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Der Pharmacia Lettre, 2021, 13(9): 05-10
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Pharmacognosy and Phytochemistry of Flavonoids

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ABSTRACT

Flavonoids commonly known as polyphenolic compounds most abundantly found in plant-originated foods, All naturally occurring Flavonoids can be classified into flavonoids, flavones, flavonols, flavanones, isoflavones, and anthocyanidins. They have been demonstrated to possess various potential activities such as strong antioxidant, antiviral, antibacterial, anticancer, and disease-preventing properties especially for various degenerative diseases such as cancers and cardiovascular diseases. This review has summarizes the key differences in pharmacokinetic properties such as log P, log Kp, solubility, half-life, absorption, metabolism etc. and focussed various biological activities of flavonoids and flavones.

Keywords: Flavonoids, Antioxidant, Anticancer, Enzyme inhibition, Pharmacokinetic study.

INTRODUCTION

Flavonoids are plant-based compounds, they belong to a class of low-molecular-weight phenolic compounds that are widely distributed in the plant kingdom, obtained from a variety of leaves, fruits, and flowers, shows enormous health benefits [1]. Naturally occurring Flavonoids are primarily classified into six types, each of which has health-promoting effects, like flavonols, flavones, flavan-3-ols, flavanones anthocyanin's, isoflavones, catechin, chalcone etc. (Figure 1). These all six types of Flavonoids can be obtained from a variety of fruits, vegetables, grains, bark, roots, stems, flowers, tea, and wine [2]. Flavonoids are present in different parts of plants, so they can be easily extracted from these. Many scientists have shown the health benefits of these phytochemicals in their respective studies. Researchers have found that eating a diet rich in flavonoids reduces the risks of cardiovascular disease, diabetes, anti-oxidative, anti-inflammatory, antiviral, alzheimer's disease, atherosclerosis, anti-mutagenic and some cancers [3]. They are also known to be potent enzyme inhibitors such as xanthine oxidase, cyclooxygenase, aromatase, lipoxygenase, and phosphoinositide 3-kinase. In addition, they play a very important role in plants, animals, and bacteria also. In-plant flavonoids are naturally synthesized in specific sites and distribute aroma and colors to

flowers, in the fruit, they are responsible for the attraction of pollinators and help in spore germination. Flavonoids protect plants from different biotic and abiotic stresses and act as unique UV filters [4]. Recent advances in ruminant nutrition researches suggest that flavonoids help on the fertility and wellness of animals, it was reported that the increase in milk yield and lactation performance in dairy cows were observed after administration of sylimarin in the feed (10 g/d) which mainly consist of flavonolignans. Flavonoids have been reported to have antibacterial activities (Figure 1).

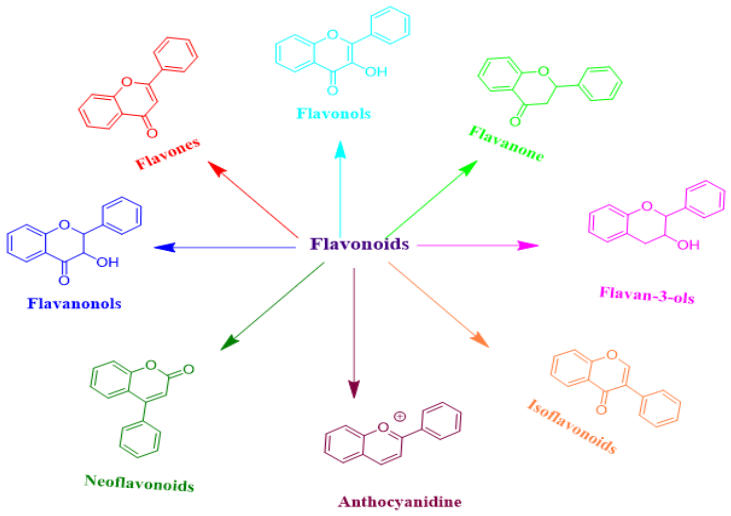

Figure 1: Classification of naturally occurring flavonoids.

