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Flavonoids: Classification, Biosynthesis and Chemical Ecology

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Abstract

Flavonoids are natural products widely distributed in the plant kingdom and form one of the main classes of secondary metabolites. They display a large range of structures and ecological significance (e.g., such as the colored pigments in many flower petals), serve as chemotaxonomic marker compounds and have a variety of biological activities. Therefore, they have been extensively investigated but the interest in them is still increasing. The topics that will be discussed in this chapter describe the regulation of flavonoid biosynthesis, the roles of flavonoids in flowers, fruits and roots and mechanisms involved in pollination and their specific functions in the plant.

Keywords: flavonoids, biosynthesis, pollination, allelochemicals, chemical ecology

1. Introduction

Flavonoids represent a highly diverse class of polyphenolic secondary metabolites, which are abundant in spermatophytes (seed-bearing vascular land plants: gymnosperms (cycades, conifers, ginkos and gnetophytes) and angiosperms) [1–3] but have also been reported from primitive taxa, such as bryophytes (nonvascular land plants, including liverworts, hornworts and mosses) [4, 5], pteridophytes (seedless vascular land plants, i.e., lycophytes, horsetails and all ferns) [6, 7] and algae [8, 9]. Overall, about 10,000 flavonoids have been recorded which represent the third largest group of natural products following the alkaloids (12,000) and terpenoids (30,000) [1, 10].

Flavonoids are essential constituents of the cells of all higher plants [11]. Plants have evolved to produce flavonoids to protect themselves against fungal parasites, herbivores, pathogens

and ultraviolet (UV) radiation [10]. They resemble in their regulatory properties most of the lipid-soluble vitamins but serve, in addition, due to their color, as communicators with the environment. Flavonoids are recognized by pollinators, for example, insects, birds and animals, which contribute to the dispersion of seeds [11]. They act as symbionts, as allelochemicals, as antimicrobial and antiherbivory factors [10, 12]. Many studies have shown that flavonoids exhibit biological and pharmacological activities, including antioxidant, cytotoxic, anticancer, antiviral, antibacterial, anti-inflammatory, antiallergic, antithrombotic, cardioprotective, hepatoprotective, neuroprotective, antimalarial, antileishmanial, antitrypanosomal and antiamebial properties [13–15].

The topics that will be discussed in this chapter describe the regulation of flavonoid biosynthesis, the roles of flavonoids in flowers, fruits and roots and mechanisms involved in pollination and their specific functions in the plant.

2. The classification and biosynthesis of flavonoids

Flavonoids can be classified according to biosynthetic origin. Flavonoids are characterized by the presence of 15 carbon atoms in their basic skeleton, arranged in the form C₆-C₃-C₆, which corresponds to two aromatic rings A and B linked by a unit of three carbon atoms, which may or may not give rise to a third ring. The rings are labeled A, B and C [15, 16]. The initial step in the biosynthesis of most flavonoids is the condensation of one *p*-coumaroyl-CoA molecule (shikimate derived, B ring) with three molecules of malonyl-CoA (polyketid origin, A ring) to give chalcone (2', 4', 6', 4-tetrahydroxychalcone). This reaction is carried out by the enzyme chalcone synthase (CHS) [14–16]. Chalcone is subsequently isomerized by the enzyme chalcone flavanone isomerase (CHI) to flavanone. From these central intermediates, the pathway diverges into several side branches, each yielding a different class of flavonoids (**Figure 1**) [14, 16, 17].

Although the central pathway for flavonoid biosynthesis was conserved in plants, depending on the species, a group of enzymes, such as isomerases, reductases, hydroxylases, modifies the basic flavonoid skeleton, leading to the different flavonoid classes [1, 16], including chalcones and flavanones which are intermediary compounds in biosynthesis and final products present in various parts of the plant. Anthocyanins, proanthocyanidins, flavones and flavonols are other classes only known as end products of biosynthesis. The other important class is the isoflavonoids, which are formed by migration reaction of 2-aryl side chain to 3-position mediated by isoflavone synthase [1, 16, 18].

