2002). White skin sweet potato resulted in improved diabetes, glucose tolerance, hyperinsulinemia and hyperlipidaemia, as well as lowered free fatty acids in Zucker fatty rats (Kusano et al. 2001). Recent investigation has shown that purple sweet potatoes (*I. batatas*) have also improved diabetes (Qin et al. 2019). Anthocyanins improved glucose stimulated glucose absorption and insulin secretion in INS-1E and human hepatoma cell (HepG2) cells (Luna-Vital and Gonzalez de Mejia 2018). It was also suggested that anthocyanins from purple corn significantly reduced gluconeogenesis by suppressing phosphoenolpyruvate carboxykinase expression and AMPK phosphorylation in HepG2 cells (Luna-Vital and Gonzalez de Mejia 2018). Mulberry (*Morus alba*) extract containing anthocyanins also improved glucose uptake, utilization, increased glycogen formation and diminished the insulin resistance in HepG2 cells (Yan et al. 2016).

Anthocyanins (Lachin and Reza 2012) especially pelargonidin-3-*O*-galactoside and its aglycone, pelargonidin was able to increase insulin secretion by selectively inhibiting COX-2 enzyme (Zhang et al. 2004). The study suggested that cherries (*Prunus* genus), grapes (*V. vinifera*) and other anthocyanin containing berries might have a role in the prevention of type-2 diabetes. Anthocyanin extracts showed potent α-glucosidase inhibitory activity, suppressing an increased postprandial glucose level in some in vitro and animal studies (Matsui et al. 2001, 2004). Cyanidin and its glycosides showed inhibitory activities of intestinal α-glucosidase and pancreatic α-amylase in vitro and also showed synergistic effect with acarbose (Akkarachiyasit et al. 2010). α-Glucosidase and pancreatic lipase enzyme inhibition was associated with anthocyanins isolated from whole berries and skin of Muscadine grapes (*V. vinifera*) (You et al. 2011). Extracts from the pulp from several sweet cherry (*P. avium*) cultivars showed α-glucosidase enzyme inhibition (Goncalves et al.

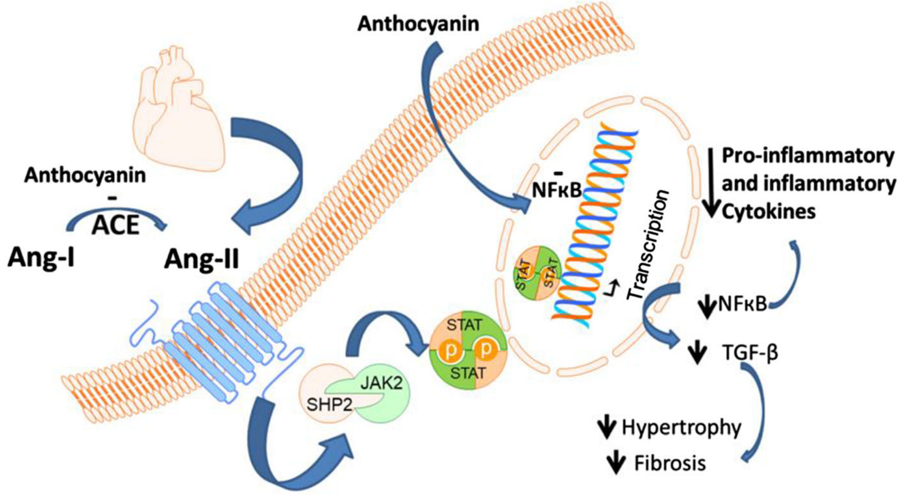

Fig. 3 Schematic representation of anthocyanin mediated prevention of inflammation, hypertrophy and fibrosis signal in the heart. Angiotensin-II is the regulating factor for the development of hypertrophic signal in the heart through activation of Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathway which may stimulate the transforming growth factor beta (TGF-β) and fibrosis in the heart. Moreover, anthocyanins such as delphinidin, malvidin 3-*O*-glucoside, cyanidine may inhibit the angiotensin-II mediated pathway and nuclear factor kuppa B (NF-κB) to reduce the pro-inflammatory and inflammatory cytokines

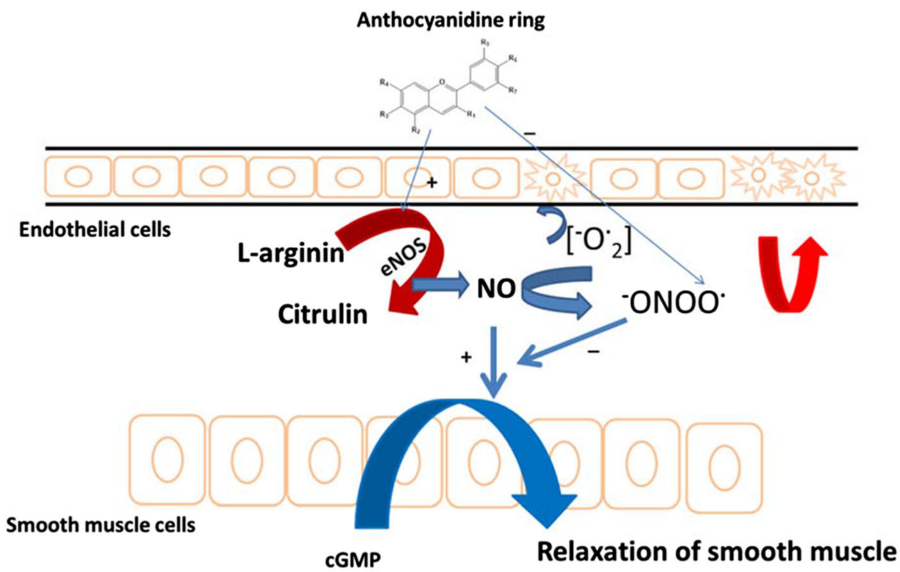

Fig. 4 Schematic representation of anthocyanin mediated prevention of oxidative stress in endothelial cells and relaxation of smooth muscle in blood vessels. Endothelial nitric oxide (eNOS) regulates the production of nitric oxide (NO) in the endothelium which is a signalling molecule responsible for vasodilation and vascular tone. Superoxide can directly interact with the NO and produces peroxynitrite radicles (•ONOO⁻). These peroxynitrite radicles may trigger endothelial cell destruction and causes vascular dysfunction. Anthocyanins such as cyanidin 3-*O*-glucoside may directly interact with superoxide to scavenge them or may increase the cyclic guanosine mono phosphate (cGMP) level to relax the smooth muscle of blood vessels

2017). Black chokeberry (*A. melanocarpa*) extracts also showed α-amylase and lipase/enzyme inhibition (Worsztynowicz et al. 2014).

Diabetes results in various microcirculatory disorders. Many of them may occur before microangiopathic lesions begin to form thickening of capillaries in many areas such as the eye and are assumed critical in the pathogenesis of microcirculatory complications involved with diabetes. The number of leucocytes sticking to the venular endothelium and microvascular permeability are increased in the diabetic microangiopathic condition (Valensi et al. 1997, 1998;). Delphinidin chloride showed a reduction of leucocytes adhering to the venular vessels and increased microvascular permeability in diabetic hamsters (Bertuglia et al. 1995). Several flavonoids, including anthocyanosides, have been effective against experimentally induced capillary filtration (Gabor 1972; Parmar and Ghosh 1977). In one animal study, it was shown that anthocyanosides can improve and even normalize capillary filtration of albumin (Cohen-Boulakia et al. 2000). Endothelium-dependent vasorelaxation by different vasodilator agonists is reduced in various conditions including diabetes (Griffiths and Smith 1972). One of the mechanisms that resulted in dysfunction of the endothelium was a decrease in the release of nitric oxide (NO) (Barton et al. 1997). Extracts from red wines, other grape products and various plant polyphenols (mainly anthocyanins) were found to produce endothelium-dependent vasorelaxation, probably through NO release or due to enhanced biological activity of NO (Fitzpatrick et al. 1993, 1995; Andriambeloson et al. 1998). A combination of anthocyanins of bilberry (*V. myrtillus*) was reported to have pharmacological and biological properties, including vasorelaxation and prevention of hypertension (Mykkänen et al. 2014).

