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# Flavonoids: Understanding Their Biosynthetic Pathways in Plants and Health Benefits

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and Maria-Goretti Chikodili Igbokwe*

## Abstract

Flavonoids are polyphenolic compounds and are one of the most abundant secondary metabolites present in plants. They are found in almost all vegetables and fruits. Flavonoids are of essence to plants and to man as well, due to their Medicinal and Pharmaceutical importance. Explicit understanding of the biosynthetic pathway of flavonoids is very essential. This will provide a stepwise explanation of the processes and mechanisms through which different forms of flavonoids are synthesized in plants, including the enzyme(s) responsible for each step. The importance in plants, medicine and pharmacy, of all the product(s) of each step will be emphasized.

**Keywords:** flavonoid, biosynthesis, plant, phenylpropanoid

## 1. Introduction

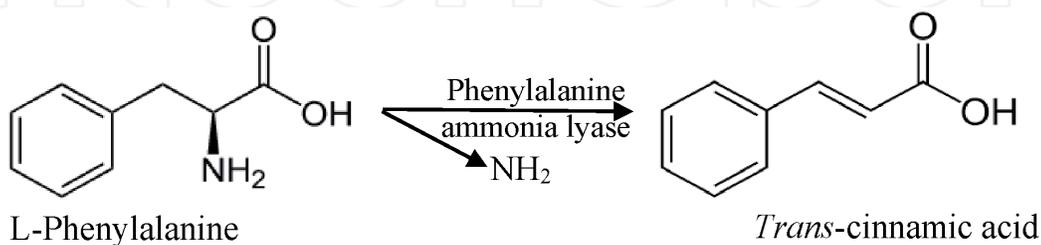
Flavonoids represent an important class of natural products; mainly, they are of the family of secondary plant metabolites having a multi-phenolic structure, found commonly in fruits, vegetables and certain beverages. They have various favorable biochemical, and antioxidant effects associated with various diseases such as cancer, Alzheimer's disease (AD), atherosclerosis and other reported pharmacological effects [1–3]. Flavonoids are associated with a wide spectrum of health-promoting effects and are crucial component in various nutraceutical, pharmaceutical, medicinal and cosmetic applications. This broad spectrum of health-promoting effect is due to their antioxidative, anti-inflammatory, anti-mutagenic and anti-carcinogenic properties coupled with their ability for cellular enzyme functions modulation [4].

In discussing the understanding of biosynthesis of flavonoids and their health benefits, we will be looking at it based on the sub headings of the enzymes involved in the biosynthetic pathway.

## 2. Phenylalanine ammonia lyase

Lyases are group of enzymes that catalyzes the removal of a functional group or a moiety from a compound by cleaving a carbon-carbon, carbon-oxygen, phosphorous-oxygen, and carbon-nitrogen bonds by mechanism of reaction other than

hydrolysis, or oxidation. This removal of a functional group or a moiety often leads to the formation of a new double bond or ring structure. The bonds cleaving usually occur by means of elimination reaction [5]. In the synthesis of flavonoids, an ammonia-lyase, Phenylalanine ammonia-lyase (PAL) is the primary enzyme in the pathway for the synthesis of phenol [6]. At the initial synthesis of flavonoids, the conversion of Phenylalanine to trans-cinnamic acid is catalyzed by Phenylalanine ammonia lyase through a mechanism of non-oxidative deamination [7] as shown below. This Phenylalanine that is deaminated is a product of another pathway, shikimic acid pathway. Shikimic acid pathway produces three amino acid; L-Tyrosine, L-Phenylalanine and L-Tryptophan. The phenylpropanoid pathway takes its root from the L-Phenylalanine generated from the shikimic acid pathway.



Cinnamic acids belong to a group of aromatic carboxylic acids (C<sub>6</sub>-C<sub>3</sub>), which occurs naturally in plant kingdom. In the biochemical process that leads to the formation of lignin, which is the naturally occurring polymeric material that is responsible for providing mechanical support to plant cell wall, cinnamic acids are produced [8]. In all green plants cinnamic acids occur [9]. They are covalently bound to cell walls in minute quantities [10]. They are also found in the reproductive organs of flowering plants [11].