The retrochalcones are unusual flavonoids and have reversed A and B rings. The biosynthesis is not yet clearly defined but is likely to be derived from the common C₁₅ intermediate of general flavonoid biosynthesis, more specifically from the reduction of dibenzoylmethanes [19–21] or by 2-hydroxylation of a flavanone [22, 23]. These compounds are restricted to relatively few plant species and have been isolated from some species of the families Leguminosae [24], Annonaceae and Basellaceae [25–28].

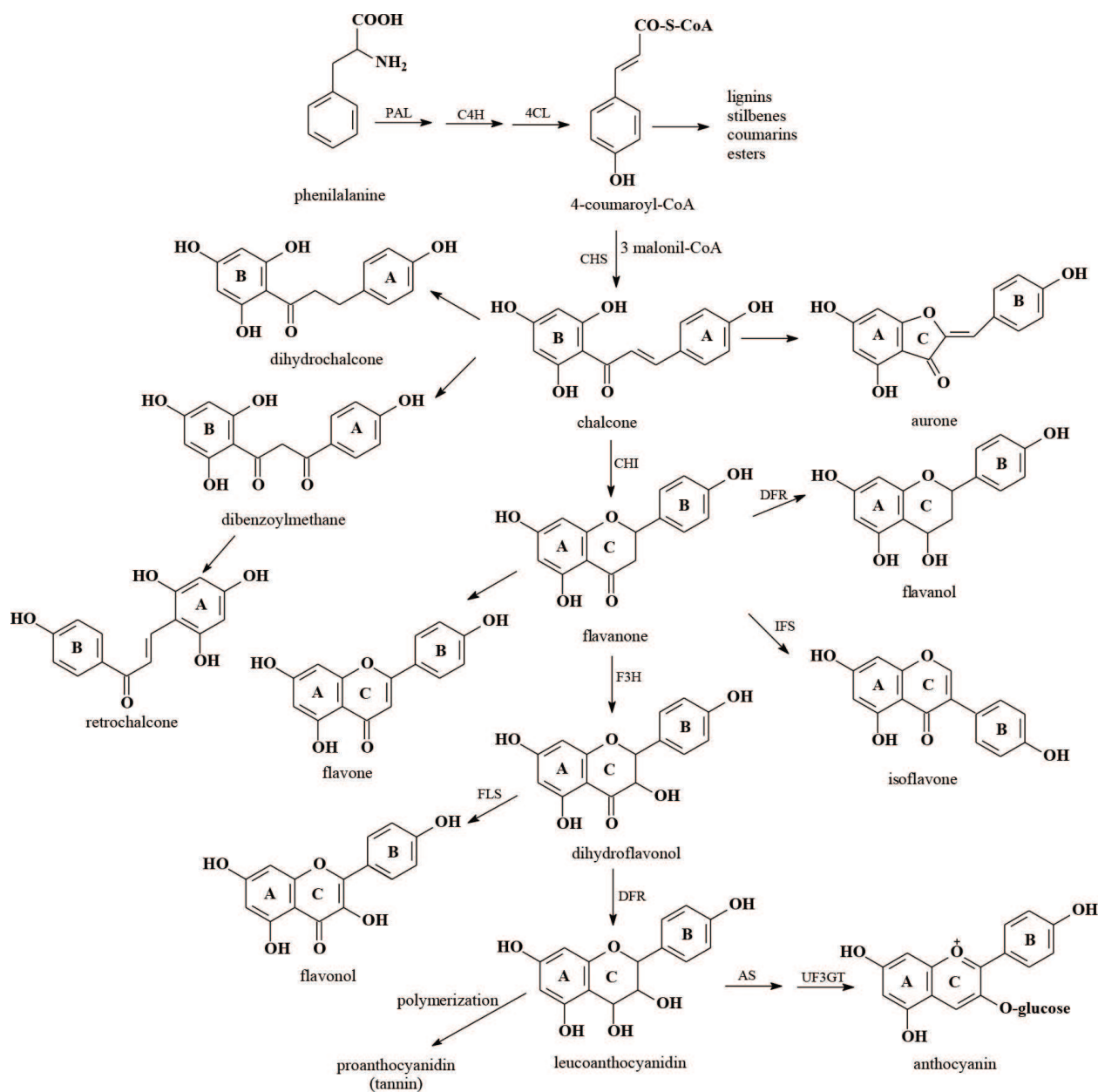


Figure 1. A diagram of the flavonoid biosynthetic pathway. Key enzymes catalyzing some reactions: PAL, phenylalanine amonialyase; C4H, cinnamate 4-hydroxylase; 4CL, 4-coumaroyl-coenzyme A ligase; CHS, chalcone synthase; CHI, chalcone flavanone synthase; F3H, flavanone 3 β -hydroxylase; DFR, dihydroflavonol 4-reductase; FLS, flavonol synthase; IFS, isoflavanoid synthase; AS, anthocianin synthase and UF3GT, UDP glucose: flavonoid 3-O-glucosyltransferase. Adapted from Ref. [17].

Several species reported the presence of chalcone dimers bound by a cyclobutane (**Figure 2**) [29–35]. The phytochemical study of the roots of *Dahlstedtia grandiflora* was observed, and for the first time, the occurrence of dimerization in retrochalcones was noted [24]. The mechanisms of [2 + 2] cycloaddition involved in the formation of these compounds are suggested [30, 35]. In spite of the lack of biosynthetic studies of these natural products, much effort has been made in elucidating the biosynthetic pathways of flavonoids from a genetic perspective.

