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Anthocyanin pigments: Structure and biological importance

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ABSTRACT

Anthocyanins are coloured water-soluble pigments representing one of the major subclasses of compounds. They rarely exist in nature as free aglycons, instead, they attach to one or more sugar moieties. Anthocyanins are found within different plant organs; flowers, leaves, fruits, roots, tubers and grains. They appear in different attractive colours depending on their structure, pH, and other factors.

These compounds gained a lot of attention in the last few years as food colourants replacing chemical dyes, besides their role in enhancing plant tolerance against many abiotic stresses such as salinity, drought, excessive light, ultraviolet radiation and cold stress. Besides, previous studies demonstrated the importance of anthocyanins in human health and their protective properties against chronic diseases. Hence, this review focuses on anthocyanins as one of the most important pigments having beneficial roles in health for plants and humans.

KEY WORDS: Anthocyanins, colourants, plant stress, antioxidants, antibacterial, anti-inflammatory, anticancer, anti-diabetic, anti-obesity, neurodegenerative diseases, cardiovascular diseases, ophthalmology.

1. INTRODUCTION

Anthocyanins (Greek anthos: flower and kyaneos: dark blue) represent a subclass of the phenolic compounds (Delgado-Vargas, 2000). They are water-soluble glycosides of anthocyanidins, which are largely responsible for the attractive pale yellow, orange, red, magenta, violet and blue colour of a wide range of plant tissues, principally flowers, leaves and fruits, besides storage organs, roots, tubers, stems and grains (Chemler, 2009; Martin, 2017). They are ubiquitous in higher plants (occurring in more than 30 families), but normally are absent in liverworts, algae, and other lower plants, even though some anthocyanins have been identified in mosses and ferns (Delgado-Vargas, 2000).

In general, anthocyanins are non-photosynthetic pigments synthesized in the cytoplasm and stored in the vacuolar lumen of epidermal cells (Andersen and Jordheim, 2006; Chemler, 2009; Chanoca, 2015; Passeri, 2016).

Within the main vacuole, different forms of anthocyanins accumulation were observed and called by several names reflecting their diversity. Most cells exhibit an evenly coloured anthocyanin vacuolar sap, but there are now many reported cases of regular or irregular shaped pigmented bodies that have been called anthocyanin vacuolar inclusions (AVIs) (Grotewold and Davies, 2008).

It’s worth mentioning that cytoplasmic anthocyanin enters the vacuole through microautophagy, which includes three stages, (Figure.1) (Chanoca, 2015; Oku and Sakai, 2018):

- Stage I: The anthocyanins aggregates (AA) associate with the outer surface of the tonoplast and become surrounded by a double membrane. The tonoplast binds closely to the surface of the AA and lines its internal holes. After that, the distant domains of the tonoplast edges fuse.
- Stage II: The AA`s two membranes start to separate, and the bulges in between are filled with the vascular lumen.
- Stage III: The two membranes separate, releasing the new AVI into the vacuolar lumen. AVI is now surrounded by one membrane derived from the tonoplast.

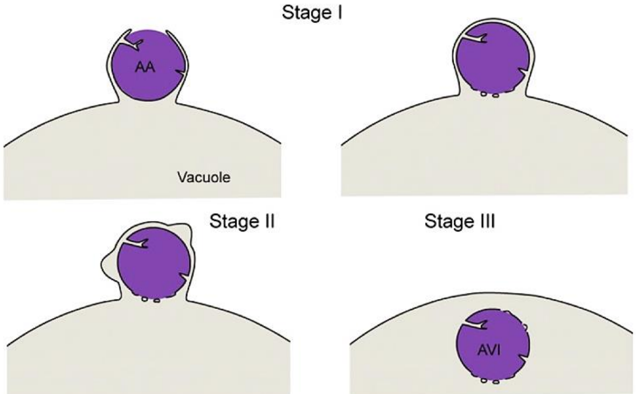
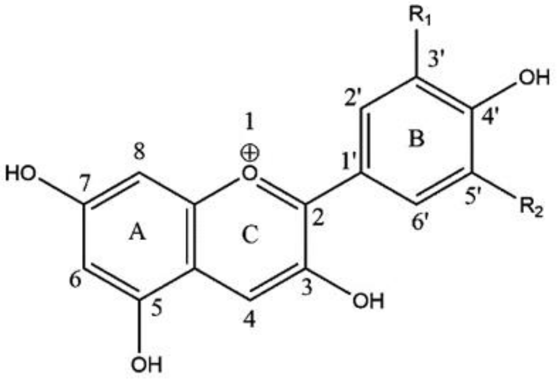