Coffee beans, tea, cocoa, apples, pears, berries, citrus, brassicas vegetables, spinach, beetroot, artichoke, potato, tomato, celery, faba beans, grape and cereals also contain cinnamic acids [12]. Cinnamic acids, with quinic acid, usually appears as conjugates known as the chlorogenic acids. With other acids, sugars or lipids they can also form esters. They can also with aromatic and aliphatic amines, form amides. Some cinnamic-related molecules have been shown in literature those possess the following pharmacological properties; anticancer [13], antituberculosis [14], antimalarial [15], antifungal [16], antimicrobial [17], antiatherogenic [18] and antioxidant [17] activities.

Also, various surveys directed towards the synthetic procedure for cinnamic acid preparation and related atoms have been shown in the literature [19-21]. Medicinal chemists have done the alteration of potency, permeability, solubility or other parameters of a preferred drug or pharmacophore with the aid of cinnamic acids [22].

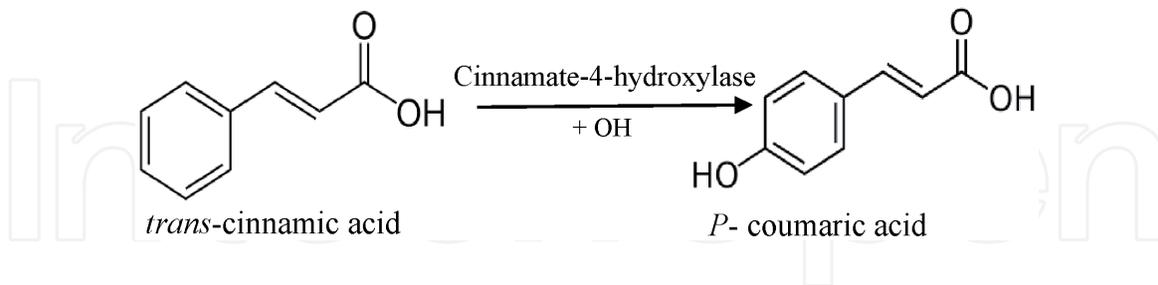
Cinnamic acid exists in two isomeric forms; trans and cis. Most often available in nature and commercially is the trans form. Cinnamic acid can be obtained from cinnamon bark and balsam resins such as storax.

In the flavors, dyes, and pharmaceuticals production, trans-Cinnamic acid is utilized. The principal use of trans-cinnamic acid is in manufacturing of its methyl, ethyl, and benzyl esters, which are an essential component of perfumes. Also, in the production of the sweetener aspartame, the acid serves as a precursor [23].

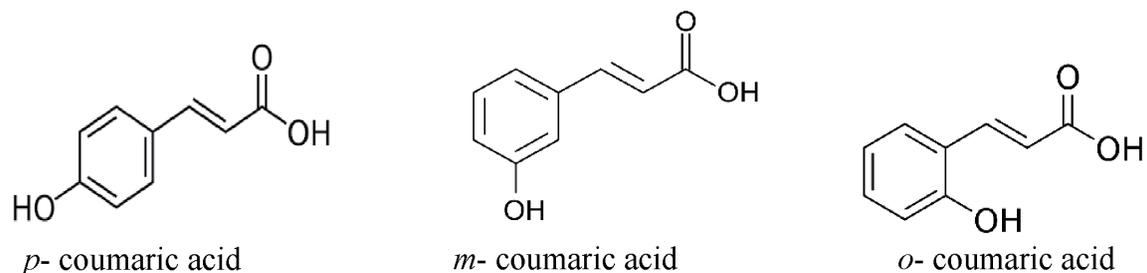
### 3. Cinnamate-4-hydroxylase (C4H)

Hydroxylases are enzymes which add hydroxyl group to organic compounds. C4H found in plants is a cytochrome P450 that catalyzes trans-cinnamic acid conversion to

*p*-coumaric acid and is the first hydroxylation step of lignin, flavonoids and hydroxycinnamic acid ester biosynthetic pathway correlating with lignifications [24–27]. Generally, in the synthesis of flavonoids, Cinnamate-4-hydroxylase catalyzes the addition of hydroxyl group to the *trans*-cinnamic acid generated from the deamination of the L-Phenylalanine, leading to the production of *p*-coumaric acid as shown below.