Increased levels of triglyceride (hypertriglyceridemia) were strongly associated with the insulin resistance syndrome, with obesity being strongly associated with insulin resistance. Thus, a reduction in insulin resistance is important in preventing the development of type-2 diabetes. It was demonstrated that cyanidin 3-*O*-glucoside-rich purple corn may improve high fat diet-induced insulin resistance in mice (Tsuda et al. 2003). Consumption by diabetic patients of pomegranate (*P. granatum*) juice resulted in antioxidative effects in their serum and reduced the oxidative stress in their monocytes/macrophages levels. These changes were attributed specifically to anthocyanins (Gil et al. 2000; Rosenblat et al. 2006). Extracts of anthocyanin and procyanidins increased high-density lipoprotein (HDL) cholesterol levels while decreasing triglycerides in rats (Al-Awwadi et al. 2005). A recent investigation showed that delphinidin effectively modulated lipid metabolic gene expression in human HepG2 Cells and reduced triglyceride accumulation in vitro (Parra-Vargas et al. 2018). However, delphinidin failed to change body weight gain, energy intake, histological abnormalities, hyperglycemia or insulin resistance elicited by the high fat high carbohydrate diet (Parra-Vargas et al. 2018). Another report suggested that cyanidin and delphinidin consumption mitigated high fat diet-induced obesity, dyslipidaemia, insulin resistance and oxidative stress followed by the inhibition of NF-κB and Jun *N*-terminal kinases (JNK) activation as well as protein tyrosine phosphatase-1B overexpression (Daveri et al. 2018). Blackberries containing 57% malvidin and 33% petunidin or peonidin increased mitochondrial respiration thus reducing metabolic damage related to a high-fat diet (Skates et al. 2018). Blueberry (*V. corymbosum* and *V. ashei*) containing anthocyanins were responsible for the reduction of glucose levels, triglyceride, cholesterol and leptin in high fat diet fed C57BL/6 mice (DeFuria et al. 2009; Wu et al. 2016a). Red cabbage (*Brassica oleracea*) and red cabbage microgreen (were harvested without roots, shipped overnight with specialized clamshell containers) supplementation reduced low-density lipoprotein and cholesterol in high fat diet fed C57BL/6 mice (Huang et al. 2016a). Mulberry (*M. australis*) and sweet cherry (*P. avium*) extract rich in cyaniding prevented the inflammatory cytokines (e.g. TNF-α, IL-6, iNOS and NF-κB) and improved insulin resistance in high fat diet fed mice (Wu et al. 2016b). Black soybean (*G. max*) extract also showed decreased triglyceride and cholesterol as well as reduced cytokine production in high fat diet fed rats (Kim et al. 2015). Black soybean (*G. max*) also showed reduced triglyceride and cholesterol level in overweight and obese Korean adults (Lee et al. 2016). A recent investigation suggested that raspberry (*R. idaeus*) anthocyanin consumption elevated GPx and serum SOD activities as well as fecal butyric acid levels which can ameliorates diet induced obesity by alleviating oxidative stress (Wu et al. 2018). Raspberry (*R. idaeus*) anthocyanin consumption also reduced hepatic lipid and serum profiles, while markedly down-regulating the expression of TNFα, IL-6 and NF-κB genes (Wu et al. 2018). Blue berry anthocyanins showed altered mitogen-activated protein kinase and NF-κB-mediated stress signalling pathways and gene expression in high fat diet fed male C57Bl/6j mice (DeFuria et al. 2009).

The primary site of energy storage is the adipocytes that are known to accumulate triacylglycerol during nutritional excess. Recently, it has been established that adipocyte dysfunction has an important role in the development of obesity and insulin resistance. Adipocytes synthesize and secrete biologically active molecules called adipocytokines among which adiponectin is important (Shimomura et al. 1996). In obese and insulin resistant state, plasma adiponectin concentration and mRNA expression level are decreased (Arita et al. 2012). Purple sweet potato (*I. batatas*) containing 3-*O*-caffeylferulysophoroside-5-*O*-glucoside and 3-*O*-caffeylferulysophoroside-5-*O*-glucoside decreased the leptin (adepogenic marker) as well as decreased the production of COX-2, MCP-1 and IL-6 in 3T3-L1 cells (Ju et al. 2011). Anthocyanins can regulate obesity and insulin sensitivity associated with adipocytokine secretion in adipocytes. This provides a biochemical basis for the use of anthocyanins which will have significant implications for the prevention of diabetes and obesity (Tsuda et al. 2003). Anthocyanin-rich mixed grape-bilberry juice supplementation in Fischer rats reduced serum leptin and resistin, but did not influence serum adiponectin and secretion of adipokines from mesenteric adipose tissue (Graf et al. 2013). Blueberry (*V. corymbosum*) powder supplementation reduced triglycerides, fasting insulin, insulin resistance, and plasma glucose level in Zucker fatty rats fed with a high fat diet (Seymour et al. 2011). Blueberry (*V. corymbosum*) intake increased adipose and skeletal muscle peroxisome proliferator-activated receptor (PPAR) activity, reduced abdominal fat mass and affected PPAR transcription involved in glucose uptake/oxidation and fat oxidation (Seymour et al. 2011). Thus, these studies demonstrated that anthocyanins can modulate the gene expression of adipocytokines in humans and may have a distinct therapeutic advantage for the regulation of adipocyte function (Tsuda et al. 2005, 2006).

Increased lipid metabolism and utilization in the liver and other organs are key pathways through which fats are removed from the body. High fat diet feeding may induce fat accumulation in the liver and started steatosis to non-alcoholic fatty liver diseases. Microarray analysis of hepatic gene expression profiles indicated that PPAR signalling pathway, steroid biosynthesis, fatty acid metabolism and biosynthesis were modulated by sweet cherry (*P. auiun*) anthocyanins in C57 BL/6 J mice fed with a high fat diet (Song et al. 2016a). Sweet cherry (*P. auiun*) anthocyanins are also capable of reducing the hepatic steatosis in high fat diet fed mice (Wu et al. 2014; Song et al. 2016a). Mulberry (*M. alba*) anthocyanin extract was tested on hepatocytes cultured with high fatty acid. This extract enhanced fatty acid oxidation and suppressed fatty acid synthesis, which contributed to ameliorating lipid accumulation induced by oleic acid (OA) in human HepG2 as the cell model (Chang et al. 2013). This investigation also identified that mulberry (*M. alba*) anthocyanin extract stimulated AMPK and inhibited acetyl coenzyme A carboxylase activities (Chang et al. 2013). Mulberry (*M. alba*) anthocyanin extract also attenuated the expression of sterol regulatory element-binding protein-1 (SREBP-1) and fatty acid synthase (FAS) in human HepG2 (Chang et al. 2013). Black elderberry (*S. nigra*) anthocyanins significantly lowered liver weights, serum TAG, serum monocyte chemo-attractant protein-1, serum insulin and TNFα, followed by the reduction of hepatic fatty acid synthase mRNA in the liver of high fat diet fed mice (Farrell et al. 2015). Based on this discussion a possible mechanism for inflammation and fat metabolism in liver has been proposed in Fig. 5 (Table 4).