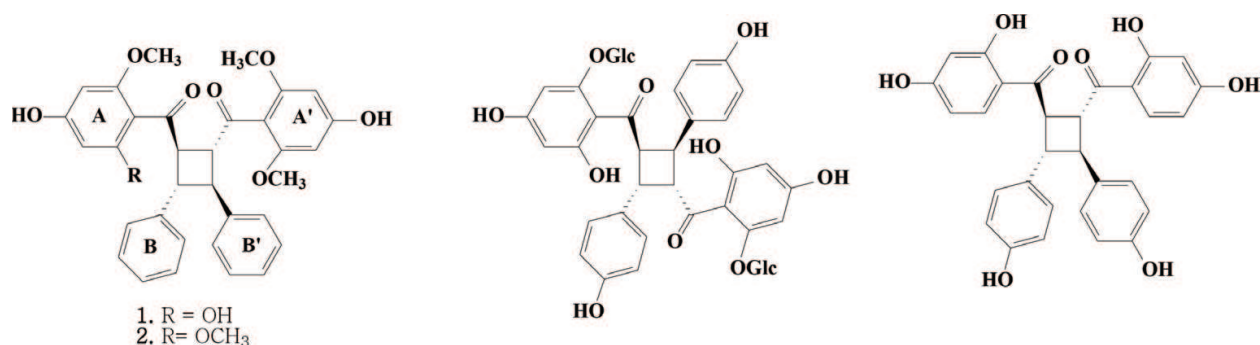


Figure 2. Chalcone dimmers isolated from *Combretum albopunctatum* [31], *Helichrysum zivojinii* [29] and *Agapanthus africanus* [30].

Flavonoids occur naturally as compounds associated with sugar in conjugated forms (glycosides), without attached sugar as aglycones [1, 36]. They are often hydroxylated in positions 3, 5, 7, 3', 4' and 5'. Some of these hydroxyl groups are frequently methylated, acetylated or sulfated. Prenylation usually occurs directly at a carbon atom in the aromatic rings, but O-prenylation has also been found [11]. When glycosides are formed, the glycosidic linkage is normally located in position 3 or 7, and the carbohydrates are commonly L-rhamnose, D-glucose, glucose rhamnose, galactose or arabinose [1, 11]. These changes often alter their solubility, reactivity and stability. The majority of flavonoids are present in the form of glycosides under natural conditions [1].

2.1. The chemical structure of flavonoids

The chemical nature of flavonoids varies according to the hydroxylation pattern, conjugation between the aromatic rings, glycosidic moieties, methoxy groups and other substituents [37–39]. Flavonoids contain conjugated double bonds and groups (hydroxyl or other substituents) that can donate electrons through resonance to stabilize the free radicals, which originate in the electronic spectra of flavonoids [40].