*p*-coumaric acid also known as 4-Hydroxycinnamic acid or *p*-Hydroxycinnamic acid, is a hydroxycinnamic acid, and also organic compound which is a hydroxy derivative of cinnamic acid. *p*-coumaric acid exists naturally in three isomers, namely; *ortho*-, *meta*- and *para*- coumaric acid [28].



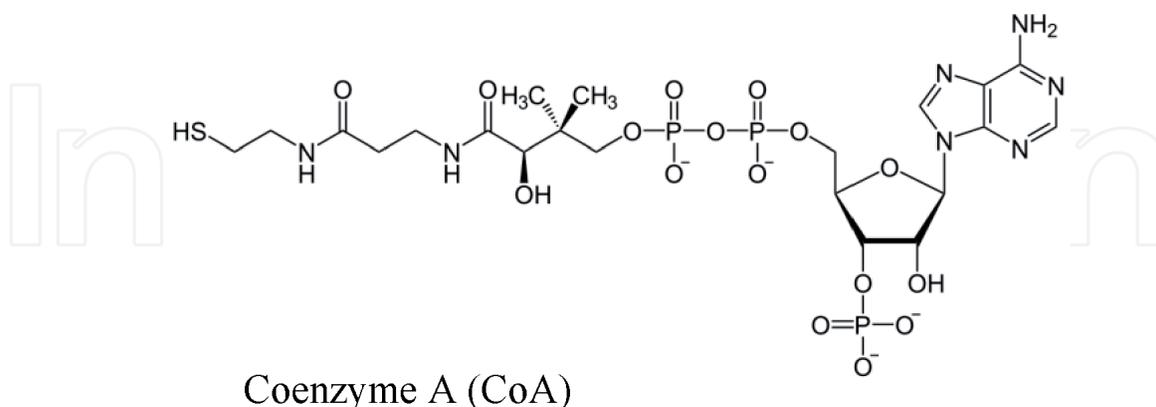
As can be observed from above, these isomers differ from each other differ by the position of the hydroxy group substitution on the phenyl group. *p*-coumaric acid (4-hydroxy-cinnamic acid) occurs widely in the cell walls of graminaceous plants and is the most abundant of the three isomers [29]. It decreases low-density lipoprotein (LDL) peroxidation [30, 31], antimicrobial activities [32, 33] and plays a vital role in human health. Coumaric acids have been shown to possess radical-scavenging effect [34–40] which reduces stomach cancer risk by suppressing carcinogenic nitrosamines formation [41–43].

*p*-coumaric acid effectively suppressed endothelial cell migration, tube formation, and rat aorta ring sprouting [44]. It reduces intracellular and mitochondrial reactive oxygen species production [44]. In vivo *p*-coumaric acid significantly suppressed tumor growth in vivo by blocking angiogenesis. *p*-coumaric acid is found in various edible plants, such as carrots, tomatoes and cereals [44].

#### 4. 4-coumarate CoA ligase

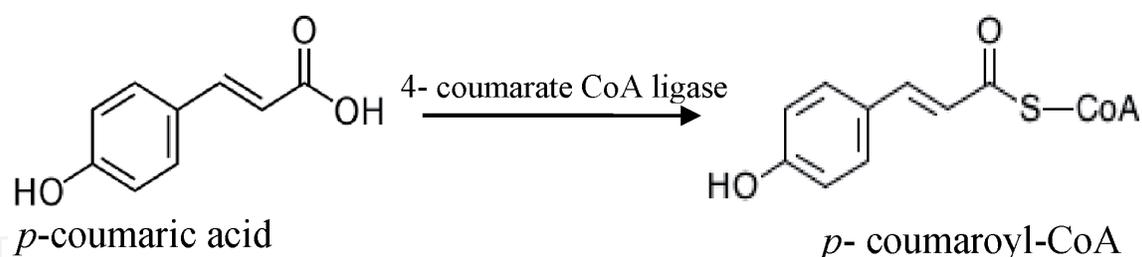
Ligases are a class of enzymes capable of catalyzing the merging of two large compounds by forming a new chemical bond, mostly accompanied by a small chemical group's hydrolysis on one of the large compounds or commonly causing the linkage of two mixtures together. Ligases are classified under EC 6 primary class of enzymes. They are also further group into six subclasses which are known as ligases that create carbon–oxygen bonds, carbon-sulfur bonds, carbon-nitrogen bonds, carbon–carbon bonds, phosphoric–ester bonds, and nitrogen–metal bonds [45, 46].