Anthocyanins in neurodegenerative diseases

Anthocyanins have a strong antioxidant capacity, which can be very effective in several models of neurodegenerative diseases (Miller et al. 2018; Stintzing et al. 2002; Shih et al. 2011; Traustadottir et al. 2009). They have a high oxygen radical absorbance capacity (ORAC) value, which is a major part of their neuroprotective function (Zafra-Stone et al. 2007; Zhu et al. 2010). In addition, anthocyanins act as antioxidants as they are able to directly trap free radicals, thus preventing ROS formation in affected cells. For example, anthocyanins can decrease the generation of ROS in in vitro models of alpha–beta peptide-induced

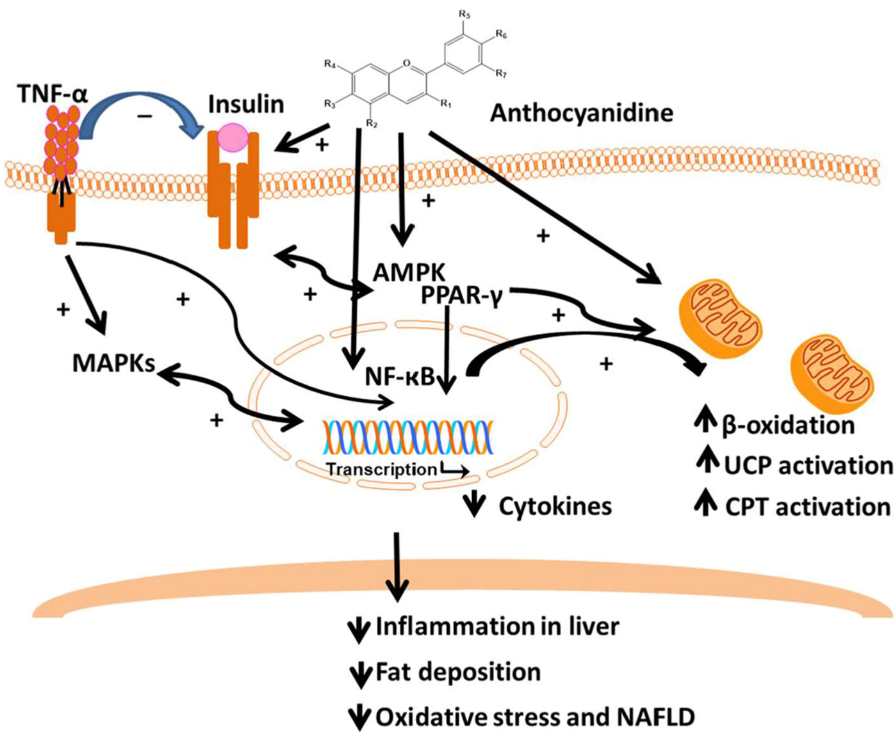

Fig. 5 Schematic representation of anthocyanin mediated prevention of inflammation and fat metabolism in liver. Inflammation and cytokines leads to insulin resistance in diabetes and obesity. TNF-α signalling stimulates the production of inflammatory cytokines in liver through NF-κB pathway. Anthocyanins from various plant sources can interact with the regulatory kinase molecule AMPK responsible for the overall metabolism and ATP production in the cell. AMPK is also responsible for the down regulation of inflammatory cytokine production. Anthocyanins stimulates AMPK pathway resulting in increased utilization of cellular glucose and fatty acids and decreasing inflammation in liver

toxicity, as well as in hydrogen peroxide injury (Shih et al. 2011; Hwang et al. 2012). Moreover, by using electron spin resonance spectroscopy it has been found that anthocyanins have a strong affinity to scavenge DPPH, alkyl, and hydroxyl free radicals in a dose dependent fashion (Hwang et al. 2012). Benefits of anthocyanins in neurodegenerative diseases are presented in Table 5.

Initiation of inflammatory gene expression and subsequent production of interleukins and pro-inflammatory cytokines is often recorded in neurodegeneration. Targeting these inflammatory processes may prove beneficial in limiting neuronal apoptosis associated with the disease. Anthocyanins display significant anti-inflammatory properties, given that they can inhibit various inflammatory biomarkers (e.g. interleukin-8 (IL-8)) (Zafra-Stone et al. 2007). As well as decreased IL-8 production, pomegranate (*P. granatum)* anthocyanins inhibit activation of NF-κB (Rasheed et al. 2009) and inflammatory markers including activated p-NF-κB (phosphorylated NF-κB) (Rehman et al. 2017) which are responsible for the expression of several pro-inflammatory genes. The anthocyanins were shown to inhibit a number of other bio-molecules associated with the expression of several pro-inflammatory cytokines. Furthermore, cherry and blackberry (*R. fruticosus*) anthocyanins have been proven to be powerful COX-2 inhibitors, which is an important pro-inflammatory enzyme employed in the synthesis of prostacyclins (Saric et al. 2009; Zdarilova et al. 2010). At high concentrations (250 μg/mL), anthocyanins have inhibited up to 95% of cyclooxygenase activity (Mulabagal et al. 2009). These findings indicate that anthocyanins may have a significant role in preventing inflammatory processes associated with neurodegenerative disease. A recent investigation also suggests that supplementation of blackcurrant (*Ribes nigrum*) anthocyanins resulted in increased cyclic glycine-proline (cGP) in the cerebrospinal fluid of patients suffering from

Table 4 Function of anthocyanin rich natural extracts and anthocyanins in the prevention of diabetes and obesity

Food extracts containing anthocyanins	Model	Dose	Experimental Outcomes	Reference
Purple maize extract	RAW 264.7 macrophages and 3T3-L1 adipocytes	Pretreated with 1 mg/mL anthocyanin-rich water extracts	Down-regulating pro-inflammatory mediator production in inflamed macrophages and adipocytes Improving insulin sensitivity in insulin-resistant adipocytes	(Zhang et al. 2019a)
Cyanidin-3-*O*-glucoside-rich purple corn	Rat and human adipocytes	100 µM extracts were used in rat and human cells	Improve high fat diet-induced insulin resistance in rat and human	(Tsuda et al. 2005, 2006)
delphinidin chloride	Eighty male (n = 10, 8 groups) BALB/c mice were used in streptozotocin (STZ)-induced diabetes	100 mg delphinidin chloride/kg/24 h was intravenously injected for eight weeks	Inhibited the protein glycation in diabetes mellitus and reduced the glycation rate of hemoglobin A1c	(Gharib et al. 2013)
Delphinidin	HT-29 enterocyte-like human cell line and RF/J mice	Cell line was treated with 50 µM delphinidin and mice were treated with100 µM delphinidin	Glucose absorption is inhibited in both mouse jejunum and a human enterocytic cell line in a free fatty acid receptor-dependent manner	(Hidalgo et al. 2017)
Grape skin or whole grapes (*V. vinifera*), berries (*Rubus*) and cherry (*Prunus*)	In vitro α-glucosidase Inhibitory, insulin secretion assay were performed on INS-1 cells in vivo was performed through male albino Wistar rats	In vivo oral study was performed via administration of 15 g/day not less than 2 weeks 0.5 mg/mL for α-glucosidase inhibitory assay	Enhance insulin secretion Inhibits COX-2 enzymes selectively Have potent alpha-glucosidase inhibitory activity that suppress the increase in postprandial glucose level Inhibitory activities for lens opacity Improve vision and prevent diabetic retinopathy	(Matsui et al. 2001; Zhang et al. 2004; Griffiths and Smith 1972)
Pomegranate (*P. granatum*) juice	In vitro ABTS, DPPH and FRAP assay 20 male participants Tested in rat model (n = 9)	Soluble solids of juice value were ranged from 15.5 to 16.6% 50 mL of pomegranate juice per day (which contain 1.5 mmol of total polyphenols) the dose of 21.42 mg/kg/day of total polyphenols orally by gavage for 6 weeks	Anthocyanins had anti-oxidative effects, which resulted in anti-oxidative effects on serum which might help reduce atherosclerosis development in these patients Decrease triglycerides and increase HDL-cholesterol levels in rats	(Al-Awwadi et al. 2005; Gil et al. 2000; Rosenblat et al. 2006)
Lingon berry extract (*V. vitis-idaea*)	In vitro and in vivo studies HCD -induced hypercholesterolaemic 40 mice divided into four groups (10 mice per group)	200 and 400 mg/kg of body weight per day for 10 weeks as dietary supplement	Reduce the inflammatory cell infiltration and attenuate steatosis and hepatocellular fat deposit in the liver	(Zhang et al. 2019c)