Studies on flavonoids by UV spectroscopy have shown that most flavonoids consist of two major absorption maxima: band II (240–285 nm) which corresponds to the benzoyl system of the A ring, while band I (300–400 nm) represents the cinnamoyl system of the B ring (**Figure 3**) [36, 41].

Functional groups attached to the flavonoid skeleton may cause a shift in absorption. The application of standardized UV (or UV-Vis) spectroscopy has for years been used in analyses of flavonoids [11].

Flavonoids have the ability to sequester free radicals, are natural antioxidants derived from plants and are commonly found in foods and beverages [40]. The main structural features of flavonoids required for antioxidant activity can be determined by three fundamental factors: (1) a 3',4'-dihydroxy (catechol) structure in the B ring favors the electron delocalization (**A**), (2) an unsaturated 2-3 bond in conjugation with a 4-keto group provides electron delocalization from the B ring (**B**) and (3) hydroxyl groups at positions 3 and 5 form intramolecular hydrogen bonding to the keto group (**C**) (**Figure 4**). These effects lead to the increases of the radical scavenging by delocalization of electrons or by donation of hydrogen [42].

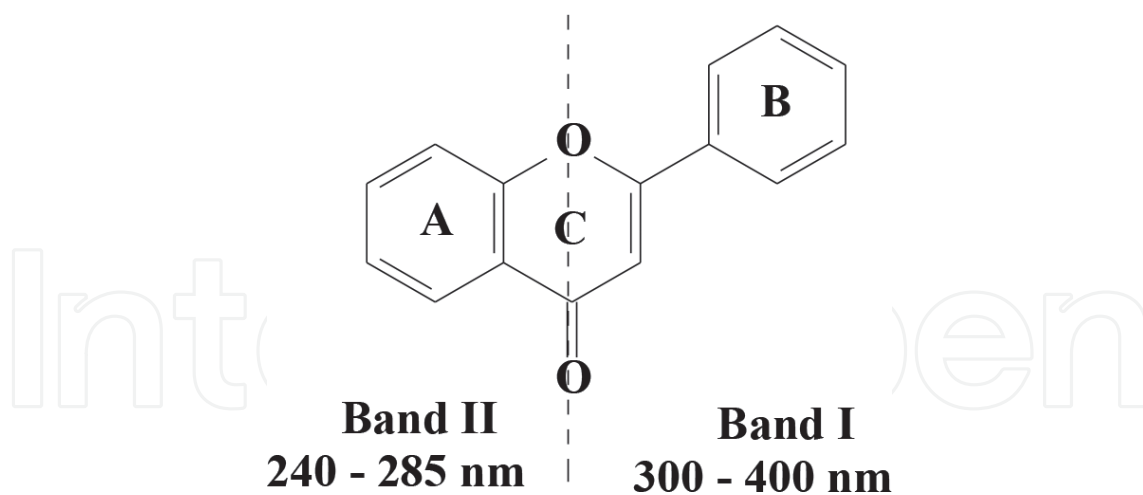


Figure 3. Band II absorption (originated from A-ring benzoyl system) and band I (from the B-ring cinnamoyl system). Adapted from Ref. [41].