Figure.1. AVI formation by micro autophagy (Chanoca, 2015)

Based on the extensive studies on AVIs, AVIs have two distinct types. One of them has spherical shaped with a liquid behavioural, mobile and usually coalesce into bigger bodies. While the second type of AVIs has a more ‘fibrous’ rigid and insoluble structure, and they have been mostly studied in petal cells of many plants (Grotewold and Davies, 2008; Deroles, 2009).

The anthocyanin molecule consists of an anthocyanidin “core” with an attached sugar moiety (Figure.2). They vary in the number and position of hydroxyl and methoxyl groups attached to anthocyanidin. Therefore, although there are nearly 25 naturally occurring anthocyanidins, more than 700 anthocyanins derivatives have been identified to date (Mortensen, 2006; Chu, 2011; Wallace and Giusti, 2015; 2019).



Anthocyanin	R_1	R_2
Pelargonidin	H	H
Cyanidin	OH	H
Delphinidin	OH	OH
Peonidin	OCH_3	H
Petunidin	OCH_3	OH
Malvidin	OCH_3	OCH_3

Figure.2. Basic structure of anthocyanidins (Zhao, 2018)

The most prevalent anthocyanidins in nature are pelargonidin (Pg), cyanidin (Cy), peonidin (Pn), delphinidin (Dp), petunidin (Pt) and malvidin (Mv) (Vermerris and Nicholson, 2006; Latti, 2009; Chu, 2011; Khoo, 2017; Wallace and Giusti, 2019):

- Pelargonidin (Pg) appears in a unique orange salmon colour. It can be found in various plants like strawberry, blueberry, banana, red radish and potato (Deroles, 2009; Bueno, 2012; Fang, 2015).
- Cyanidin (Cy) usually appears in magenta and crimson colours. The major sources of Cy are apples, blackberry, black raspberries, elderberry, mulberry, bilberry, gooseberry, peach, pear, fig, cherry, red onion, red cabbage, blood orange, plum, grape, red sweet potatoes, potatoes, strawberry and purple carrot (Deroles, 2009; Usenik, 2009; Chu, 2011; Bueno, 2012; Fang, 2015).
- Peonidin (Pn) has a magenta colour. It can be found in many fruits like mango, grape, potatoes, sweet potatoes and plum (Deroles, 2009; Usenik, 2009; Bueno, 2012; Fang, 2015).
- Delphinidin (Dp) normally is found in different colours; purple, mauve and blue. The blue hue of flowers is due to this pigment (Khoo, 2017). The main sources for it are passion fruit, eggplant, green bean, pomegranate, blueberry, bilberry and grape (Deroles, 2009; Chu, 2011; Bueno, 2012; Fang, 2015).
- Petunidin (Pt) has a purple colour. Pt is found in blueberry, bilberry and grape (Deroles, 2009; Chu, 2011; Bueno, 2012; Fang, 2015).
- Malvidin (Mv) has a purple colour. It is primarily responsible for the colour of bilberry, blueberry and red grape (Deroles, 2009; Chu, 2011; Bueno, 2012; Fang, 2015).

Anthocyanidins rarely occur in nature as free aglycones due to their instability, so when they are glycosylated with one or more sugar molecules they are called anthocyanins. The most common sugar that binds to anthocyanidins is glucose, but there are other sugars involved in anthocyanins formation, such as arabinose, galactose, xylose, and rhamnose (Vermerris and Nicholson, 2006; Tomic, 2017).

During glycosylation, if one sugar bonds with anthocyanidin, it will mainly attach at the 3-position on the C-ring to form the 3-glycoside, and if a second sugar is present, it will almost always attach at the 5-position on the A-ring and form di-glycoside. Yet, there are a few rare exceptions with 3,7-substitutions or trisaccharide forms of anthocyanins (Harborne and Williams, 2001; Wu and Prior, 2005; Prior and Wu, 2006; Vermerris and Nicholson, 2006; Latti, 2009).

