

Anti-Inflammatory Properties Anthocyanins in Edible Flowers

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Contributor: Grzegorz Łysiak

The word 'anthocyanin' derives from two Greek words: anthos, which means flowers, and kyanos, which means dark blue. Anthocyanins are secondary metabolites in land plants that contribute to the color of leaves and flowers. These pigments are primary blue, red, and purple. They are synthesized via the flavonoid pathway, which is part of the general phenylpropanoid pathway.

Keywords: agroecosystem ; anti-inflammatory ; antioxidant properties ; biological activity

1. Chemistry and Biochemistry of Anthocyanins

The word 'anthocyanin' derives from two Greek words: anthos, which means flowers, and kyanos, which means dark blue [6].

Anthocyanins are secondary metabolites in land plants that contribute to the color of leaves and flowers [7]. These pigments are primary blue, red, and purple. They are synthesized via the flavonoid pathway, which is part of the general phenylpropanoid pathway [8]. The entry to the biosynthesis of phenylpropanoids is the shikimate pathway. In this pathway, plants biosynthesize, in three steps, hydroxycinnamic acids and their derivatives, which are the precursors for a large variety of aromatic metabolites [9]. The next step before the synthesis of anthocyanidins is the conversion of a chorismic acid to phenylalanine by the enzyme phenylalanine ammonia-lyase [10], from which cinnamic acid is formed. The conversion of cinnamic acid to anthocyanins requires a series of reactions: the first reaction is catalyzed by cinnamate 4-hydroxylase to form a coumaric acid and by 4-hydroxy-cinnamoyl CoA ligase to create 4-Coumaroyl CoA, which is a direct precursor to kaempferol. After four steps of enzymatic reaction from 4-Coumaroyl CoA, the leucoanthocyanidins are formed [11]. By the catalysis of anthocyanin synthase (ANS), the colorless leucoanthocyanidins (flavan-3,4-diols) are oxidized to the colored anthocyanidins [9]. Flavan-3,4-diols, also known as leucoanthocyanidins, are not particularly prevalent in the plant kingdom, instead being themselves precursors of flavan-3-ols (catechins), anthocyanidins, and condensed tannins (proanthocyanidins). Anthocyanidins are unstable under physiological conditions, so they are immediately glycosylated in the 3-OH positions by UDP-glucose-flavonoid 3-O-glucosyltransferase (UFGT) to form the more hydrophilic and stable anthocyanins [12].

It has been experimentally demonstrated that all anthocyanin pigments are derived from one of three aglycones (pelargonidin, cyanidin, and delphinidin). The differences in the color of anthocyanins result from the pattern of hydroxylation and methylation and the amount and type of sugars [13]. Anthocyanins display different colors (red, blue, or purple) depending on their accumulation and chlorophyll complementary light absorbance. At low pH values, anthocyanins are present as flavylum cations (oxonium charged oxygen), while under neutral conditions, uncharged quinones are formed [14]. At a pH around 2.0–3.5, anthocyanins have a pink-coral color, while at 5.5–6.5, they are blue to purple [13]. The chromophore of conjugated double bonds carrying a positive charge on the heterocyclic oxygen ring is responsible for the intense red-orange to blue-violet color produced by anthocyanins under acidic conditions [15].

There were 635 identified anthocyanins in 2010 [16]. Anthocyanins are present in nature mainly in the form of heterosides. The aglycon form of anthocyanins are called anthocyanidin. The basic structure of anthocyanins is composed of flavylum cation (C6-C3-C6), which could be linked to different sugars or hydroxyl or methoxyl groups [17]. The most abundant anthocyanins are delphinidin, cyanidin, petunidin, peonidin, malvidin, and pelargonidin. Glucose is the most common sugar attached to anthocyanins, but rhamnose, xylose, galactose, arabinose, and rutinose have also been reported to be linked to these compounds [6]. Depending on the number of attached sugars, anthocyanins can be mono-, di-, or tri-glycosides [17]. The presence of sugars gives more stability and water solubility than their corresponding glycosides [9]. Glycosylation, primarily at the C-3 residue, results in reduced maximum wavelength absorption [18].