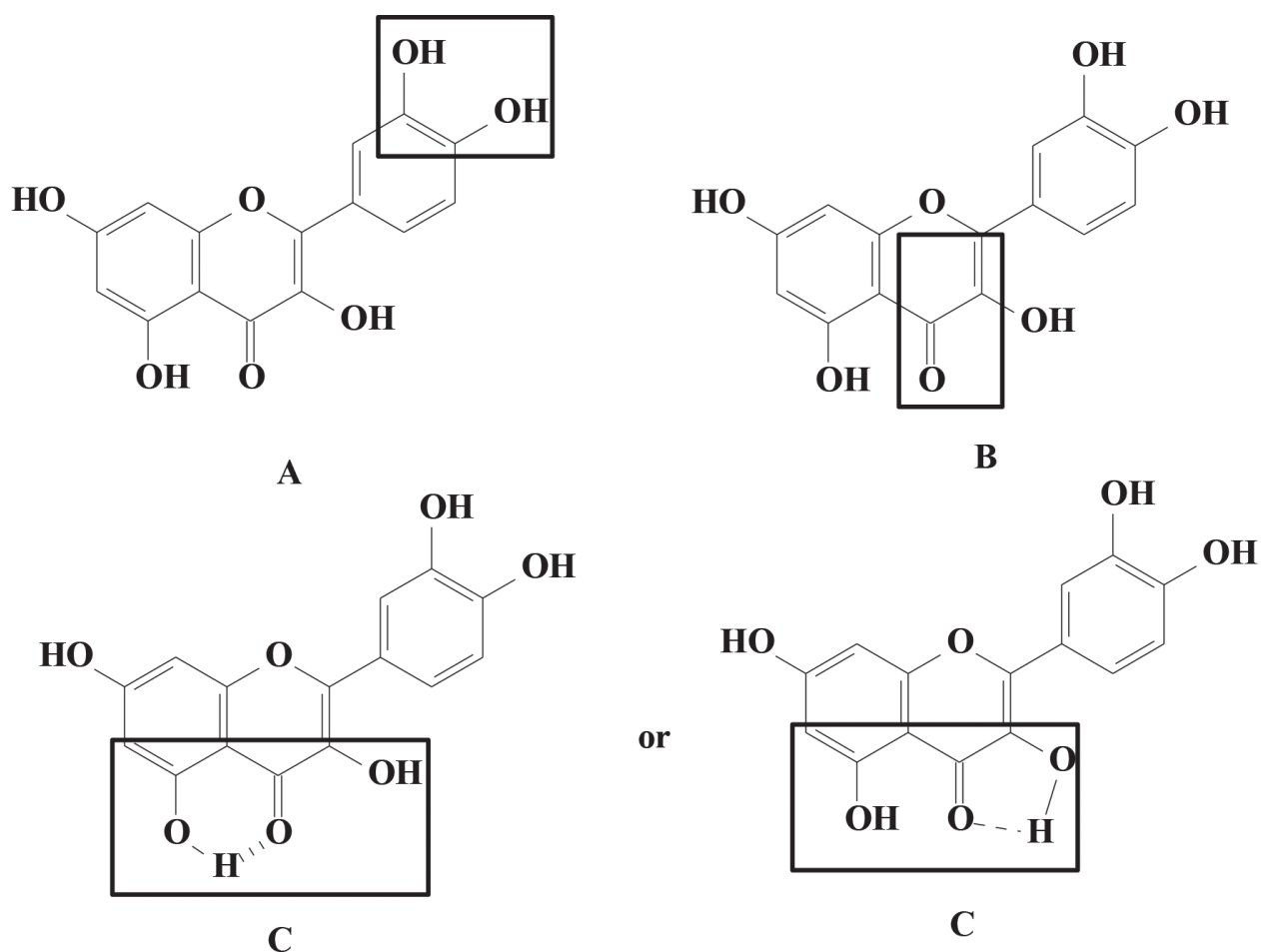


Figure 4. Structural groups for radical scavenging [42].

Flavonoids have different activity mechanisms such as free radical scavenging, inactivation of peroxides and other reactive oxygen species, chelation of metals and quenching of secondary

lipid oxidation products [40]. The radical scavenging properties associated with the structure of flavonoids defend against oxidative stress and in doing so reduce heart disease, prevent cancer and slow down the aging processes in cells responsible for degenerative diseases [40, 42].

3. Ecology chemicals

3.1. Pigments and pollination

Plant compounds that are perceived by humans to have color are generally referred to as “pigments.” The three main classes of pigments for coloration in plants are: betalains, carotenoids and flavonoids (anthocyanins) [43, 44]. All three classes of pigments act as visible signals to attract insects, birds and animals for pollination and seed dispersal [11, 43].

The pigments that color most flowers, fruits and seeds are flavonoids, which have the widest color range, from pale-yellow to blue [12]. Anthocyanins occur in all plant tissues and provide a wide range of colors ranging from orange/red to violet/blue [44]. They are formed by glycosides that may have several sugars in position 3; when there are no glycosides, the pigments are called anthocyanidins [12]. In addition to various modifications to their structures, their specific color also depends on pH, copigments and metal ions [11, 45].