The sugar moiety may be acylated by aromatic acids, mainly hydroxycinnamic acids (such as caffeic, ferulic, p-coumaric and sinapic acids) and sometimes by aliphatic acids (particularly malonic and acetic acids). These acyl moieties are usually linked to the sugar at the 3-position on the C-ring (Pereira, 2009; Bueno, 2012).

The Colour of Anthocyanins: Intensity and type of anthocyanin colour are affected by the number of hydroxyl and methoxyl groups in their structure. If it contains more hydroxyl groups (OH), the colour goes toward a more bluish shade. On the other hand, the redness increases if it includes more methoxyl groups (OCH_3) (Mortensen, 2006; Tanaka, 2008; Bueno, 2012; Martin, 2017).

Similarly, the colour of anthocyanin depends on pH, due to their ionic nature. In acidic conditions, some of the anthocyanins appear red. They have a purple hue in neutral pH, while the colour changes to blue in an increasing pH condition (Khoo, 2017).

However, the colour of anthocyanin depends on other factors, including metal ions present and the extent of anthocyanin glycosylation and acylation, beside the combinations of several anthocyanidins and other pigmentation (Gould, 2002; Andersen and Jordheim, 2006; Vermerris and Nicholson, 2006). Finally, storage may also affect anthocyanin stability leading to colour change (Santos-Buelga, 2014).

Anthocyanins as Antioxidants: Living cells produce byproducts during metabolism in the form of reactive oxygen species (ROS) and free radicals, under normal and stressed conditions. ROS are a group of reactive molecules derived from molecular oxygen, such as superoxide (O_2^-), singlet oxygen ($^1O_2$), hydrogen peroxide (H_2O_2) and hydroxyl radical (OH^-). They can induce cellular damage when excessively produced (Martin, 2017).

Anthocyanins and anthocyanidins have a higher antioxidant property compared to other flavonoids, due to their special chemical structure. The antioxidant capacity of these compounds can be attributed to chelate metal ions involved in free radicals production, thereby reducing metal-induced peroxidation (Dai, 2012; Martin, 2017). Additionally, their positive charge, number and position of hydroxyl and methoxyl groups, the presence of electron-donating and electron-withdrawing substituents made anthocyanins very effective donors of hydrogen to ROS and free radicals, thereby detoxifying them and preventing further radical formation. This effect protects the important biomolecules (proteins, lipids and DNA) from oxidative damage, which leads to ageing and various diseases (Pojer, 2013; Martin et al., 2017).

The antioxidant activity of anthocyanins increases with the number of hydroxyl groups in the B-ring (Liu, 2018). On the other hand, glycosylation of anthocyanins decreases scavenger activity as compared with their aglycones, because it minimizes the hydrogen donating and metal chelating abilities (Wang and Stoner 2008; Pojer, 2013; Liu, 2018). Moreover, different attached sugars influence antioxidant activity differently (Sadilova, 2006; Liu, 2018).

Anthocyanins can scavenge free radicals through two hypothesized pathways. The first pathway is the attack of OH group(s) of the B-ring, and the second is the attack of oxonium ion on the C-ring. Some of them are considered among the strongest antioxidants via adopting both pathways (Gaulejac, 1999; Pojer, 2013; Khoo, 2017).

Most of the widely distributed anthocyanidins and anthocyanins show more scavenging activity than that of the well-known strong antioxidants, for instance, the cyanidin has an antioxidant capacity up to 4.4 times greater than those of ascorbic acid and the vitamin E analogue (Gould, 2002).

The Importance of Anthocyanins: Anthocyanins are believed to play vital roles in plants, animals and human lives. As a major subclass of secondary metabolites in plants commonly consumed as food, they are important in the food industry and human nutrition. Anthocyanins in the flower petals attract insects and birds, so they help in cross-pollination. Similarly, anthocyanins in the colourful skins of fruits attract herbivorous animals that may eat them and disperse the seeds (Hirsch and Martins, 2015). Anthocyanins are important as natural colourants. Furthermore, they possess many functions in plants exposed to abiotic stresses as well as in human health promotion.

Anthocyanins as natural colourants: Anthocyanins are used as food colourants instead of synthetic colourants, as they are safe to be consumed even at relatively high doses (Chemler, 2009; Khoo, 2017).