Sugar residues may be further acylated with cinnamic acids, such as p-coumaric, ferulic, and sinapic acid, as well as aliphatic acids, such as acetic, malonic, and oxalic acid [19].

3. Antioxidant Capacity and Anti-Inflammatory Property of Anthocyanins

3.1. Antioxidant Activity

The antioxidant potential of anthocyanins depends on the ring orientation (which determines the ease with which a hydrogen atom from a hydroxyl group can be donated to a free radical), the ability of the anthocyanin to support an unpaired electron [20], the number of free hydroxyls around the pyrone ring and their positions, and the presence of other types of radicals in the main structure [21]. The protection of these pigments against the oxidation process depends on their structures. Principally, the antioxidant capacity of anthocyanins is associated with the number of free hydroxyls around the pyrone ring. Higher antioxidant capacity is due to the number of hydroxyls [20].

Individual anthocyanins differ in their ability to remove highly active radicals depending on the radical. For instance, pelargonidin is the most efficient against the hydroxyl radical, whereas delphinidin is the most active against the superoxide anion [22]. Free radical damage contributes to the etiology of many chronic diseases, and thus, antioxidants may have beneficial effects on human health at different levels [23]. Improving the diet through the consumption of products containing natural antioxidants is one of the best strategies to create a balance between the activity of free radicals and the antioxidant system in the human body [24].

The antioxidant capacity of consumed products can be measured using chemical, in vitro methods generally performed on extracts. The literature mentions nearly 20 methods [9,11,13], but in general, if there are many methods, none of them is perfect. In addition, we must remember that the indicators give us a picture of the potential of the product, but they will not answer the question of how many substances will be absorbed and what impact they will have on the body. The most popular methods of measuring antioxidant capacity are based on the ability to bind free radicals (DDPH, ABTS), to reduce cupric or ferric ions (FRAP, CUPRAC), to protect a target molecule exposed to a free radical source (ORAC, TRAP), and to inhibit the oxidation of low-density lipoprotein (LDL) [25].

Antioxidant capacity is a function of the content and types of phytochemicals that are present in fresh tissues. However, individual groups of compounds may differ considerably in terms of antioxidant capacity. Many studies indicate that phenols and flavonoids contribute more strongly to antioxidant capacity than ascorbic acid, vitamins, carotenoids, and other compounds [26]. Anthocyanin molecules, due to their structure, stand out from flavonoids as a group of compounds exhibiting very high antioxidant capacity [27]. Still, some research suggests that the bioavailability of anthocyanins is lower than that of other flavonoids. Anthocyanins were initially perceived as poorly absorbed and metabolized compounds, which cast doubt on whether they could have a biological effect in humans. They were found only in the plasma in their intact form (glycosylated). However, most of those studies were based on plasma and urine analysis for anthocyanin metabolites derived from glucuronidation and sulphation metabolism. More recent studies increasingly allow to identify metabolites of anthocyanins at higher concentrations than the parent compounds [28]. According to some research, anthocyanins may be metabolized by intestinal microflora, producing a group of new products that have not yet been identified, not to mention quantified. In addition, recent studies indicate that anthocyanins are rapidly absorbed, with a maximum plasma concentration (C_{max}) between 45 min to 4 h after ingestion of a meal containing anthocyanins, depending on the conditions of the trial. When anthocyanins were ingested alone and after a night, C_{max} was reached after only 1 h [29], but if they were consumed together with other food, the absorption decreased; especially if food contained fat, C_{max} was reached only after 4 h [30]. The structure of anthocyanins affects their absorption by the human body. It has been shown that 3-monoglucosides of anthocyanidins are less bioavailable than their corresponding rutinoides [31]. The absorption differences between malvidin and petunidin may also be due to the fact that a large number of hydroxyl groups in the molecule decreases its bioavailability. However, it should be remembered that the absorption capacity will also depend on the number of anthocyanins and the presence of other compounds. It was found out that the ingestion of anthocyanins together with sugar slowed down their absorption, while the consumption of anthocyanins together with alcohol significantly accelerated their intake [32].

