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FLAVONOIDS: CHEMISTRY AND BIOLOGICAL ACTIVITIES

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In this article is described the general characteristic of flavonoids, their chemical and biological activity. The article analyses the peculiarities of flavonoids and described their importance for plant and human health.

Keywords: *flavonoids, biological activities, chemistry of flavonoids*

Introduction. In the early 1960s, flavonoids were widely viewed as metabolic waste products that were stored in the plant vacuole. Whilst there was interest at that time in their function as flower colorants, and in their distribution between plant taxa, the earliest investigations of their biosynthesis had just begun.

Flavonoids — Advances in Research Since 1986 (edited by Jeffrey B. Harborne), appeared over a decade ago. Since then, advances in the flavonoid field have been nothing short of spectacular. These advances are particularly evident in the contributed chapters that cover: the discovery of a variety of new flavonoids; the application of advanced analytical techniques; genetic manipulation of the flavonoid pathway; improved understanding of flavonoid structures and physiological functions in plants and animals; and, perhaps most importantly, the significance of flavonoids to human health [1].

Flavonoids (figure 1) consist of a large group of polyphenolic compounds having a benzo-γ-pyrone structure and are ubiquitously present in plants. They are synthesized by phenylpropanoid pathway. Available reports tend to show that secondar metabolites of phenolic nature including flavonoids are responsible for the variety of pharmacological activities [1, 2]. Flavonoids are hydroxylated phenolic substances and are known to be synthesized by plants in response to microbial infection [3].

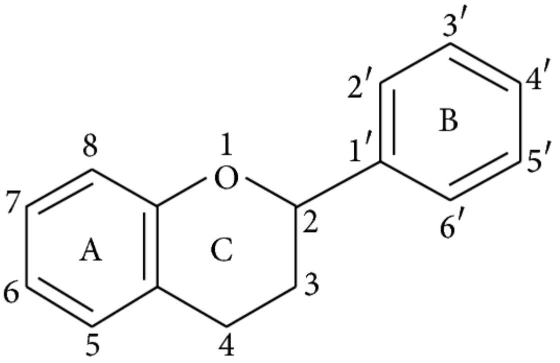

Fig.1. Basic flavonoid structure

The basic flavonoid structure is aglycone. Six-member ring condensed with the benzene ring is either a α-pyrone (flavonols and flavanones) or its dihydroderivative (flavonols and flavanones). The position of the benzenoid substituent divides the flavonoid class into flavonoids (2-position) and isoflavonoids (3-position). Flavonols differ from flavanones by hydroxyl group at the 3-position and a C2–C3 double bond [4]. Flavonoids are often hydroxylated in positions 3, 5, 7, 2, 3′, 4′, and 5′. Methyl ethers and acetyl esters of the alcohol group are known to occur in nature. When glycosides are formed, the glycosidic linkage is normally located in positions 3 or 7 and the carbohydrate can be L-rhamnose, D-glucose, glucorhamnose, galactose, or arabinose [5].

Chemistry and Biological Activities of Flavonoids. Flavonoids are a group of natural compounds with variable phenolic structures and are found in plants. In 1930 a new substance was isolated from oranges. At that time it was believed to be a member of a new class of vitamins and was designated as vitamin P. Later on it became clear that this substance was a flavonoid (rutin) and till now more than 4000 varieties of flavonoids have been identified [6].

Chemically flavonoids are based upon a fifteen-carbon skeleton consisting of two benzene rings (A and B as shown in Figure 1) linked via a heterocyclic pyrane ring (C). They can be divided into a variety of classes such as flavones (e.g., flavone, apigenin, and luteolin), flavonols (e.g., quercetin, kaempferol, myricetin, and fisetin), flavanones (e.g., flavanone, hesperetin, and naringenin), and others. Their general structures are shown in Table 1. The various classes of flavonoids differ in the level of oxidation and pattern of substitution of the C ring, while individual compounds within a class differ in the pattern of substitution of the A and B rings [6].

Flavonoids occur as aglycones, glycosides, and methylated derivatives. The basic flavonoid structure is aglycone (Figure 1). Six-member ring condensed with the benzene ring is either a α-pyrone (flavonols and flavanones) or its dihydroderivative (flavonols and flavanones). The position of the benzenoid substituent divides the flavonoid class into flavonoids (2-position) and isoflavonoids (3-position).Flavonols differ from flavanones by hydroxyl group at the 3-position and a C2–C3 double bond [5]. Flavonoids are often hydroxylated in positions 3, 5, 7, 2, 3’, 4’, and 5’. Methyl ethers and acetyl esters of the alcohol group are known to occur in nature. When glycosides are formed, the glycosidic linkage is normally located in positions 3 or 7 and the carbohydrate can be L-rhamnose, D-glucose, glucorhamnose, galactose, or arabinose [6].

Flavonoids are the most common and widely distributed group of plant phenolic compounds, occurring virtually in all plant parts, particularly the 3hotosynthesizing plant cells. They are a major coloring component of flowering plants. Flavonoids are an integral part of human and animal diet. Some food sources containing different classes of flavonoids are given in Table 1.