Different hues can be achieved, depending on anthocyanin chemical structure of anthocyanin, the extraction method and pH of the food matrix. Anthocyanin acylation usually improves colour and pigment stability (Giusti and Wrolstad, 2003; Wallace and Giusti, 2019). For example, acylated pelargonidin derivatives from radish and potato can give an attractive red colour under acidic conditions and acylated cyanidin derivatives from black carrots or cabbage provide hues ranging from deep red to purple, depending on pH (Giusti and Wrolstad, 2003).

Anthocyanin-derived colourants are classified as one of the nine accepted natural colourants under classification E 163 in the European Union (Wrolstad, 2004; Bueno, 2012). However, in 2013, a group of scientific experts for European Food Safety Authority inferred that anthocyanins from various natural sources have been inadequately characterized by safety and toxicological studies to approve their use as food additives (European Food Safety Authority, 2013).

While in the United States, they can be used as natural colourants without certifications (Code of Federal Regulations, 2020). They are also considered appropriate for food use in Asian, Central American, and South American countries; with some differences in their sources and permitted a degree of purity (Wrolstad and Culver, 2012).

Anthocyanins and plant stresses: There is a piece of increasing evidence that anthocyanins have a role to play in the physiological survival of plants under different abiotic stresses, particularly when they are located at the upper surface of the leaf or in the epidermal cells (Gould, 2002; Andersen and Jordheim, 2006; Manetas, 2006; Passeri, 2016).

Cold stress: Low temperatures reduce membrane fluidity, enzymes activities (including the most important one in photosynthesis; RubisCO), and stomatal conductance. Consequently, the photosynthetic rate declines, which induce ROS generation. As toxic substances, ROS attack cellular biomolecules, destroy bio-membranes and accelerate cell damage (Schulz, 2016; Zhang, 2019). Low temperature stimulates anthocyanin biosynthesis by up-regulating the expression of anthocyanin biosynthetic genes which in turn increase the anthocyanins accumulation (Ahmed, 2015; Schulz, 2015; Schulz, 2016; Zhang, 2019; He, 2020). The main purpose of this accumulation is to increase antioxidant capacity and reduce oxidative stress (Ubi, 2006; Ahmed, 2015; Zhang, 2019).

Salt stress: Anthocyanins content increases under salt stress in many plants (Eryilmaz, 2006; Chakovari, 2015; Kovinich, 2015; Chunthaburee, 2016; Kielkowska, 2019). This increment helps plants to maintain turgidity and water uptake, which is essential for osmo protectant (Close and Beadle, 2003; Iseri, 2015). Besides, the presence of phenyl groups in these compounds induces salt-tolerance by binding with toxic ions, thereby protecting the cells from oxidative damage (Chunthaburee, 2016).

Drought stress: Anthocyanins can mitigate water stress (drought) in different plants, according to previous studies (Sperdouli and Moustakas, 2012; Nakabayashi, 2014; Shoeva, 2017; Kebbas, 2018; Omidi, 2018). These compounds could play a dual role under drought stress as osmoregulatory and antioxidants, which allow anthocyanins leaves to tolerate suboptimal water levels (Chalker-Scott, 2002; Kebbas, 2018; Omidi, 2018).

High light stress: Foliar anthocyanins concentrations increase in many plants under excessive light condition, acting as photo-protectants (Steyn, 2002; Zhang, 2010; Kovinich, 2015; Trojak and Skowron, 2017; Zhu, 2018). Generally, light energy capturing is much faster than electron transport in the thylakoid membranes; hence, over-excitation of the photosynthetic apparatus is a constant threat (Steyn, 2002).

Besides their antioxidant capacity, anthocyanins have the potential to reduce both the incidence and the severity of photo-oxidative damage. Due to the existence of these pigments in the vacuole apart from chloroplasts, therefore the light energy absorbed by them can’t be transferred to chlorophyll to be used in photosynthesis (Gould, 2002). Which means that anthocyanins intercept a portion of supernumerary photons that would otherwise strike the chloroplasts, thus causing photo inhibition and increasing the ROS production and ROS-triggered damage (Gould, 2000). Accordingly, anthocyanins function as simple light filters, especially from the green – orange regions of the spectrum, and probably re-dissipate the absorbed energy as heat (Merzlyak and Chivkunova, 2000; Gould, 2002; Steyn, 2002; Landi, 2015; Trojak and Skowron, 2017).