Coenzyme A (CoA) is a type of coenzyme that contains pantothenic acid, adenosine 3-phosphate 5-pyrophosphate, and cysteamine; which take part in the transfer of acyl groups, notably in transacetylations [47]. Coenzymes can be defined as organic molecules or compounds that many enzymes required to elicit a catalytic effect [48].



4-coumarate-CoA ligase (4CL) is essential to the general phenylpropanoid pathway and takes part in monolignol biosynthesis through the production of *p*-coumaroyl-CoA, a precursor for the biosynthesis of *p*-coumaryl alcohol and coniferyl alcohol in conifers. Essentially, *p*-coumaroyl-CoA is also involved in the production of other metabolites of plant as a precursor, including stilbenes and flavonoids [49].

4-coumarate-CoA ligase causes the joining of Coenzyme A to *p*-coumaric acid, leading to the formation of *p*- coumaroyl-CoA.



Coumaroyl-coenzyme A is a molecule or compound present in plants. It is the THIOESTER of coenzyme-A and coumaric acid. Coumaroyl-coenzyme A is a basic or fundamental intermediate in the biosynthesis of various natural products found in plants [50].

## 5. Chalcone synthase

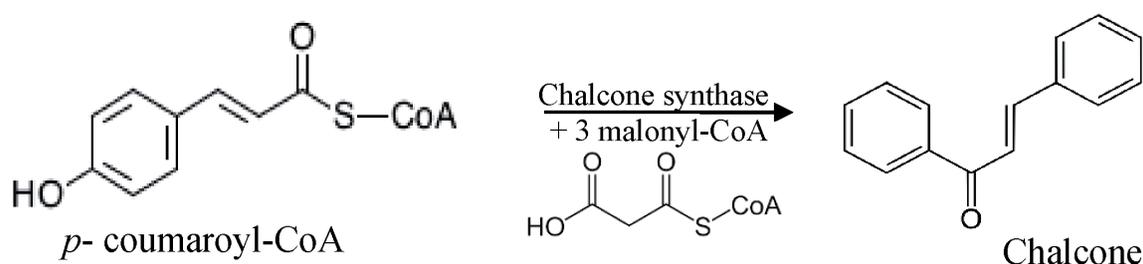
Synthases are enzymes that catalyze the formation of a particular compound. Chalcone synthase catalyzes the production of chalcone, in phenylpropanoid metabolic pathway.

Chalcone synthase (CHS) or naringenin-chalcone synthase is a member of the plant polyketide synthase superfamily, which also includes stilbene synthase (STS), acridone synthase, pyrone synthase, bibenzyl synthase, and *p*-coumaroyl triacetic acid synthase [51]. Polyketides are a ubiquitous group of secondary metabolites which contain either alternating carbonyl and methylene groups (-CO-CH<sub>2</sub>-)

or are derived from precursors which have alternating carbonyl and methylene groups [52].

Chalcone synthases, the most well-known representatives of this family, make available the materials needed to initiate various sets of metabolites (flavonoids). These metabolites have important diverse role to play in flowering plants, like the provision of floral pigments, antibiotics, UV protectants and insect repellents [53].

In the production of chalcone, one molecule of *p*-coumaroyl-CoA and three malonyl-CoA molecules condensation is required. This is catalyzed by the enzyme, chalcone synthase. This process starts with the transfer of a coumaroyl moiety from a *p*-coumaroyl-CoA which is the starter molecule to an active site cysteine (Cys164) [54]. The next that follows is the series of condensation reactions involving three acetate units obtained from three malonyl-CoA molecules, each proceeding through an acetyl-CoA carbanion derived from malonyl-CoA decarboxylation, extends the polyketide intermediate. Following generation of the thioester-linked tetraketide, a regiospecific intramolecular Claisen condensation forms a new ring system to yield chalcone [55, 56].