The basic chromophore of anthocyanins is the flavylium ion [45, 46]. In acidic medium (pH below 2.5), anthocyanins show intensely reddish coloration or orange due the presence of flavylium cation form. When the pH increases from 2.5 to 4–6, the violet anhydrobase is formed first, but it decolorizes rapidly due the predominance of pseudobase carbinol formed by hydration (**Figure 5**) [11, 39, 47].

Since the flower cell sap is usually weakly acidic, in this pH region, most of the anthocyanins are in colorless form Ref. [47]. Hydration of the flavylium cation, which causes decoloration, may be prevented by formation of a complex between this ion and other substances. This phenomenon is called copigmenting [11, 47]. Such complexes are formed by intermolecular, intramolecular rearrangements and self-association, with organic molecules such as flavonoids, tannins, aromatic acids or metal for chelation [46, 47]. The copigmentation has a stabilizing effect as well as a bathochromic effect on anthocyanins [47]. Various flavonols and flavones act as copigments, with anthocyanins leading to an intensification of flower color [32, 45, 46]. So far, the main pigments targeted for flower and fruit color modifications are anthocyanins that contribute to a variety of colors such as red, pink and blue [44].

Humans recognize the color of a compound by perceiving reflected or transmitted light of wavelengths between 380 and 730 nm, while insects recognize light of shorter wavelengths [43]. Anthocyanins contribute to the UV patterns that are visible to insects and serve to signal flowers and fruits that are attractive to pollinators [45]. The light absorption of anthocyanins extends over most of the spectrum. Particularly, anthocyanins have an intense absorption in the 450–560 nm region (visible region), attributed to the hydroxyl cinnamoyl system of the B ring, while the absorption in the 240–280 nm region (UV region), characteristic of all flavonoids, corresponds to the A ring [32, 39].