Ultraviolet radiation-B (UV-B) stress: UV-B provokes ROS production in the living cells, which is very toxic because they react with vital biomolecules, altering their biological activities and causing oxidative damage. Anthocyanins, like other flavonoids, are well known for their ROS scavenging properties (Mahdavian, 2008; Goto, 2016). Moreover, since anthocyanins accumulate in the epidermal tissues of plants, they may contribute partially in preventing the penetration of UV-B to the photosynthetic mesophyll tissue (Mahdavian, 2008; Hatier and Gould, 2009; Landi, 2015). Numerous studies have indicated to anthocyanins increment under UV-B stress (Close and Beadle, 2003; Mahdavian, 2008; Tsurunaga, 2013; Goto, 2016; Li, 2020). UV-B induces a decline in anthocyanidin reductase (ANR) activity, which shifts the metabolic flux toward anthocyanin biosynthesis (Li, 2020). The common anthocyanin glycosides have negligible absorption in the UV region, but after acylation with phenolic acids, they gain the capacity to absorb parts of UV spectra (UV-A: 315–400 nm and UV-B: 280–315 nm) in addition to visible light (Hatier and Gould, 2009; Landi, 2015). However, UV filtering is not likely to be the main role of anthocyanins because acylated anthocyanins are not as common as the non-acylated forms in plant tissues (Hatier and Gould, 2009).

Anthocyanins and human health: Recently, anthocyanins have garnered a lot of attention for their potential preventative and /or therapeutic effects on health, including obesity prevention, cardiovascular diseases, antibacterial, anti-inflammatory and anticancer effects (Wu and Prior, 2005; Prior and Wu, 2006; Wallace and Giusti, 2015; Khoo, 2017).

Antibacterial effects: Previous studies referred to the antibacterial activity of anthocyanins against a wide range of microorganisms. This can be attributed to several mechanisms, such as destabilization and permeabilization of the plasma membrane (Burdulis, 2009), as well as induction cell damage and deformation by destroying the cell wall, membrane, and intercellular matrix integrity (Cisowska, 2011; Pojer, 2013; Khoo, 2017; Ma, 2019). Antibacterial property may also be related to the anti-adherence of bacteria to epithelial cells, which is essential for colonization and infection for many pathogens (Puupponen-Pimia, 2005).

Investigation of the antibacterial properties showed that anthocyanins-rich extracts inhibited the growth of a wide range of human pathogenic bacteria, both gram-negative and gram-positive (Puupponen-Pimia, 2005; Wu, 2008; Burdulis, 2009; Lacombe, 2010; Cote, 2011; Pagliarulo, 2015; Genskowsky, 2016; Aly, 2019). Although the inhibition is significantly more evident in gram-negative compared to gram-positive bacteria due to their structural variation (Puupponen-Pimia, 2001).

The cells of gram-negative bacteria are surrounded by an outer membrane, which acts as a preventive barrier against hydrophobic, but not hydrophilic compounds, due to the presence and features of lipopolysaccharide molecules in it (Puupponen-Pimia, 2005; Nohynek, 2006). These bacteria regulate the permeability of their cell through hydrophilic channels called porins, which allows nutrients to enter the cell cytoplasmic membrane (Nohynek, 2006).

Anti-inflammatory effects: Inflammation is the body's defence against stimuli. Usually, it is considered good for the body, but prolonged chronic inflammation can be harmful and result in different diseases such as obesity, type II diabetes, cardiovascular diseases and many types of cancer (Semaming, 2015; Yazhen, 2020).

Under acute inflammation, macrophages produce ROS while eliminating foreign particles and inducing inflammatory cytokines. ROS levels in the cell are balanced through detoxifying antioxidant enzymes (Medzhitov, 2010; Yazhen, 2020). Nevertheless, when the acute inflammation converts into chronic inflammation, the generation of ROS increases and becomes out of control, which will promote the inflammatory factors activated, aggravate the inflammatory response and gene mutations and finally lead to cancer. Many studies indicated that anthocyanins have strong anti-inflammatory activity in both in vivo and in vitro, and their effective mechanism may be the ability to scavenge ROS, reduce pro-inflammatory cytokines, and regulate antioxidants activity such as superoxide dismutase (Vendrame and Klimis, 2015; Pereira, 2017; Abdin, 2020; Yazhen, 2020).