Table 1

Classification, structure, and food sources of some dietary flavonoids

Class	Flavonoid	Dietary source
1	2	3
Flavanol	(+)-Catechin (−)-Epicatechin Epigallocatechin Chrysin, apigenin	Tea
Flavone	Rutin, luteolin, and luteolin glucosides	Fruit skins, red wine, buckwheat, red pepper, and tomato skin

1	2	3
Flavonol	Kaempferol, quercetin, myricetin, and tamarixetin	Onion, red wine, olive oil, berries, and grapefruit.
Flavanone	Naringin, naringenin, taxifolin, and hesperidin	Citrus fruits, grapefruits, lemons, and oranges
Isoflavone	Genistin, daidzin	Soyabean
Anthocyanidin	Apigenidin, cyanidin	Cherry, easberry, and strawberry

Table 2 summarizes some of the medicinal plants rich in flavonoid contents.

Table 2

Medicinal plants rich in flavonoids contents

Plant	Family	Flavonoid
Aloe vera	Asphodelaceae	Luteolin
Acalypha indica	Euphorbiaceae	Kaempferol glycosides
Azadirachta indica	Meliaceae	Quercetin
Andrographis paniculata	Acanthaceae	5-hydroxy-7,8-dimethoxyflavone
Bacopa moneirra	Scrophulariaceae	Luteolin
Betula pendula	Betulaceae	Quercetrin
Butea monospermea	Fabaceae	Genistein
Bauhinia monandra	Fabaceae	Quercetin-3-O-rutinoside
Brysonima crassa	Malphigaceae	(+)-catechin
Calendula officinalis	Compositae	isorhamnetin
Cannabis sativa	Compositae	Quercetin
Citrus medica	Rutaceae	hesperidin
Clerodendrum phlomidis	Verbenaceae	Pectolinarigenin
Clitoria ternatea	Fabaceae	kaempferol-3-neohesperidoside
Glyccheriza glabra	Leguminosae	Liquiritin
Mimosa pudica	Mimosoideae	Isoquercetin
Limnophila indica	Scrophulariaceae	3,4-methlenedioxyflavone
Mentha longifolia	Lamiaceae	Luteolin-7-O-glycoside
Momordica charantia	Curcurbitaceae	Luteolin
Oroxylum indicum	Bignoniaceaea	Chrysin
Passiflora incarnate	Passifloraceae	Vitexin
Pongamia pinnata	Fabaceae	Pongaflavonol
Tephrosia purpurea	Fabaceae	Purpurin
Tilia cordata	Tiliaceae	hyperoside

Flavonoids possess many biochemical properties, but the best described property of almost every group of flavonoids is their capacity to act as antioxidants. The antioxidant activity of flavonoids depends upon the arrangement of functional groups about the nuclear structure. The configuration, substitution, and total number of hydroxyl groups substantially influence several mechanisms of antioxidant activity such as radical scavenging and metal ion chelation ability [4, 7]. The B ring hydroxyl configuration is the most significant determinant of scavenging of ROS and RNS because it donates hydrogen and an electron to hydroxyl, peroxyl, and peroxynitrite radicals, stabilizing them and giving rise to a relatively stable flavonoids radical [8].

Mechanisms of antioxidant action can include (1) suppression of ROS formation either by inhibition of enzymes or by chelating trace elements involved in free radical generation; (2) scavenging ROS; and (3) upregulation or protection of antioxidant defenses [9, 10]. Flavonoid action involves most of the mechanisms mentioned above.

Major molecular mechanisms of flavonoids action are given as follows: downregulation of mutant p53 protein, cell cycle arrest, tyrosine kinase inhibition, inhibition of heat shock proteins, estrogen receptor binding capacity, inhibition of expression of Ras proteins.

Metabolism of flavonoids in humans. The flavonoids secreted with bile in intestine and those that cannot be absorbed from the small intestine are degraded in the colon by intestinal microflora which also break down the flavonoid ring structure (Figure 2).

Oligomeric flavonoids may be hydrolyzed to monomers and dimers under influence of acidic conditions in the stomach. Larger molecules reach the colon where they are degraded by bacteria. The sugar moiety of flavonoid glycosides is an important determinant of their bioavailability. Dimerization has been shown to reduce bioavailability. Among all the subclasses of flavonoids, isoflavones exhibit the highest bioavailability [11]. After ingestion of green tea, flavonoid content is absorbed rapidly as shown by their elevated levels in plasma and urine. They enter the systemic circulation soon after ingestion and cause a significant increase in plasma antioxidant status [12].