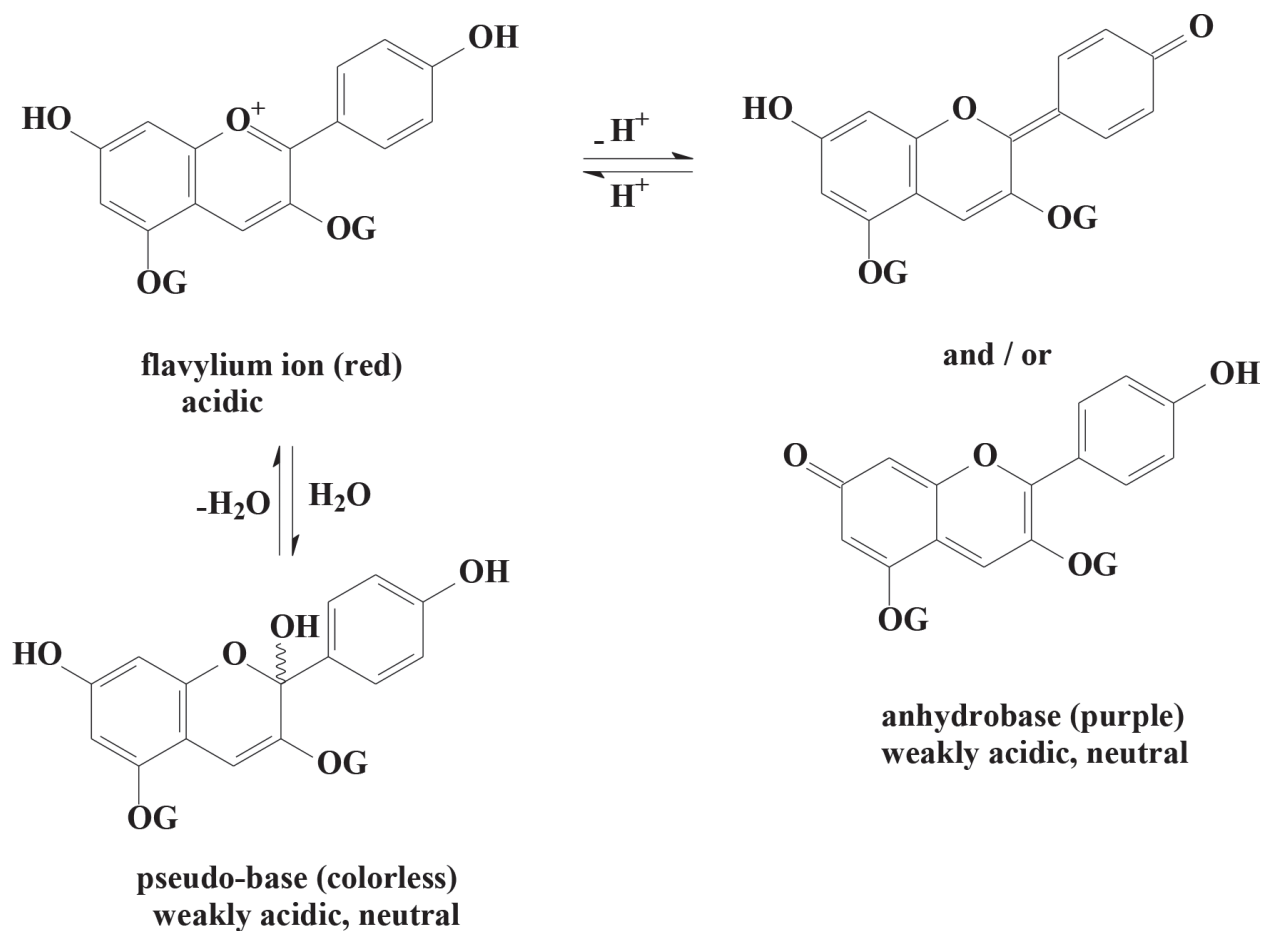


Figure 5. A change in the structure of an anthocyanin in aqueous solution as a function of pH [47].

The different colors produced by pigments are visible only to animals with the right photoreceptors, and many insects have limited color vision at the red end of the spectrum [40]. Due to the structural diversity of anthocyanins, the presence of one determined anthocyanin in the flower might affect the type of pollinators visiting the plant. The color preferences are different for different pollinators, and blue anthocyanins, for example, appear to attract bees more than red ones. Some butterfly and birds species visit red flowers, suggesting that both groups of animals are attracted to red anthocyanins [12, 40, 48].

A study of anthocyanins in two species of the genus *Schizanthus* Ruiz & Pav (Solanaceae) showed that the hummingbird-pollinated red flowers of *S. grahamii* contained a higher proportion of delphinidin 3-O-rutinoside (anthocyanin), whereas the bee-pollinated bluish-pink flowers of *S. hookeri* contained a higher proportion of petanin-derivatives (anthocyanin) [48].

Flavones and flavonols also contribute to flower color hue. Both groups of compounds comprise unpigmented or pale yellow flavonoids and are mostly invisible to the human eye [43, 44]. Studies on flavonoids by spectroscopy have revealed that most flavones and flavonols exhibit two major absorption bands: band I (320–385 nm) represents the B ring absorption, while band II (250–285 nm) corresponds to the A ring absorption [39]. As they absorb UV, which insects recognize, they give color and patterns to flowers to attract insects [43].

Chalcones and aurones, which provide yellow pigmentation in the flowers of several ornamental species, are relatively rare types of flavonoids [49]. The UV spectra of both compounds are characterized by an intense band I and diminished band II absorption [50]. The major absorption band in chalcones (band I) usually occurs in the range 340–390 nm. Band II is usually a minor peak in the 220–270 nm region, while the long wavelength absorption band in aurones is usually found in the 370–430 nm region. They produce the strongest yellow colors owing to their absorbance at longer wavelengths compared to the other types [50, 51]. Chalcones, flavonols, flavones or anthocyanins usually accumulate in sex organs of flowers, including the pollen. In contrast to man, some insects, especially bees, can perceive in the near ultraviolet (340–380 nm) as well as in the visible region. However, insects are possibly attracted to pollen whose color contrasts against petals due to UV reflective or absorptive flavonoids [46].