3.2. Anti-Inflammatory Activity and Protection against Chronic Diseases

The health benefits of anthocyanins have been studied in a variety of models, ranging from human clinical trials to animal and cell culture screening to epidemiological studies [17]. The human body is in constant contact with external factors that can cause various types of damage, irritation, or allergies [9], often leading to inflammation. Inflammation is a complex set of relationships between soluble compounds that can arise in any tissue in defensive response to traumatic, infectious, post-ischemic, toxic, or autoimmune injury. It is typically induced by microbial infections but can also be triggered by tissue

injury or trauma that occurs without the intervention of pathogens (sterile inflammation). The inflammation process usually leads to recovery from infection and healing [33].

Adaptive innate immune response induces rapid activity following infection. A wide range of molecular patterns are detected, commonly found in pathogens but are foreign to mammals. They are called pathogen-related molecule patterns (PAMP) [34]. Such particles are lipopolysaccharides, surface phosphatidylserine, and aldehyde derivatized proteins, as well modified forms of the classic risk factor for atherosclerosis, oxidatively modified low-density lipoprotein (LDL), or glycation [35]. The cellular response may be lysosomal endocytosis, degradation-bound ligands. Involvement in the process of Toll-like receptors causes the activation of the nuclear factor kappa B (NF-κB) and protein kinase. It can induce increased phagocytosis, production of reactive oxygen, and release of cytokines, autacoids, and lipids coordinating and strengthening local inflammation [36,37]. Recent research demonstrates that metabolites of anthocyanins can reduce the activation of NF-κB [38]. Protein kinases, cellular stress kinases, extracellular signal-regulated kinases, and mitogen-activated protein kinases (AMPK) are other molecular targets of anthocyanins and have been shown to be sensitive to anthocyanin treatment, reducing downstream cellular signaling networks associated with serious diseases, such as chronic inflammation [17]. AMPK-activated protein kinase involved in cellular energy (glucose) metabolism-caused diabetes appears to be one of the main targets of anthocyanins [39]. AMPK is an important regulator of energy homeostasis and is a molecular target of drugs used for the treatment of obesity and other metabolic diseases [40]. Another target of anthocyanins are thrombin receptor-activating peptide and vascular endothelial growth factor, which are responsible for angiogenesis, cancer, and atherosclerotic risk [41].

The biological activity of isolated anthocyanins and anthocyanidins, or foods rich in anthocyanins, can be manifested in the prevention of cardiovascular disease [42], influence on cholesterol distribution, protection of endothelial cells from CD40-induced proinflammatory signaling [43], anticancer, antitumor, and antimutagenic activity [44], beneficial effects in diabetes [45], protective effects against oxidative liver damage [46], protective effects on gastric inflammation and damage [47], antimicrobial and antiviral activity [48,49], slowing down neuronal and behavioral aging [50], and protection from some neurodegenerative diseases such as Alzheimer's disease [51]. Anthocyanins and anthocyanidins also effectively induce insulin secretion when tested in pancreatic cell lines [11]. The effectiveness of insulin secretion depends on the number of hydroxyl groups in the B-ring of their structures [45].

Cyanidin (C₁₅H₁₁O₆) and its derivatives are the most common anthocyanins in flowers (Table 1). The study carried out by Samarpita and Rasool [52] suggests that cyanidin is a potent inhibitor of Interleukin (IL)-17A signaling associated with the pathogenesis of rheumatoid arthritis, the most common autoimmune arthropathy. Cyanidin not only effectively blocks interleukin 17A/p38 but also suppresses osteoclastogenesis. This study suggests that cyanidin has great potential as a small molecule drug to be used in clinics to treat rheumatoid arthritis patients [52]. Moreover, there is evidence that cyanidin as well as delphinidin have the chemo preventive effect against skin cancer [53].

Table 1. Anthocyanin content in edible flowers grown in containers.