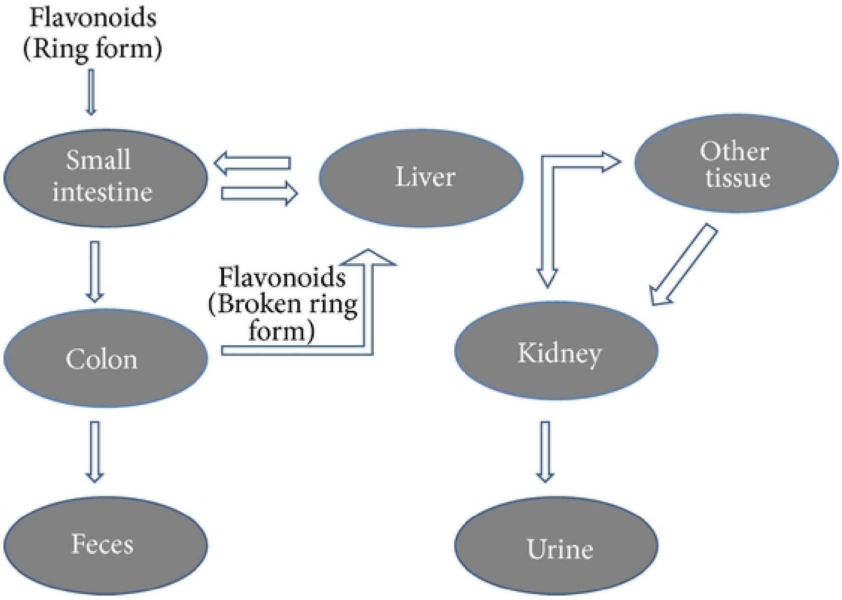

Fig. 2. Compartments involved in the metabolism of flavonoid

Flavonoids in Plants. Flavonoids have long been reported as serving multiple functions in plants [13]. Various abiotic and biotic factors helps in the generation of ROS in plants leading to oxidative stress. Flavonoid biosynthesis in plants is almost exclusively enhanced due to oxidative stress. They have capacity to absorb the most energetic solar wavelengths (i.e., UV-B and UV-A), inhibit the generation of ROS, and quench ROS once they are formed [14]. Flavonoids discharged primary UV-B screening functions when early plants moved from water to colonize the land. Extent of antioxidant capacity and ability to absorb UV-wavelengths depends upon the nature of substitution on different rings of flavonoids. Dihydroxy B ring substituted flavonoids have a greater antioxidant capacity, while their monohydroxy B ring substituted counterparts have greater ability to absorb UVwavelengths [14].

The most reactive hydroxyl groups (7-OH in flavones or the 3-OH in flavonols) in flavonoids are generally glycosylated. Glycosylation increases solubility in the aqueous cellular environment, protects the reactive hydroxyl groups from autooxidation [15], and allows the transport of flavonoids from the endoplasmic reticulum to various cellular compartments and their secretion to the plasma membrane and the cell wall [16]. Recent evidence shows that antioxidant flavonoids are located in the nucleus of mesophyll cells and within centers of ROS generation, that is, the chloroplast. Here they can easily quench H_2O_2, hydroxyl radical, and singlet oxygen [15, 16].

Oxidative stress due to an excess of excitation energy in the chloroplast may be aggravated under conditions that limit the diffusion of CO_2 to the carboxylation sites and the efficiency of carboxylation [15]. The environmental limitations to CO_2 assimilation rate include drought/salinity, low/high temperature, and nutrient scarcity. Under these conditions the activity of ROS detoxifying enzymes may significantlyreduce in the chloroplast [16, 17], which in turn upregulates the biosynthesis of ROS scavenging flavonoids. The reducing functions of flavonoids are of key significance in plants under severe stress conditions. These functional roles are concomitant with the very high concentration of dihydroxy B ring substituted flavonoids [18]. Flavonoids have been suggested as representing a secondary antioxidant defense system in plant tissues exposed to different stresses [14]. Lipid peroxidation is the common consequence of oxidative stress which disrupts the cell membrane integrity. Quercetin 3-O-rutinoside (rutin) may interact with the polar head of phospholipids at water lipid interface, enhancing membrane rigidity and consequently protecting membranes from oxidative damage [19].

CONCLUSIONS

Variety of flavonoids found in the nature possesses their own physical, chemical, and physiological properties. Structure function relationship of flavonoids is epitome of major biological activities. Medicinal efficacy of many flavonoids as antibacterial, hepatoprotective, anti-inflammatory, anticancer, and antiviral agents is well established. With the use of genetic modifications, it is now possible to produce flavonoids at large scale. Further achievements will provide newer insights and will certainly lead to a new era of flavonoid based pharmaceutical agents for the treatment of many infectious and degenerative diseases.

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ФЛАВОНОЇДИ: ХІМІЯ ТА БІОЛОГІЧНА АКТИВНІСТЬ

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У статті описана загальна характеристика флавоноїдів, їх хімія та біологічна активність. Проаналізовані особливості флавоноїдів та описана їх важлива роль для рослин і здоров'я людини.

Ключові слова: *флавоноїди, біологічна активність, хімія флавоноїдів.*

ФЛАВОНОИДЫ: ХИМИЯ И БИОЛОГИЧЕСКАЯ АКТИВНОСТЬ

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В статье описана общая характеристика флавоноидов, их химия и биологическая активность. Проанализированы особенности флавоноидов и описана их важная роль для растений и здоровья человека.

Ключевые слова: *флавоноиды, биологическая активность, химия флавоноидов.*