Pollination is an essential step in the reproductive process of the world's nearly 300,000 species of flowering plants because it is usually required for the production of seeds. Pollination can result from the action of abiotic forces such as wind and water, but 80% of the Angiosperms rely on animals, including bats, flies, butterflies, beetles and other insects [52]. Such diversity is acquired through evolutionary processes to ensure successful reproduction [44].

3.2. Allelopathy

The interactions between organisms are fundamental for the determination of plant abundance and distribution pattern in the community, of the productivity of several cultivated species and of the degree of interference on weeds [53]. Weeds are one of the most important factors that impose limitations on the development of agricultural activity in the world and are difficult to eradicate. The success of weeds in different cropping systems is associated, in part, with their ability to produce, store and release to the environment chemicals with allelopathic properties [54].

Allelopathy can be defined as a process by which compounds from the metabolism of a plant are released, preventing the germination, growth and development of other neighboring plants [55]. These compounds are involved in plant-plant interactions or allelopathy [56] and may influence, for example, in the vegetation of a local, in the succession of plants, in the germination of seeds and in the cultures productivity, among others [57]. Among the main groups of compounds with allelopathic potential are highlighted the benzoquinones, coumarins, flavonoids, terpenoids, glycosides, phenolic acids, alkaloids, rotenoids, catechins and tannins [58, 59].

Although flavonoids have many roles in plants, in relation to their role in allelopathy and the inhibition of seedling root growth [56], the activity of flavonoids in plant-plant interactions can be positive or negative [60]. The negative relations are mainly based on inhibiting germination and growth of other plants seedlings [56], as depicted in **Table 1**.

Some flavonoids present a level of phytotoxicity, indicating that allelopathy could be a beneficial function of the flavonoids to the producing plant [65]. Although the relative role of flavonoids in allelopathic interference has been less well-characterized than of some secondary metabolites, some examples of their involvement in autotoxicity and allelopathy are reported

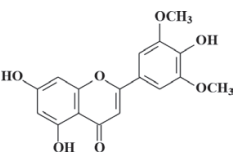
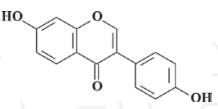
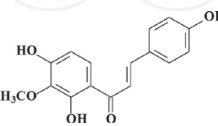
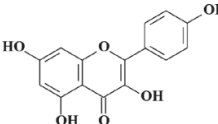
Plant organism	Flavonoid	Function	References
<i>Oryza sativa</i> L.		Allelopathic inhibitor of weeds and pathogens	[61]
-		Allelopathic inhibitor of seed germination	[62]
<i>Helianthus annuus</i>		Inhibitor of seedling growth	[63]
-		Allelopathic inhibitor of seedling growth	[64]

Table 1. Flavonoids of different classes with allelopathic potential.

[56]. In a previous study, see [65], presented flavonoids as are at least partly responsible for the strong phytotoxic effects of *Stellera chamaejasme* L. The potential allelopathic behavior may facilitate this weed to become a good competitor against other plant species in the environment.

Allied to the need for understanding the mechanism action of flavonoids, the importance of the study of allelopathy gains more and more attention in agriculture because these interactions could be employed for reducing weed growth.

Biopesticides based on flavonoids displaying allelopathic properties against weeds can potentially be an efficient natural defense against them [62]. In the study [63], the inhibiting activity against weeds of the species *Echinochloa crus-galli*, *Cyperus difformis* and *Cyperus iria* using the 5,7,4'-trihydroxy-3',5'-dimethoxyflavone is shown.

4. Conclusion

Flavonoids are found in most plant tissues, provide a range of colors that attract pollinators, and, in fruit, they probably serve to attract frugivores that assist in seed dispersal. All of these pigments also function as antioxidants and sunscreens, absorbing wavelengths of ultraviolet. Their biosynthesis appears to be ubiquitous in plants and evolved early during land plant (from primitive green algae) evolution, aiding in plant protection and signaling. The precise mechanism by which flavonoids participate in allelopathy is still unknown, but the significance of allelopathy has gained more attention in agriculture, for example. Plant-plant interactions can influence or determine diversity, productivity and reproduction of a plant community beyond reduction or inhibition of weed growth.

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