Anticancer effects: The carcinogens can be induced by different factors, including pollutants and junk food. These carcinogens can be activated to produce free radicals that attack DNA and cause cancer. The anticancer property of anthocyanins is strongly related to their antioxidant capacity and cytotoxic action induction against cancer cells (Reddivari, 2007; Rugina, 2012; Diaconeasa, 2015; Thibado, 2018).

Pure anthocyanins and anthocyanin-rich extracts inhibit cell proliferation by blocking various stages of the cell cycle and their regulatory proteins (Wang and Stoner 2008). Interestingly, they can selectively inhibit the proliferation of cancer cells while having little influence on the proliferation of normal cells (Wang and Stoner 2008; Rugina, 2012; Bunea, 2013; Diaconeasa, 2017). Besides that, anthocyanins suppress angiogenesis, thereby inhibiting the growth and metastasis of tumours (Joshua, 2017; Tsakiroglou, 2019).

Besides, anthocyanins also can induce the apoptosis of cancer cells, which is not present in the tumour cells, through the internal mitochondrial pathway and the external death receptor pathway (Chang, 2005; Reddivari, 2007; Wang and Stoner 2008).

Anti-obesity effects: Obesity is characterized by an excessive accumulation of adipose tissue due to an imbalance between energy intake and expenditure. This condition is linked to lack of physical activity and unhealthy diet. Obesity may increase the risk of several diseases such as hypertension, heart disease and type II diabetes (Pojer, 2013; Jayarathne, 2019).

The role of anthocyanins in obesity is still controversial. However, previous studies indicated that anthocyanin consumption might aid in maintaining or reducing the bodyweight of obese healthy patients. In addition to improving lipid metabolism and energy balance (Bertoia, 2016; Azzini, 2017; Istek and Gurbuz, 2017; Sivamaruthi, 2020), inhibiting lipid absorption, suppressing food intake and regulating gut microbiota (Xie, 2018; Jayarathne, 2019).

Anti-diabetic effects: Diabetes mellitus is a metabolic syndrome caused by a combination of genetic and lifestyle patterns and arises when produced insulin is insufficient or inefficient. Diabetes leads to hyperglycemia, which in turn results in various short-term metabolic changes in lipid and protein metabolism and long-term irreversible vascular changes. Type II diabetes is commonly characterized by insulin resistance (reduced cell's sensitivity to insulin), an insulin deficiency, or both. Moreover, it occurs usually in adulthood to obese patients (Kosti and Kanakari, 2012).

Several studies demonstrated that anthocyanins can lower blood glucose levels via different mechanisms. In addition to their antioxidant capacity, anthocyanins can ameliorate insulin resistance, increase insulin secretion, improve liver function, and inhibit carbohydrate hydrolyzing enzymes (Prior and Wu, 2006; Belwal, 2017; Gowd, 2017).

Effects against cardiovascular diseases: As people age, the elastic fibres of arteries are oxidized and become harder, which represents a major cause of cardiovascular disease in the elderly (Yazhen, 2020).

The cardiovascular protective role of anthocyanins is strongly related to their properties against oxidative stress (Wallace, 2011). Besides, anthocyanins are well known for their capacity to decrease low-density lipoprotein cholesterol (LDL) (Pojer, 2013; Kruger, 2014; Lee, 2016; Reis, 2016), triglyceride (Reis, 2016) and blood pressure (Basu, 2010; Kruger, 2014; Reis, 2016; Igwe, 2017). Besides that, they inhibit platelet aggregation and activation (Saluk, 2012; Yang, 2012; Reis, 2016; Thompson, 2017). Anthocyanins normally reduce the risk of myocardial infarction (Cassidy, 2013) and inflammation in atherosclerosis (Reis, 2016). On the other hand, they improve high-density lipoprotein cholesterol (HDL) (Erlund, 2008; Hassellund, 2013; Kruger, 2014; Reis, 2016). Moreover, anthocyanin isolates and anthocyanin-rich mixtures of flavonoids may protect from lipid peroxidation, anti-inflammatory activity (Semaming, 2015), decreased capillary permeability and fragility, and membrane strengthening (Wallace, 2011).