Flower Species	Anthocyanins *							Source
	Cyanidin	Delphinidin	Pelargonidin	Malvidin	Peonidin	Petunidin	Total	
<i>Ageratum houstonianum</i>							27.85 ₈	ORAC/FRAP ¹ (TE/100 g) ^A 2.99 ^{A,8} (mmol FeSO ₄ /100 g) ^B [5],
<i>Argyranthemum houstonianum</i>							2.99 ₈	27.85 ^B [5]
<i>Begonia</i> sp.	p ^D		p ^D	759.1			5.09 ₈	21.18 ^B [5,54,55]
<i>Bellis perennis</i>	p ^D		p ^D				no data	[56]
<i>Campanula</i> sp.		p ^D	p ^D					[57,58]
<i>Calendula officinalis</i>							22.1 ₇	3.68 ^A 58.05 ^B [5,59,60]

Flower Species	Anthocyanins *						Total	ORAC/ FRAP ¹ (TE/100 g) ^A (mmol FeSO ₄ /100 g) ^B	Source
	Cyanidin	Delphinidin	Pelargonidin	Malvidin	Peonidin	Petunidin			
<i>Dahlia</i> sp.	121.2		2.65				17.6– 257.5 7,9	17–24 5,9	[61,62]
<i>Dianthus</i>	52.4	p ^D	p ^D				0.73– 13.35 8,9	5.4– 10.2 ^{A,9}	[5,63,64]
<i>Dendranthema</i>	p ^D	p ^D	p ^D					168– 182 ^B	[56,65,66]
<i>Phaseolus coccineus</i>									no data
<i>Fuchsia</i> sp.	p ^D				p ^D		7.58 8,9	47.52 ^B	[5,67]
<i>Glechoma hederacea</i>	p ^D	p ^D					no data		[68]
<i>Heliotropium oxalis</i>									no data
<i>Helichrysum</i>								419.8 ^B	[69]
<i>Hemerocallis</i>								21.0– 29.0 ^A	[70]
<i>Hibiscus</i> sp.	2080	5650					155– 206 ⁸	83.1 ⁵	[71,72,73,74]
<i>Impatiens</i>			p ^D	p ^D	p ^D		no data		[75]
<i>Lavandula</i>								277.60 ^B	[68]
<i>Lobelia</i>									no data
<i>Lobularia maritima</i>	p ^D		p ^D				no data		[76,77]
<i>Myosotis</i>								171.60 ^A	[68]
<i>Pelargonium spp.</i>	p ^D	p ^D	p ^D	p ^D	p ^D	p ^D	12.52 ⁸	34.78 ^{B,9}	[5,78]
<i>Petunia</i>	53.2 ²	31.3 ²	49.0 ⁴	2.6 ⁴	87.1 ³	8.5 ³	28– 114 ⁹	5.4– 10.22 ^{B,9}	[5,79,80]
<i>Rosa</i>	357.0		31.2		140.4– 153.1 ¹⁰		2.3– 7.0 ⁸	71.4– 397.4 ^{A,9}	[58,62,81,82,83]
<i>Tagetes erecta</i>	33		3.8				0.75 ⁸	70.42 ^B 266.11 ^A	[5,84]
<i>Tagetes patula</i>	0.25 ^{6,9}	p ^D		p ^D		p ^D		0.076– 0.433 ^{6,9}	[60,85]
<i>Torenia</i> sp.	0.9–41.0 ⁹	210.96		4.2– 134.9 ⁹			5.0– 152.7 ⁹	8907.50 ^A	[55,86,87],

The effect of anthocyanins on microbial pathogens has not been studied in depth up to now. However, the results obtained so far are very promising.

Anthocyanins *

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Flower Species	Cyanidin	Delphinidin	Pelargonidin	Malvidin	Peonidin	Petunidin	Total	ORAC/ FRAP ¹ (TE/100 g) ^A (mmol FeSO ₄ /100 g) ^B	Source
<i>Tropaeolum majus</i>	4.77 ⁸	32.208 ⁸	32.06 ⁸	–	–	–	68.12 ₈	7111– 18,719 _{A,9}	[88]
<i>Tulipa</i> sp.	p ^D	p ^D	p ^D				3.8– 4.0 ⁹	29.23 _{B,11}	[89,90,91,92]
<i>Viola cornuta</i>	70.0 ⁷	1350 ⁷						25.0 ^B	[60,93]
<i>Viola wittrockiana</i>	1.9–16.7 ₉	8.6–21.8 ⁹		8.8–14.2 ₉		1.2–15. ⁹	0.35– 13.6 ₉	0.82– 36.55 _{B,9}	[5,94,95]