Table 4 continued

Food extracts containing anthocyanins	Model	Dose	Experimental Outcomes	Reference
Anthocyanins and anthocyanosides from *Cornus* species	In vitro rodent pancreatic beta-cells and male Wistar rats with streptozotocin (STZ)-induced diabetes in 3 groups of 15 rats	Daily dosage of 40 mg/kg for 12 weeks	Protect pancreatic β-cells from glucose induced oxidative stress and improve and normalize capillary filtration of albumin	(Cohen-Boulakia et al. 2000; Jayaprakasam et al. 2005)
Polymerized anthocyanin	40 male C57bl6/J mice divided into 4 groups induced nonalcoholic fatty liver disease	400 mg/kg/day were given orally once a day for 12 weeks	Effectively reduced TC and LDL-C Inhibited the activation of inflammatory pathways, depressing oxidative stress through increased antioxidant levels, and increasing β-oxidation to inhibit mitochondrial dysfunction	(Fan et al. 2019)
Bark of the Indian banyan tree (*F. bengalensis*)	Moderately diabetic mice, rats and alloxan diabetic dogs	Different range of diet from 0.2–1.8 g/kg/day to different groups of animals for one month	Significant hypoglycaemic, hypo-lipidemic and serum insulin-raising effects	(Cherian et al. 1992; Augusti et al. 1994; Daniel et al. 2003)
Blackcurrant (*Ribes nigrum*) extract	OVX female Sprague–Dawley and sham surgery rats (3 groups, n = 9–10 rats/group)	Consumed 38 g/100 g blackcurrant extract (3%) orally for 3 months	Decreased expression of hepatitis-related genes, such as tumour necrosis factor-α, *IL-6*, and *IL-1β* Levels of serum triglycerides, total cholesterol, and LDL cholesterol decreased	(Nanashima et al. 2020)
Tart cherry extract	35 High fat diet fed mice were divided into 3 groups and	Consumed 60 mg/kg anthocyanin-rich tart cherry extract in a daily dosage for 6 weeks	Failed to reverse the effects of the high fat diet on body weight and glucose tolerance Significantly reduced the leptin and IL-6 levels Significant enhancement in antioxidant capacity and SOD activity	(Nemes et al. 2019)
Sweet cherries (*P. auiun*)	48 male C57BL/6 high-fat diet mice were divided into four groups	Consumed 2 mg/kg of body weight for 12 weeks	Purified sweet cherries reduce the expression levels of IL-6 and TNFα genes and markedly increase the SOD and GPx activity	(Wu et al. 2014)
Cornelian Cherry (*Cornus mas*) and Japanese cornelian cherry (*C. officinalis*)	32 high-fat-fed insulin resistance C57BL/6 mice were divided into 4 groups Streptozotocin induced diabetes rats model took 6 groups in each group contained average 10 rats and dose	C57BL/6 mice were fed with high-fat diet plus 1 g/kg of anthocyanins for 8 weeks Streptozotocin induced diabetic rats were treated with 50 mg/kg intravenous administration	Body weight was decreased, normalized glucose intolerance, elevated circulating insulin, and a dramatic decrease in liver lipid	(Yamahara et al. 1981; Jayaprakasam et al. 2006)

Table 4 continued

Food extracts containing anthocyanins	Model	Dose	Experimental Outcomes	Reference
Blueberries *V. ashei* and yoghurt supplement	Diet induced obese C57BL/6 mice divided into eight groups (n = 10 for each group)	Consumed 6.4 g/kg of blueberries, 0.02 g/kg of cyanidin-3-*O*-*β*-glucoside and 3 g/kg of yoghurt body weight/day during the 8 week treatment period	Cyanidin-3-*O*-β-glucoside and the combination of peptides showed significant reduction of body fat and improved intraperitoneal glucose tolerance	(Shi et al. 2019)
Chokeberry (*A. melanocarpa*) purple maize; (*Z. mays*)	72 male Wistar rats were divided into six separate groups (n = 12 each)	Supplemented orally with chokeberry juice 50 ml/kg/day or purple maize flour 50 g/kg/day for 16 weeks	Reduced visceral adiposity index and total body fat mass; improved glucose tolerance and liver structure and function	(Bhaswant et al. 2017)
Anthocyanins	169 participants with dyslipidemia randomized, double-blind, placebo-controlled human trial	Two capsules (dose 40, 80, and 320 mg/day) twice daily preferably 30-min after breakfast and supper for 12 weeks	320 mg/day anthocyanin supplementation reduced serum IL-6, TNF-α, MDA and urine 8-iso-$PGF_{2\alpha}$ and 8-OHdG than 80 mg/day and 40 mg/day anthocyanins Improved the anti-oxidative and anti-inflammatory capacity in a dose–response manner	(Zhang et al. 2020a)
Purified anthocyanins	Randomized, double-blind, placebo-controlled human trial (Participants n = 111)	Orally five doses of anthocyanins (20, 40, 80, 160, or 320 mg/d) were asked to take once daily after meals for 14 days	80 mg/day of anthocyanin showed the lowest baseline-adjusted fasting plasma glucose level 8-iso-prostaglandin F2α levels decreased with increasing anthocyanins dose Plasma interleukin-10 levels were negatively correlated with increasing anthocyanin	(Guo et al. 2020)

Table 5 Function of anthocyanin rich natural extracts and anthocyanins in neurodegenerative diseases

Food extracts containing anthocyanins	Model	Dose	Experimental Outcomes	References
Anthocyanins	In vitro models of alpha–beta peptide-induced toxicity and hydrogen peroxide injury Inhibitory effect of berry anthocyanins on human gastric cancer cells MKN45	50 µM of extract for ROS assay and $\alpha\beta$ peptide-induced toxicity, 30 µL anthocyanin oligomers solution for DPPH, 2 mL of the sample solution for lipid peroxidation inhibition assay 0.5% of berry extract were used to examine the inhibitory effect of berry anthocyanins on *Helicobacter pylori*-induced IL-8 production in gastric MKN 45 cells	Decrease the generation of ROS. Scavenge DPPH, alkyl, and hydroxyl free radicals in a dose dependent fashion Anthocyanins display significant anti-inflammatory properties by inhibiting various inflammatory biomarkers, including IL-8	(Hwang et al. 2012; Shih et al. 2011; Zafra-Stone et al. 2007)
Pomegranate (*P. granatum*)	KU812 cell line, Enzyme-linked immunosorbent assay, western blot analysis and transient transfection and luciferase activity assay	Pomegranate fruit extract (20–100 µg/mL)	Inhibit the activation of nuclear transcription NFκB responsible for the expression of several pro-inflammatory genes Inhibit other bio-molecules responsible for the expression of pro-inflammatory cytokines	(Rasheed et al. 2009)
Pomegranate extract	U-87 cells and rats (n = 4)	Receiving 600 mg/kg/day oral administration	Decreasing the MORs and cAMP protein levels in U-87 cells A significant decrease in cAMP responsive element binding protein (CREB) level and an increase in Brain-derived neurotropic family (BDNF) as compared to rats treated with morphine	(Ridzwan et al. 2020)
Bilberry anthocyanins	44 Alzheimer's disease model APP/PSEN1 mice (n = 5–6)	20 mg/kg/day bilberry anthocyanins was given via gavage for three months	Improves learning and memory abilities and reverses defects to cognitive functions Decreases serum and brain lipopolysaccharide (LPS) levels and increases fecal short-chain fatty acid content Downregulates the expression of inflammatory factors (TNF-α, NF-Kβ, IL-1β, IL-6, COX-2, iNOS and CD33) and chemokine receptor CX3CR1 Decreases hippocampal neuroinflammatory responses, and induces phagocytosis of microglia to beta-amyloid protein plaques	(Li et al. 2020)

Table 5 continued

Food extracts containing anthocyanins	Model	Dose	Experimental Outcomes	References
Anthocyanin	Mice were subjected to laparotomy 7groups and each groups contains 12 mice	50–100 mg/kg orally and 10 mg/kg intraperitoneal injection for 4 weeks before surgery and then once per day for 4 week after surgery	Improved learning and memory in mice after surgery Significantly reduced neuroinflammation and microglia activation	(Zhang et al. 2020b)
Anthocyanins	LPS-induced neurotoxicity, 15–20 mice/group divided into three groups. Mice injected with LPS	24 mg/kg/day for 2 weeks	Prevented ROS production, inhibited neuroinflammation and neurodegeneration, and improved memory functions in LPS-treated mice Prevented neuroinflammation by lowering the levels of inflammatory markers (p-NF-kB, TNF-α, and IL-1β)	(Khan et al. 2019)
Cherry (*Prunus cerasus*)	Male CBA/Hr mice 3 groups and 10 mice in each group	5 g per day for 14 days of commercial food pellets containing 4 mL of 10 and 50% dilution of original cherry juice	Inhibits COX-2 responsible for pro-inflammatory enzyme required in the synthesis of prostacyclin	(Saric et al. 2009)
Purple sweet potato (*I. batatas*)	Male Sprague–Dawley (SD) rats for brain homogenate preparation and male ICR mice (4 groups)	25 mg/kg body weight orally once a day for 7 days	Enhance cognitive performance Inhibits lipid peroxidation	(Cho et al. 2003)
Blueberry (*V. corymbosum*)	40 male Fischer 344 rats were divided into 4 groups	1.86% blueberry (w/v) as a supplement for 8 weeks	Effective reversal of age-related deficits in various neural and behavioural parameters	(Joseph et al. 1999)
Lycium ruthenicum extract	d-galactose (d-gal)-treated rats were divided in 5 groups	50–200 mg/kg once daily for 7 weeks	Anthocyanins reduced receptor for advanced glycation end products (RAGE) and suppressed oxidative stress caused by d-gal Anthocyanins suppressed microgliosis and astrocytosis Reduced the overexpression of nuclear factor kappa B (NF-κB), interleukin-1-β (IL-1β), cyclooxygenase-2 (COX-2), and tumour necrosis factor-α (TNF-α) Lowered C-jun N-terminal kinase (p-JNK), caspase-3 levels, and the B-cell lymphoma 2-associated X protein/B-cell lymphoma 2 (Bax/Bcl-2) ratio	(Chen et al. 2019)