Effects against neurodegenerative diseases: Neurodegenerative diseases are characterized by the loss of specific neuronal populations within the brain, brain stem, and spinal cord, resulting in significant cognitive and/or motor disorders (Radi, 2014).

The high oxygen consumption of the brain (20% more oxygen compared to mitochondrial respiratory tissues) increases the possibility of producing a large number of free radicals and makes the brain more vulnerable to oxidative stress. Taking into account that the neuron (the basic functional unit of the brain) contains a large number of polyunsaturated fatty acids, it can interact with ROS, leading to lipid peroxidation and apoptosis (Thakur, 2018).

Apoptosis is involved in many human diseases, including neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD). In these cases, the apoptotic rate increase causing tissue damage (Radi, 2014).

Diets rich in anthocyanins is associated with decreased risk of developing neurodegenerative diseases (Winter, 2017), through direct scavenging of ROS, increasing the activity of antioxidant enzymes (superoxide dismutase (SOD) and catalase (CAT)), elevating reduced glutathione GSH content, and reducing malondialdehyde MDA (Winter and Bickford, 2019; Yazhen, 2020).

Positive findings have been shown for the treatment of Alzheimer's disease with anthocyanin-rich extracts. These extracts can reduce the levels of the β-amyloid peptide (Aβ) and convert Aβ aggregation to an alternate, non-toxic form (Yamakawa, 2016; Andrade Teles, 2018; Winter and Bickford, 2019), besides decrease tau phosphorylation induced by Aβ (Badshah, 2015; Belkacemi and Ramassamy, 2016).

Moreover, anthocyanin consumption by old people at risk for dementia improves memory impairment via increasing neuronal signaling in brain centers mediating this function (Cho, 2003; Krikorian, 2010; Andrade Teles, 2018; Winter and Bickford, 2019; Yazhen, 2020).

Additionally, taking into consideration that anthocyanins are potent antioxidants, they can effectively prevent free radicals from damaging the dopamine-producing cells in the brain, thus inhibiting the development of Parkinson's disease (Kim, 2010; Strathearn, 2014; Qian, 2019). They may also alleviate neuro degeneration in Parkinson's disease by enhancing mitochondrial function (Strathearn, 2014).

Effects against ophthalmology: The blue light harm becomes greater with the increased usage of various electronic devices such as mobile phones, computers, and LED lights. The long term exposure to blue light irradiation to the retina can cause excessive free radical production. These free radicals can induce retinal pigment epithelial cell apoptosis, intraocular metabolic abnormalities and hindering the blood circulation, which in turn cause various dysfunctions such as myopia, cataracts, retinopathy, and other eye diseases (Yazhen, 2020).

The possible effective mechanism of anthocyanins is related to their scavenging ability for free radical, enhancing antioxidants activity, inhibiting intracellular calcium overload, in addition to the optic nerve protection (Yazhen, 2020), and suppression of retinal pigment epithelium apoptosis (Liu, 2012; Wang, 2015). Furthermore, anthocyanins have a relaxing effect on the ciliary muscle, which is important to treat myopia and glaucoma (Shim, 2012; Nomi, 2019).

It's worth noting that anthocyanins intake improves transient myopic shift, dark adaptation and the retinal blood circulation in normal-tension glaucoma patients (Yanamala, 2009; Ohguro, 2007; Nomi, 2019).

The Side Effects of Anthocyanins: Anthocyanins toxicity has not been shown in currently published human intervention studies (Wallace and Giusti, 2015). They are generally regarded as safe and well-tolerated in humans, taking into account the long history of consumption of foods-rich in such flavonoids (Corcoran, 2012).

Nevertheless, there is considerable evidence that such compounds are not risk-free (Lambert, 2007). A scientific expert team for the European Food Safety Authority considered the currently available toxicological studies for anthocyanins inadequate to determine a numerically acceptable daily intake (ADI) for them (European Food Safety Authority, 2013).

However, it is worth noting that the potential side effect of anthocyanin or any other flavonoid can be associated with high doses of intake even for a short duration (Azzini, 2017).

2. CONCLUSIONS

In the past decades, interest in dietary phenolic compounds, including anthocyanins, has increased substantially. Anthocyanins are phytopigments found in several plants. They are well known for their antioxidant activities, which is due to their unique structure. The studies summarized in this review demonstrate the importance of these compounds as natural colourants, plant stress markers and preventives for many human chronic diseases.

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