Malonyl-CoA is the starting molecule for the synthesis of fatty acid and its elongation. Malonyl-CoA is one of the foundations for the biosynthesis of some phytoalexins, flavonoids, and many malonylated compounds [57]. In plants and also in animals, malonyl-CoA is almost entirely obtained from acetyl-CoA by acetyl-CoA carboxylase [58].

Chalcone is an essential and resourceful molecule. It is a biogenetic precursor for flavonoids and isoflavonoids, which are bountiful in consumable plants. Chalcone contains two aromatic rings, linked together by a three-carbon- $\alpha$ ,  $\beta$  unsaturated carbonyl system, i.e., 1,3-diphenyl-2-propen-1-one derivative. Structurally, chalcones are one of the most divergent forms of flavonoids. Chalcone derivatives exhibit a wide range of therapeutic activities which include anticancer [58–62] antioxidants [63–67], anti-inflammatory [68–73], antihypertensive [74], antimalarial [75], antiulcer [76, 77], antiviral [78–81], antiprotozoal [82], cardiovascular activity [83] and mutagenic properties [84], and many other pharmacological properties.

## 6. Chalcone isomerase

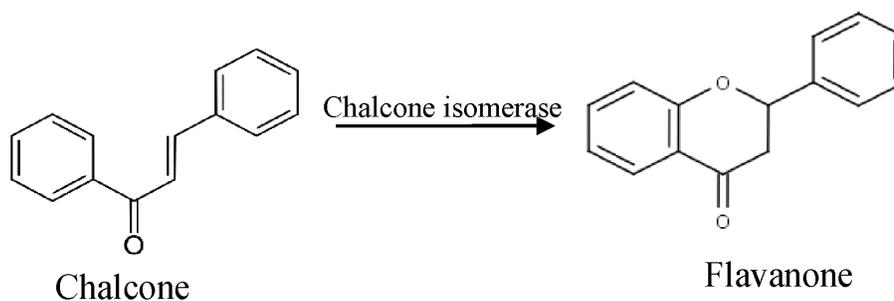
Isomerases are class of EC 5 primary enzymes that catalyze the reactions that involve the rearrangement of a molecule structure [46].

The first detected flavonoid pathway enzyme was Chalcone isomerase. It catalyzes the stereospecific cyclization of chalcones to (2*S*)-flavanones, which were found to be the exclusive substrates for the reactions to the formation of other classes of flavonoids [85].

Although this type of isomerization reaction can go on spontaneously, the rate of turnover can be increased by  $10^7$  fold in the presence of CHI [86]. The CHIs present in plants can be divided into four types (type I to type IV). This

division depends on its phylogenetic relationships [87]. Type I and type II are considered bona fide catalysts with representative CHI enzymatic activity. Type I CHIs are mostly found in vascular plants; they are responsible for forming general flavonoids [88, 89].

In comparison with Type I CHIs, type II CHIs have wider substrate acceptability, besides making use of naringenin chalcone as substrate, they also undertake the conversion of isoliquiritigenin to isoflavonoid which appear to be the specific metabolites in legume [90, 91]. Both type III and type IV CHIs do not participate in chalcone cyclization activity, unlike type I and type II CHI proteins. Due to this, they are termed CHI-like proteins (CHIL). Type III CHIs, which is extensively dispersed in land plants and green algae, have been shown to be fatty acid-binding proteins that function to influence the synthesis and storage of fatty acid in plants [92]. Nonetheless, the action of type IV CHIs which completely lose the bona fide CHI activity is not well known, yet new studies have revealed type CHI-fold proteins might serve as the enhancer of colouration of flowers and production of flavonoid in diverse plant species [93]. All CHIs have a similar backbone arrangement and type III CHIs are thought to be the common forebear of bona fide CHIs [92, 94]. CHI, also regarded as chalcone flavanone isomerase.



Flavanones are primarily found in about 42 larger plant families, specifically in Compositae, Leguminosae, and Rutaceae. Depending on the type of plants, flavanones can be found in all of the parts above and below ground, from vegetative parts to generative organs: branches, bark, stem, leaves, roots, flowers, fruits, seeds, rhizomes, peels, and others [95].