Table 5 continued

Food extracts containing anthocyanins	Model	Dose	Experimental Outcomes	References
Freeze-dried blueberry	13 men and 24 women, (60–75 years) were participated in a randomized, double-blind, placebo-controlled trial	24 g/day, equivalent to 1 cup of fresh blueberries for 90 days	On the California verbal learning test, participants in the blueberry group showed significantly fewer repetition errors which may improve cognition among older adults	(Miller et al. 2018)
Whole frozen blueberries	94 participants were participated in a randomized, double blind, parallel groups, and placebo-controlled trial	Intake of 12.5 g/day orally for 12 to 24 weeks trial	Supplementation improved cognition	(McNamara et al. 2018)

Parkinson disease (Fan et al. 2018). Anthocyanins increased cGP, which is a neuropeptide that facilitates IGF-1 function in brains of the patients with Parkinson disease (Fan et al. 2018). Moreover, anthocyanin could also reduce cerebral oedema while reducing the matrix metallopeptidase-9 activity in reperfusion injury (Pan et al. 2018). In addition, NF-κB and the NOD-like receptor pyrin domain-containing protein-3 inflammasome pathways were inhibited and TNF-α, IL-6 and interleukin-1β levels were decreased by anthocyanin treatment (Pan et al. 2018). Anthocyanin extracts from blackcurrants (*R. nigrum*), blueberries (*V. corymbosum*) and hibiscus (*H. sabdariffa*) prevented dopaminergic cell death, microglial activation and amelioration of mitochondrial dysfunction in rotenone-induced cell culture model of Parkinson diseases (Strathearn et al. 2014). Another report showed that cyanidin 3-*O*-glucoside exerted a neuroprotective effect against ischemic stroke in mice (Min et al. 2011). Black soybean (*G. max*) anthocyanin extract showed significant U87 glioma cells survival when exposed to oxidative stress induced by oxygen–glucose deprivation (Kim et al. 2012).

An extract high in anthocyanins from blackcurrant (*R. nigrum*) and bilberry (*V. myrtillus*) showed beneficial effects and reduced behavioural abnormalities in a mouse model of Alzheimer's disease (Vepsalainen et al. 2013). In addition, Qin et al. (2013) suggested that cyanidin 3-*O*-glucoside rescued the cognitive impairments in beta-amyloid peptide-induced cognitive deficits in the rat model of Alzheimer's disease (Qin et al. 2013). Cyanidin 3-*O*-β-glucopyranoside was shown to improve cerebral glucose uptake, alleviate cognitive impairment and decrease fasting blood glucose levels in the APPswe/PS1ΔE9 mouse model of Alzheimer's disease (Song et al. 2016b). Moreover, black soybean (*G. max*) anthocyanins have been investigated against beta-amyloid induced neurotoxicity in vitro on cell line and in vivo in rat model. The results showed increased amyloid beta production in the nervous system which ultimately protected beta-amyloid-induced neurodegeneration (Badshah et al. 2015). Shah et al. (2015) also worked on black soybean (*G. max*) anthocyanins but used the ethanol-induced oxidative stress (Shah et al. 2015) and glutamate-induced oxidative stress (Shah et al. 2016) rat models. They found neuroprotection via inhibition of glutamate related neurotransmission, neuronal apoptosis (Shah et al. 2015) and protection against glutamate-induced AMPK induction, ROS production, neuroinflammation and neurodegeneration (Shah et al. 2016).

Anthocyanins also have the capacity to modulate cognitive and motor function, to enhance memory, and to possibly reduce age-related declines in neural function. Administration of isolated, semi-purified anthocyanins from purple sweet potato (*I. batatas*) improved cognitive performance in mice, and also inhibited peroxidation of lipids in rat brain tissues (Cho et al. 2003). Administration of blueberry extracts with significant anthocyanin content (but not purified pigments), led to reversal of age-related deficits in various neural and behavioural parameters (motor and memory functions) (Joseph et al. 1999). Further investigations demonstrated that anthocyanins were extremely bioavailable in endothelial cells, which was correlated with their prevention of neurodegenerative disorders and atherosclerosis (Youdim et al. 2000, 2002). Anthocyanins improved memory and learning of rats with an estrogen deficit triggered by ovariectomy (Varadinova et al. 2009). *Pandanus amaryllifolius* (Pandan leaves) and *Z. mays* (purple waxy corn) extracts possess anthocyanins and showed cognitive enhancing effects, improved memory function, prevented oxidative stress and modulated cholinergic function in ovariectomized rats (Kirisattayakul et al. 2017). Another report suggests that supplementation with pure cyanidin 3-*O*-galactoside and blueberry extracts improves spatial memory and regulates hippocampal extracellular signal-regulated kinases expression in senescence-accelerated mice (Tan et al. 2014).

Anthocyanins in cancer

Oxidative stress predominantly triggers the mutation in normal cellular DNA which may lead to the development of cellular proliferation and tumour formation (Aggarwal et al. 2019). Moreover free radical generation may also change the cellular signalling cascade and contribute to the cellular differentiation and inflammation in tumour environment (Aggarwal et al. 2019). The anthocyanins and related natural products may prevent the cancer and tumour development by several ways such as inhibiting oxidative stress mediated DNA mutation, modulates the cellular signalling processes, enhances the phase II reaction enzymes for detoxification, prevents angiogenesis, and inhibits cellular differentiation and proliferation (Lin et al. 2017; Wang and Stoner, 2008). In both in vitro and in vivo research trials, anthocyanins have shown significantly reduced proliferation of cancer cells (Medic et al. 2019) and inhibited tumour formation (Koide et al. 1997; Meiers et al. 2001; De-Xing 2003; Kang et al. 2003). Comparisons of the antiproliferative effects of anthocyanins on normal as well as cancer cells have surprisingly revealed that they selectively inhibit cancer cell growth while having insignificant effect on normal cell growth (Fakhri et al. 2020; Matsumoto et al. 2001; Zhang et al. 2005). Moreover, anthocyanidins have a greater potential to inhibit cell proliferation than anthocyanins (Zhang et al. 2005; Hudlikar et al. 2020). Key features of anthocyanin mediated anticancer effects are presented in Table 6.

The ability of anthocyanin to impede with carcinogenesis seems to be related to numerous potential mechanisms of action that include inhibition of cyclooxygenase enzymes and potent antioxidant potential (Reddy et al. 2005). Previous literature reported that cyanidin 3-*O*-glucoside or peonidin 3-*O*-glucoside administration activated caspase-3, chromatin condensation and initiated cancer cell death (Chen et al. 2005). Anthocyanins also have been found to inhibit tumour formation by blocking activation of a mitogen-activated protein kinase pathway (Hou et al. 2004). This provides the first indication of a molecular basis for why anthocyanins display anti-carcinogenic properties. Fruit extracts from *Vaccinium* species (low bush blueberry, bilberry, cranberry, and lingonberry) having significant anthocyanin concentrations were effective against various stages of carcinogenesis (Bomser et al. 1996; Kandil et al. 2000; Kang et al. 2003; Smith et al. 2008). In addition, Seeram et al. (2006) found that extracts of *Vaccinium* species showed significant pro-apoptotic effects against human oral (KB, CAL-27), breast (MCF-7), colon (HT-29, HCT116) and prostate (LNCaP) tumour cell lines. Previous studies also suggested that malvidin inhibited AGS, HCT-116, NCI-H460, MCF-7 and SF-268 cell growth while pelargonidin inhibited AGS, HCT-116, NCI H460, MCF-7 and SF-268 cell growth (Zhang et al. 2005).