Flavanones show strong antioxidant and radical scavenging activity [96–103] and appear to be associated with a reduced risk of certain chronic diseases [98, 99] the prevention of some cardiovascular disorders [104–107] and certain kinds of cancer [108–112]. Flavanones also exhibit antiviral [113], antimicrobial, [114] and anti-inflammatory activities, [115] beneficial effects on capillary fragility, [116] and an ability to inhibit human platelet aggregation, [117] anti-ulcer [118, 119] and anti-allergenic [120] properties.

From flavanones other classes of flavonoids are biosynthesized with the aid of specific enzymes.

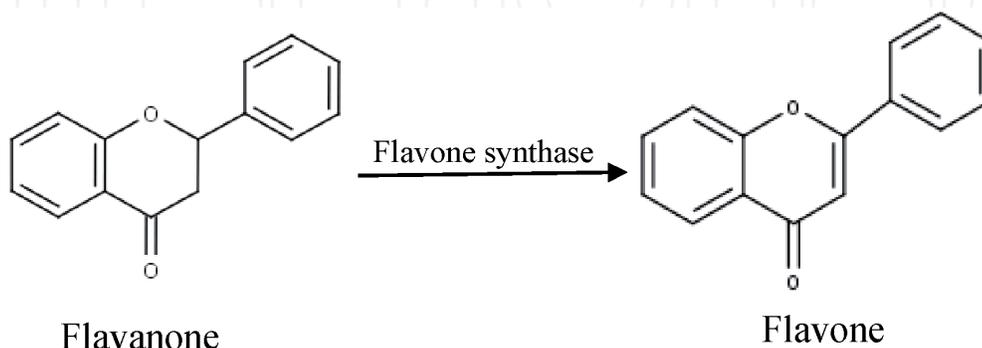
#### a. Flavones

Flavones are biosynthesized from flavanone with the aid of flavone synthase as catalyst. This enzyme catalyzes a double bond formation between C2 and C3 of flavanones.

Two FNS (I and II) enzyme systems have been described in dicots for flavone biosynthesis. FNSI is a soluble 2-oxoglutarate-dependent dioxygenase (2-ODD),

while FNSII is a cytochrome P-450-dependent monooxygenase enzyme system. FNSI and most FNSII enzymes convert flavanones to flavones directly [121].

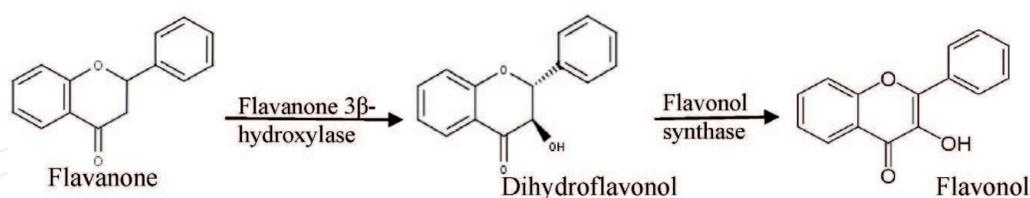
Flavones are one of the largest subgroups of flavonoids [121]. Flavones are involved in various interactions with microbes, insects, and other plants [122–124]. In addition to their extensive functions in plants' biochemistry and physiology, flavones are also essential for human nutrition and health [121, 125]. Their pharmacological effects, such as antioxidant, antiviral, anti-inflammatory activities and potential, have made these compounds increasingly popular as dietary constituents or supplements [121].



### b. Flavonol

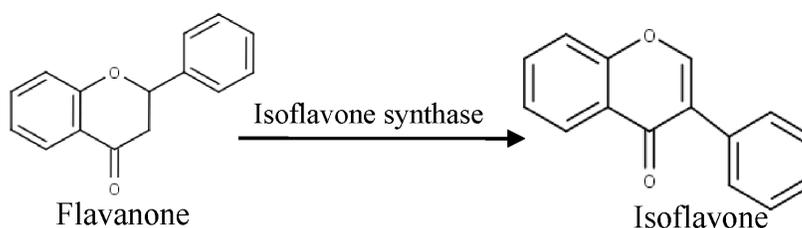
Flavonols are a major class of the family of flavonoids, molecules that have interesting biological activity such as antioxidant, antimicrobial, hepatoprotective, anti-inflammatory, and vasodilatation effects, and they have been considered as potential anticancer agents [126, 127]. Examples of flavonol include fisetin, quercetin, kaempferol, myricetin etc.