The anticancer activity of anthocyanins is linked to their phenolic structures. These effects have been verified in vitro using several cell culture systems including breast (Singletary et al. 2007; Olsson et al. 2004), colon (Parry et al. 2006; Renis et al. 2008), endothelial (Bagchi et al. 2004), leukemic (Feng et al. 2007), and liver cells (Meyers et al. 2003; Shih et al. 2007), as well as keratinocytes (Afaq et al. 2007). Anthocyanins have shown multiple anti-toxicant and anti-carcinogenic effects in various cell culture systems such as: directly scavenging (ROS), increasing the oxygen-radical absorbing capacity of cells, stimulating the expression of Phase II detoxification enzymes and reducing the formation of oxidative adducts in DNA. Other detoxification processes include decreasing lipid peroxidation, inhibiting mutagenesis by environmental toxins and carcinogens, and reducing cellular proliferation by modulating signal transduction pathways. Anthocyanins have also been found to function by chelating metals and by direct binding to proteins in their anti-carcinogenic

Table 6 Function of anthocyanin rich extracts and anthocyanins in the prevention of cancer

Food extracts containing anthocyanin	Model	Dose	Experimental Outcomes	Reference
Anthocyanins (plant species particularly in berries and cherries)	Human colon cancer HT29 cells	50, 100, 200, or 400 mg/L of anthocyanins were used against colorectal cancer cell lines	Anthocyanins promoted apoptosis of colorectal cancer cells (CRC) and inhibited growth of xenografted tumors Mechanically, the PI3K/AKT/survivin pathway was targeted which enhanced the Bcl-2/Bax and caspase-dependent apoptotic pathways, ultimate result was impairment growth of CRC	(Zhao et al. 2019)
Pomegranate (*P. granatum*) fruit extract and pure anthocyanin	Human epidermal keratinocytes, colon cancer cell Female CD-1 mice were divided into 4 groups	Concentration ranges from 10 to 40 µg/mL 2 mg of extract repeated twice weekly up to the termination of the experiments at 30 weeks	Inhibiting UV-B–induced modulations of NF-κB and MAPK pathways and protecting cells against the adverse effects of UV-B radiation Inhibiting Akt phosphorylation, COX-2 expression and NFκB DNA binding activity	(Afaq et al. 2005a, 2005b, 2007; Sharma et al. 2017)
Juice from strawberry (*Fragaria x ananassa*), raspberry (*R. idaeus*), black currant (*R. nigrum*), red currant (*R. rubrum*), white currant (R. sativum), gooseberry (*R. hirtellum*), high-bush blueberry (*V. corymbosum*), low-bush blueberry (*V. angustifolia*), velvet leaf blueberry (*V. myrtilloides*), serviceberry (*Amelanchier sanguinea*), blackberry (*R. allegheniensis*) and sea buckthorn (*Hippophae rhamnoides*)	Adenocarcinoma cell lines from stomach, mammary gland, prostatic and colorectal gland	Berry juice at 0, 10, 20, 30, 40 or 50 µg/mL	Markedly inhibited TNF-induced expression of COX-2 and activation of nuclear transcription factor NFκB	(Boivin et al. 2007)

Table 6 continued

Food extracts containing anthocyanin	Model	Dose	Experimental Outcomes	Reference
Black raspberries (*Rubus occidentalis*)	Mouse epidermal cell line, human oral squamous and 30 colorectal 5-weeks-old male C57BL/6 J mice (n = 10)	Concentrations range from 1 to 100 µg/mL for epidermal cell line 10 to 100 µg/mL concentration for human oral squamous cell Orally 7·0 µmol/g/day of anthocyanins for 9 weeks	Inhibits benzo(*a*)pyrene diol-epoxide-induced activator protein 1 activation, NF-κB factor and VEGF transcription by targeting the phosphotidylinositol 3-Kinase/Akt pathway Induced both terminal and apoptosis differentiation, suppressed nitric oxide synthase activity	(Huang et al. 2002, 2006; Rodrigo et al. 2006; Zhang et al. 2018)
Cyanidin-3-*O*-rutinoside from black raspberry (*R. occidentalis*)	human leukaemia and lymphoma cell lines	50 to 120 µM or greater	Induced apoptosis by promoting p38 MAP kinase and JNK-mediated Bim phosphorylation	(Feng et al. 2007)
Apple (*Malus domestica*), black raspberry (*R. occidentalis*), black currant (*R. nigrum*), black chokeberries (*A. melanocarpa*), blueberries (*V. corymbosum*), chardonnay grape (*V. vinifera*), sea buckthorn (*H. rhamnoides*), plum (*Prunus domestica*), lingonberries (*V. vitis-idaea*), cherries (*P. avium*), and raspberries (*R. idaeus*)	Human keratinocytes, colon cancer cells HT29, breast cancer cells MCF-7 and thyroid HTh-7	Four different concentrations were used (0.025, 0.05, 0.25, and 0.5% of plant dry matter, final concentration 0.01–350 µg/mL) for colon cancer cells HT29 and breast cancer cells MCF-7 10 µg/mL for thyroid HTh-7 cells	Significant chelating capacities against Fe^{2+} Increased cell oxygen-radical absorbing capacity Significantly inhibited breast cancer cells MCF-7 and colon cancer (HT-29) cell proliferation Inhibited basal monocyte chemotactic protein-1 and inducible NFκB transcriptions through H_2O_2 and TNFα-induced VEGF expression Suppressed the activated Akt, mammalian rapamycin, and ribosomal protein S6 via reduced apoptosis and autophagy-dependent cell death	(Bagchi et al. 2004; Long et al. 2018; Olsson et al. 2004; Parry et al. 2006)
Pure cyanidin-3-*O*-glucopyranoside	Human leukaemia cell line	The concentrations of pure compound used was from 3.1 to 200.0 µg/mL	-Effect on protein kinase C, phosphatidylinositol 3-kinase and also induction of apoptosis and cytodifferentiation and to prevent and treat cancer	(Fimognari et al. 2004)

Table 6 continued

Food extracts containing anthocyanin	Model	Dose	Experimental Outcomes	Reference
Anthocyanins (cyanidin, delphinidin, malvidin, pelargonidin, peonidin and their derivatives)	Human gastric adenocarcinoma, mouse neuroblastoma Neuro-2A cell line and e rat hepatocyte Clone 9 cell line	Tested concentrations ranges from 0 to 200 µM or greater	Malvidin treatment significantly increased p38 kinase expression and inhibited the extracellular signal-regulated kinases pathway, including mitogen-activation protein kinases, protein kinase c and phosphatidylinositol 3-kinase Stimulated the expression of Phase II detoxification enzymes regulated through phosphorylation by several protein kinases Prevent amyloid-β-peptide-mediated neurodysfunction	(Shih et al. 2005, 2007, 2011)
Beetroot (*Beta vulgaris*)	MCF-7 (breast), HCT-116 (colon), AGS (stomach), CNS (central nervous system), and NCI-H460 (lung) tumour cell lines	Concentration ranges from 10 to 200 µg/mL	Anti-toxicant and anti-carcinogenic effects by decreasing lipid peroxidation, inhibition of COX-1 and COX-2 and decreasing of tumour cell growth	(Reddy et al. 2005)
Cyanidin-3-*O*-glucopyranoside and cyanidin chloride	Human colon cancer cells	Concentration ranges from 5 to 200 µmol/L	Effect on cell growth, directly scavenging reactive oxygen species (ROS) formation and cell cycle/stress proteins modification, including ataxia teleangectasia mutated protein Reducing the formation of oxidative adducts in DNA Counteracting H_2O_2-induced DNA damage	(Renis et al. 2008)
Cultivated strawberries	Liver cancer cells	Concentration ranges from 5 to75 mg/mL	Anti-toxicant and anti-carcinogenic effects by increasing the oxygen-radical absorbing capacity of cells and inhibiting cell proliferation	(Meyers et al. 2003)

Table 6 continued

Food extracts containing anthocyanin	Model	Dose	Experimental Outcomes	Reference
Black raspberries (*R. occidentalis*)	Mouse epidermalJB6 cell	concentrations ranging from 1 to 100 µg/mL	Down-regulation of VEGF expression resulting in anti-angiogenic effect	(Huang et al. 2006)
Black rice (*O. sativa*)	In vitro enzyme inhibition assay	concentrations ranging from 50 to 200 µg/mL	Inhibited invasion of cancer cells by reducing the expression of MMP and urokinase-plasminogen activator (u-PA)	(Chen et al. 2006)
Delphinidin	18 Four-week-old male C57BL/6Nhsd mice	15 mg/kg body weight, administered by oral gavage for 16 weeks	Reduced triglyceride accumulation in vitro through the modulation of lip id metabolic gene expression but no effect on either metabolic alterations or histological abnormalities associated with HFHC diets	(Parry et al. 2018)

functions (Kong et al. 2003). Anthocyanins have also been proven to induce phase II antioxidant and detoxifying enzymes in cultured cells that contribute to its anti-carcinogenic properties (Shih et al. 2005).

In addition, apoptosis or programmed cell death plays a major role in the development and regulation of normal cellular function. Anthocyanin-rich extracts from berries (*Vaccinium* species) and grapes (*V. vinifera*) as well as several pure anthocyanidins and anthocyanins, have been found to exhibit pro-apoptotic effects in multiple cell types in in vitro studies (Martin et al. 2003; Olsson et al. 2004; Chen et al. 2005; Seeram et al. 2006; Afaq et al. 2007; Reddivari et al. 2007). This is via both intrinsic (mitochondrial) and extrinsic FAS pathways (Reddivari et al. 2007; Chang et al. 2005). Inflammation, on the other hand, has been shown to have role in the promotion of some cancer types in animals and probably in humans (Kwon et al. 2011). Abnormal up-regulation of two inflammatory proteins, NF-κB and COX-2, is a common phenomenon in many cancers, and their inhibition can result in significant anti-carcinogenic effects (Martin et al. 2003; Chang et al. 2005). Anthocyanins can inhibit mRNA and/or protein expression levels of COX-2, NF-κB and other various interleukins, and showed anti-inflammatory effects in multiple cell types in vitro (Huang et al. 2002; Afaq et al. 2005a; Reddy et al. 2005; Rodrigo et al. 2006; Boivin et al. 2007).

Angiogenesis is the formation of new blood vessels from the existing vascular network and it is an important part of tumour growth and metastasis (Huang et al. 2006). Some of the strongest angiogenesis-activating molecules are the vascular endothelial growth factors (VEGF), whose expression is rapidly enhanced in developing tumours (Huang et al. 2006). The anti-angiogenic effects of anthocyanins have been demonstrated using cultured endothelial cells (Bagchi et al. 2004), oral cancer cells (Rodrigo et al. 2006) and mouse epidermal JB6 cells (Huang et al. 2006). Anthocyanins in all these cases have suppressed angiogenesis by several mechanisms. Firstly, anthocyanins cause inhibition of H_2O_2 and TNF-α-induced VEGF expression in epidermal keratinocytes (Bagchi et al. 2004). Secondly, anthocyanins showed an anti-angiogenesis effect by reducing VEGF and VEGF receptor expression in endothelial cells (Bagchi et al. 2004). In addition, mouse epidermal JB6 cells, when treated with an anthocyanin-rich black raspberry (*R. occidentalis*) extract, caused down-regulation of VEGF expression (Huang et al. 2006).

Proteolysis, an important and early invasion event, is the degradation of basement membrane collagen (Kelley et al. 2014). To degrade the extracellular matrix, barriers secrete proteolytic enzymes for successful invasion of tumour and stromal cells. Basement membrane degradation not only depends on the quantity of proteolytic enzymes present, but also on the balance between activated proteases and their naturally occurring inhibitors. Matrix metalloproteinases (MMP) and plasminogen activators are involved in the regulation of degrading the basement membranes (Brandstetter et al. 2001). Anthocyanin extracts from black rice (*O. sativa*), eggplant (*S. melongena*) and different berries have been investigated for their inhibition invasion of multiple cancer cell types. They were found to inhibit invasion of cancer cells by reducing the expression of urokinase-plasminogen activator (u-PA) and MMPs (Brandstetter et al. 2001).

Induction of cellular differentiation can be used to prevent and treat cancer through a cell-specific approach that will probably be less toxic than chemo/radiotherapy (Fimognari et al. 2004). In vitro treatment with anthocyanin (25–200 l g/mL) in leukemic cells showed the reduction of nitro blue tetrazolium, (a functional marker for granulocyte/monocyte differentiation) and increased adherence of cells to plastic which indicated differentiation of the cells into a monocyte/macrophage-like phenotype (Fimognari et al. 2004). Anthocyanins treatment also initiated the naphthol AS-D chloroacetate activity which is a marker for granulocytic differentiation in leukemic cells. Additionally, anthocyanin treatment increased the number of α-naphthyl acetate esterase positive cells which also indicates a differentiation toward a monocytic/macrophagic lineage (Fimognari et al. 2004). Moreover, anthocyanins have also been found to induce differentiation in melanoma cells characterized by a significant increase in dendritic outgrowth along with a remodelling of the microtubular network (Serafino et al. 2004).

Anthocyanins in visual activity

Significantly improved visual activity can be achieved through administration of anthocyanins to humans and animals (Table 7), and their role has been well documented in improving night vision (Matsumoto et al. 2001; Nomi et al. 2019). Improvements in night vision adaptation occurred in humans following oral intake of black currant anthocyanosides (Nakaishi et al. 2001), and similar outcomes were recorded after administration of anthocyanins from bilberries (Muth et al. 2000). Regeneration of rhodopsin (a G-protein-coupled receptor localized in the retina of the eye) was stimulated by three anthocyanins from black currant and formation of regeneration intermediate was accelerated by cyanidin 3-*O*-rutinoside (Matsumoto et al. 2003). Anthocyanin-rich bilberry (*V. myrtillus*) extract prevented inflammation of endotoxin-induced uveitis using a mouse model (Miyake et al. 2012). A bilberry (*V. myrtillus*) extract rich in anthocyanins prevented the impairment of photoreceptor cell function, ameliorated the intracellular elevation of ROS and inhibited NF-κB (Miyake et al. 2012). Thus, enhancement of rhodopsin regeneration has been proven to be one of the mechanisms by which anthocyanins improve visual activity.

A positive effect of anthocyanins on vision improvement was suggested by early clinical trials carried out in France and Italy (Rouher et al. 1972; Jayle et al. 1965). A controlled clinical trial of cyanoside chloride and heleniene on 31 patients suffering from functional disturbances of vision in the dark, reported that both compounds significantly improved photopic visual activity (Sole et al. 1984). In a German clinical trial, Difrarel®E (anthocyanosides and vitamin E) was given to 36 patients with progressive myopia for about 14 months. In around 50% of patients an increase in myopia was suppressed by approximately 50%, along with 29 patients showing stabilisation of fundus-alterations, and an overall improved and stable visual acuity was obtained (Politzer 1977). Anthocyanins from blackcurrant (*R. nigrum*) in the form of a concentrated extract powder were examined for their effects on asthenopia, an ophthalmological condition with nonspecific symptoms such as fatigue, red eyes, eye strain, pain in or around the eyes, blurred vision, headache and occasional double vision, and is a result of continuous exposure of the eye to video displays (Nakaishi et al. 2001). Oral administration of blackcurrant (*R. nigrum*) anthocyanins to such individuals at various doses decreased the dark adaptation threshold in a dose dependent fashion (Nakaishi et al. 2001). The photooxidation of pyridinium disretinoid A2E, an autofluorescence pigment accumulating in retinal pigment epithelial cells with age and also associated with some retinal disorders, was also found to be suppressed by

Table 7 Function of anthocyanin rich extracts and anthocyanins in the improvement and protection of visual activity