The biosynthetic pathway for the synthesis of flavonols is shown below.



### c. Isoflavones

Isoflavones are a polyphenol class usually found in legumes, including soybeans, chickpeas, fava beans, pistachios, peanuts, and other fruits and nuts [128]. Soybeans are the richest source of isoflavones, and soy foods and ingredients contain varying concentrations of isoflavones [129]. Isoflavones can be biosynthesized from flavanone with the aid of isoflavone synthase as a catalyst, as shown below.

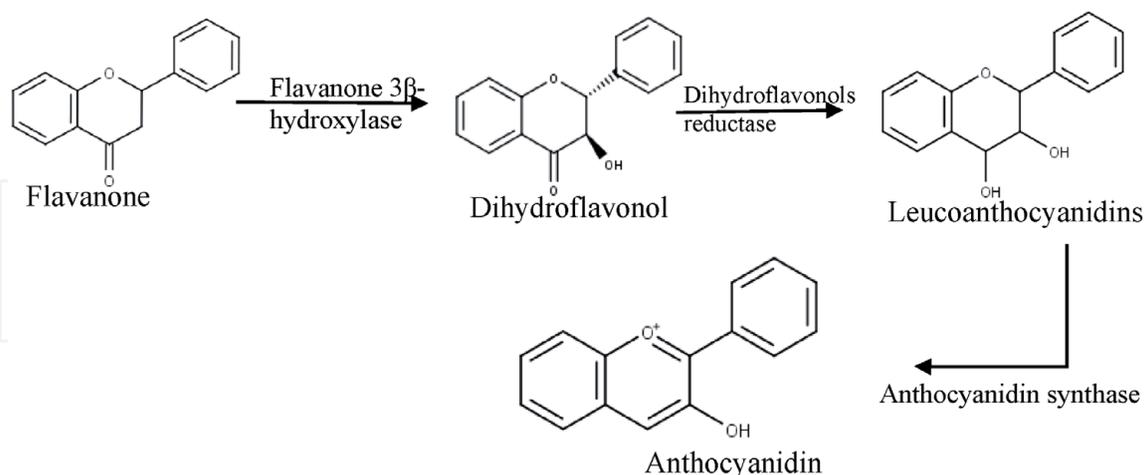


Common isoflavones include daidzin, genistin, biochanin A, and formononetin [130]. Isoflavones exhibit antioxidant, anticancer, antimicrobial, anti-inflammatory, antiosteoporotic, and estrogenic properties [131–136]. Several studies have also shown that isoflavonoids may contribute to other multiple additional health benefits by reducing cardiovascular risk, osteoporosis, and decreasing the intensity of bone resorption [137].