Food extracts containing anthocyanin	Model	Dose	Experimental Outcomes	Reference
Bilberry (*V. myrtillus*)	Human adult retinal pigment epithelial cells	100 µM bilberry extract	The photooxidation of pyridinium disretinoid A2E was suppressed by scavenging singlet oxygen	(Jang et al. 2005)
Black currants (*R. nigrum*)	Human subjects with asthenopia	12.5, 20, and 50 mg/subject	Significantly improved night vision	(Nakaishi et al. 2001)
	Thirty-five male Wistar rats and 16 Japan White male rabbits 6 groups (five groups consisted of 3 rabbits and the control group of one rabbit)	Rats intraperitoneally received 500 mg blackcurrant anthocyanins powder per kg body weight (108 mg anthocyanins per kg body weight) rabbits received 92.6 mg/kg body weight of blackcurrant anthocyanins (anthocyanins 20 mg/kg body weight) solution intravenously via an ear vein	BCAs were absorbed and distributed in ocular tissues as intact forms and passed through the blood-aqueous and blood-retinal barriers, indicating that can used to treat myopia and glaucoma	(Matsumoto et al. 2006; Lee et al. 2007)
Cyanoside chloride and heleniene	Human subjects with functional disturbances of vision in the dark	31 patients were treated with 200 mg of cyanoside chloride and heleniene thrice a day for at least 4 weeks	Significantly improved photopic visual acuity	(Sole et al. 1984)
	Human subjects with progressive myopia		Cyaninoside chloride only improved visual functions related to mesopic and scotopic vision	

scavenging singlet oxygen, upon administration of nine anthocyanins from bilberry (*V. myrtillus*) extracts (Jang et al. 2005). Black soybean (*G. max*) seed anthocyanins protected retinal neurons from *N*-methyl-*N*-nitrosourea-induced functional and structural damage (Paik et al. 2012). Anthocyanin from black soybean (*G. max*) protected human lens epithelial (HLE-B3) cells in H_2O_2-induced oxidative stress and prevented apoptosis (Mok et al. 2014).

The ocular distribution of blackcurrant (*R. nigrum*) anthocyanins in rats and rabbits after oral, intravenous and intraperitoneal administration was investigated (Matsumoto et al. 2006). Blackcurrant (*R. nigrum*) anthocyanins (BCA) were absorbed and distributed in ocular tissues as intact forms and passed through the blood-aqueous and blood-retinal barriers in both species. This study revealed that oral intake of anthocyanins or anthocyanin-rich extracts can be used to treat ophthalmological diseases such as glaucoma and myopia. Investigation of the effect of purified high-dose anthocyanin oligomers on nocturnal visual function and clinical symptoms were carried out on 60 patients with asthenopia and refractive errors in both eyes. About 73% of patients were reported with improved symptoms (Lee et al. 2007). A randomized, placebo-controlled, double-masked trial showed that blackcurrant (*R. nigrum*) anthocyanins increased ocular blood flows during the two year trial in comparison with placebo-treated patients (Ohguro et al. 2012). However, significant changes were not observed in ocular or systemic conditions, including intraocular pressure, during the experiment (Ohguro et al. 2012). Another study suggests that bilberry (*V. myrtillus*) anthocyanins improved visual function in patients with normal tension glaucoma (Shim et al. 2012).

Flavonoids have a probable role in the prevention of diabetic cataracts (Varma and Kinoshita 1976). Flavonoids have also been found to delay or prevent the occurrence of cataracts in rat lenses perfused with a high-glucose solution or in diabetic rabbits (Varma and Kinoshita 1976; Laurens et al. 1985). Many naturally extracted or synthetized anthocyanin combinations with novel anti-cataract or anti-glaucoma activity have been reported in patents (Dilip and

Tetsuya 2007). Reduction in the control of lens opacity was related to high levels of reducing sugars in in vitro and in vivo studies, i.e. the formation of experimental diabetic cataracts, which is a complication of diabetes occurring in about 10% of diabetic patients. It has been proven that caloric and food intake greatly influences the progression of diabetes and its complications (Thiraphatthanavong et al. 2014a). Inhibitory activities for lens opacity were shown by five anthocyanin monomers isolated from grape skin extract (Thiraphatthanavong et al. 2014a). Medium to high doses of *Z. mays* (purple waxy corn) extract, an important source of anthocyanins, reduced lens opacity along with a decreased MDA level, followed by improved experimental diabetic cataract in enucleated rat lenses (Thiraphatthanavong et al. 2014b).

Toxicological aspects of anthocyanins

This review work showed that regular intake of anthocyanins rich colourful fruits and vegetables play an important role to maintain a healthy lifestyle which may protect against chronic diseases such as CVS, diabetes and cancer. Though no deficiency disorder has been reported which are associated with the lack of the consumption of anthocyanins (Wallace and Giusti, 2015). However, toxicological effects of anthocyanins and related food products need to be assessed scientifically to support the claims about its potential non-toxic effect. The daily intake of anthocyanins, established by the FAO/WHO expert committee, is 2.5 mg/kg per day, extracted from grape-skin (Wallace and Giusti, 2015). However, no recommended intake level of general anthocyanins for optimal health benefit or to avoid adverse effects is published yet. Low or no acute toxicity symptoms were reported for anthocyanin consumption, both in vitro and in vivo (animals and humans) models at usual dietary intake levels (Burton-Freeman et al. 2016; Harlinda et al. 2016; Khoo et al. 2017; Pojer et al. 2013). Moreover, a study on guinea pigs receiving 3 g/day of anthocyanins extract for 15 days followed by a washout period of one month reported no adverse effect developed in the animals (European Food Safety Authority, 2013). Toxicity testing report on *Lepisanthes alata* (Blume) *Leenh* fruits which are enriched with anthocyanins suggested that the fruits of the plant tested are safe for consumption (Anggraini et al. 2019). Furthermore, no negative effects developed due to the administration of very high doses of anthocyanin derivatives have been reported (Eker et al. 2019). In addition, the consumption of anthocyanins also increased the gut microbiota such as *Bifidobacterium* spp., or *Lactobacillus* spp. which showed benefit in metabolic dysfunction (Eker et al. 2019).

Conclusion and future direction

The prevention of disease and wellbeing of health is an important aspect for a healthy life in modern society. Since the beginning of human history, nature has been considered as a provider of food and natural healing substances in the form of herbal plants. Even in modern medicine, drug development largely depends on the ancient knowledge of healing. Public health policy strongly encourages preventative health measures so as to reduce dependence on costly treatments. In this regard, anthocyanin serves as 'potential drug', with robust protective efficacy in several lifestyles related disorders. The majority of such attributes are due to its anti-inflammatory and antioxidant activities. There are many studies currently being conducted to further evaluate the health beneficial effects of this extraordinary pigment, as researchers, nowadays, are focusing on extracting health benefits from functional foods. Apart from direct antioxidant activity, a wide range of complex mechanisms have been proposed to explain most of the health promoting mechanisms of anthocyanins. Anthocyanin covers a large number of targets which include oxidants, xenobiotics, and excess of metals, radiations and pro-inflammatory factors. Furthermore, anthocyanin can interact directly with proteins and enzymes, which results into modulation in signalling pathways and related changes in cellular metabolism.

Overall, in vitro and in vivo results and clinical evidence indicates that anthocyanins could be a promising therapeutic agent against an extended range of diseases and disorders, which includes cardiovascular diseases, neurological impairments, diabetes, viral diseases, cancer, toxin-induced liver and kidney damage, inflammation and oxidative radical-induced pathologies. While anthocyanins may have a low bioavailability, research indicates that the metabolites may be responsible for much of their health promoting properties. Available reports on cellular and animal models have provided sufficient clinical outcomes, which could influence researchers to study further and establish the anthocyanin based lead molecule for the benefits of mankind. The present study could assist in the very same process by providing a gross notion on the molecular mechanisms of anthocyanin action. However, lack of adequate knowledge about actual molecular mechanisms hinders the application of anthocyanin as a therapeutic drug for many lifestyle disorders. More studies are required to find the real activities of anthocyanins and their metabolites and the specific mechanisms that health promoting properties of anthocyanins are realised. We can hope to see anthocyanins contributing significantly in the manufacture of therapeutics in the near future and facilitate people to benefit from the gifts of nature rather than artificial products.

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Declaration

Conflict of interest Authors declared that there is no conflict of interest regarding this manuscript.

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