#### d. Anthocyanidins

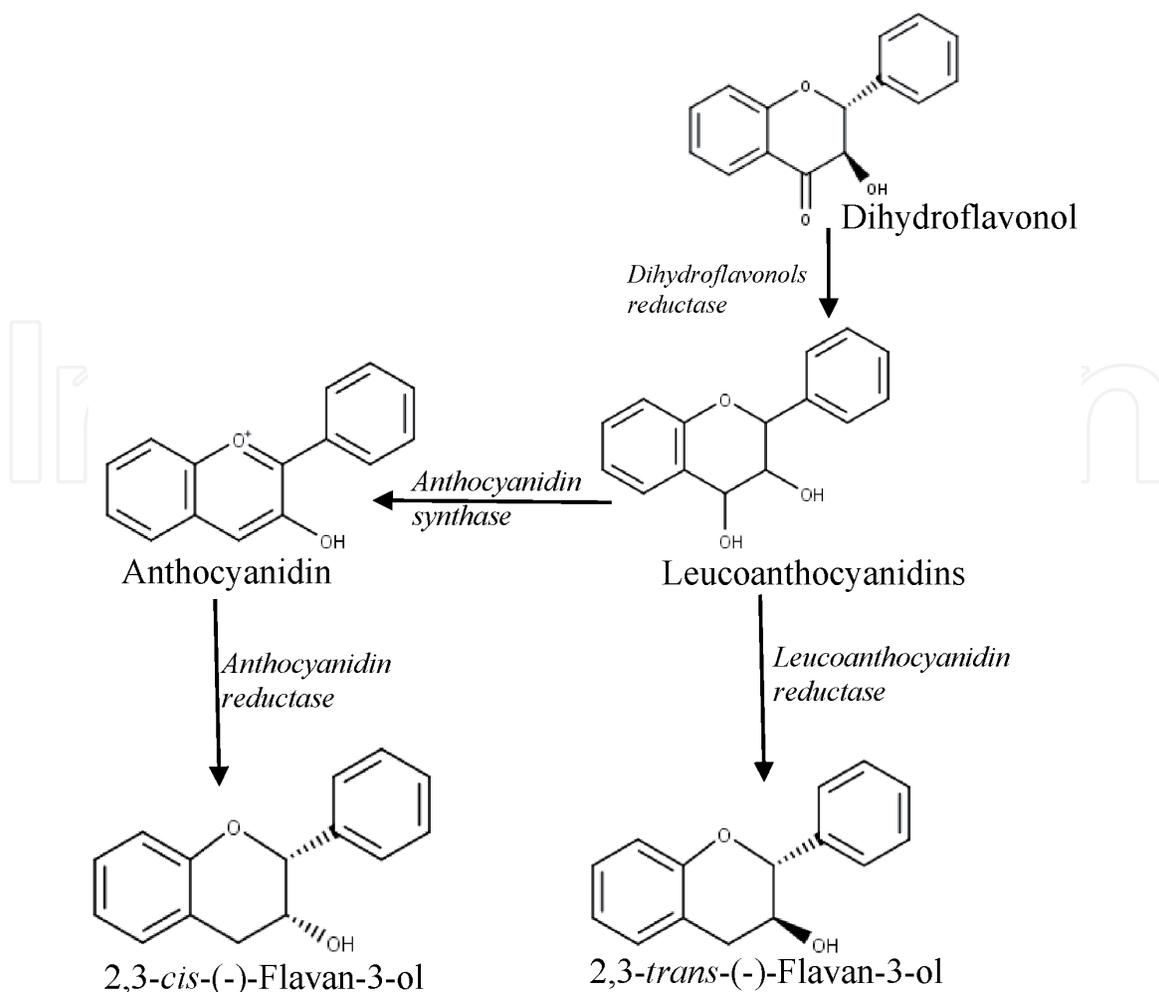
Anthocyanidins are a group of phytochemicals, which are natural pigments responsible for blue, red, purple and orange colors present in many fruits and vegetables and many fruits- and vegetable-based food products. Over and above 500 different anthocyanidins are known and described in the literature [138, 139]. This flavonoid group dominates teas, honey, fruits, vegetables, nuts, olive oil, cocoa and cereals. They can also be found in berries (e.g. black currant, blueberries, strawberries, elderberries), their juices, as well as red wine [140]. Cyanidin, pelargonidin, delphinidin, malvidin, petunidin and peonidin are the most common anthocyanidins present in fruits and vegetables.

The number and position of the hydroxyl and methoxyl moiety is the determinant of different types of anthocyanidins [141]. Anthocyanidins have been reported to have some essential pharmacological role in cardiovascular disease, cholesterol decomposition, visual acuity, as well as antioxidant efficacy, and cytotoxicity [142]. Anthocyanidins can be synthesized as shown below.



#### e. Flavan-3-ol

The most common flavonoids in the diet, flavan-3-ols are considered functional ingredients of beverages, fruits and vegetables, food grains, herbal remedies, dietary supplements, and dairy products. Flavan-3-ols have been reported to exhibit several pharmacological effects by acting as an antioxidant, anticarcinogen, cardio-preventive, antimicrobial, anti-viral, and neuroprotective agents [143]. Flavan-3-ol can be synthesized as shown below, from dihydroflavanol.



Flavonoids are an essential group of secondary metabolites that play so much role for the benefit of plants in which they exist or in their surroundings and for the health benefit of humanity. Understanding the biosynthetic processes of flavonoids and their pharmacological effects will aid proper utilization of flavonoids for health benefits and also draw more attention to the development of a synthetic laboratory process for the synthesis of flavonoid classes.

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