PHARMACOKINETICS OF FLAVONOIDS

Virtual prediction of ADME properties was done from chemical structure by using ACD/ADME suite free version that is a collection of software modules that provide predictions relating to the pharmacokinetic profiling of compounds. Pharmacokinetic parameters of some flavone and flavonoids [5].

Average daily intake

Worldwide the mean intake of flavonoids ranges between 150 and 600 mg/day, this range may get vary in negligible amount in the population with low/high black tea intake, such as UK (from 500-1000 mg/day). This intake may vary from country to country, quercetin is the most important component estimated in the intake of Flavonoids (Table 1).

Compound	Log P	Log Kp	Half life	Absorption	Bioavailability score
Flavone	3.96	-4.78 cm/s	26-46 h	GIT	0.55
Flavonol	2.84	-4.23 cm/s	2.4 h	GIT	0.55
Isoflavone	3.09	-5.40 cm/s	4-8 h	Intestine	0.55
Quercetin	1.23	-7.05 cm/s	25 h	GIT	0.55
Apigenin	1.73	-6.25 cm/s	12 h	lumen and the wall of the stomach	0.55

Table 1: Pharmacokinetic parameters of few Flavonoids.

Absorption

In nature flavonoids present in both glycone and aglycone form, but most predominantly present in the glycosylated form [6]. Research has shown that glycosylated form (quercetin) absorbs more readily than the aglycone form, but this statement of research remains in doubt as catechins, which is not glycosylated in nature, is absorbed relatively efficiently.

Sources of flavonoids and health benefits

Black tea is a rich supply of a variety of polyphenols including flavones, flavonols, and phenolic acids. From these catechins, theaflavins, kaempferol, quercetin and gallic acid are present in plenty amount in black tea [7]. Black tea boosts internal antioxidant property and regulates many biological processes like inflammatory responses, blood sugar level, lower the risk of cancer, may improve the perception, reduces cardiovascular risks, resist skin from UV radiations. Flavonoids are present in many fruit's like citrus fruits which have antioxidant, antibacterial and antiviral properties [8]. Consumption of flavonoids rich vegetables protects us from chronic diseases from the vegetable source onion shows good antioxidant property along with helps to prevent tooth decay, boost immunity. Different sources and their average intake in different countries are shown in Table 2.

Countries	Intake of Flavonoids (mg/day)	Source
Australia	696	Black tea
Spain	443	Fruit
France	436	Fruit, tea, red wine
Italy	364	Fruit
Finland	209	Berries, Fruit
Poland	898	Tea, Cocoa
Brazil	54.6	Citrus fruit, beans
China	225	Soy, Pome, Fruit
Korea	318	Fruit, tofu, onions

Table 2: Average intake of flavonoids in different countries.

Metabolism

After oral absorption flavonoids are extensively metabolized in the small intestine and go through the liver as conjugates of O-methylation, sulfation, and glucuronidation [9]. Non absorbed flavonoids go to the colon where it is degraded by colonic microflora and metabolized in the liver. All the metabolites are eliminated through biliary or urinary routes [10].

Contraindications

Researchers found that lipo-flavonoid plus is contraindicated with the following.

Allergies: Ascorbic acid (Vitamin C), Niacin preparations, Nicotinamide analogues, Riboflavin (Vitamin B-2), Vitamin B, Vitamin B_6 Preparations–Pyridoxine, Vitamin B_1 preparations–Thiamine, Bioflavonoids.

Toxicities: Due to the consumption of a high dosage of flavonoids daily, potential safety issues may be persisted to a normal human being. Flavonoids with phenolic ring oxidized by peroxidase enzyme to form cytotoxic phenoxyl radicals, catechol containing flavonoids have been observed to bind with DNA, Protein, hepatotoxicity found by epigallocatechin gallate which is present in green tea.

Biological activities

Flavonoids and their derivatives manifest enormous pharmacological activities, in literature, they are good cardio protective, anti-inflammatory, antioxidants, anticancer, antiviral, anti-HIV, along with it also found that they are good hormones suppressor and enzymes inhibitors, few of them are discussed below [11].

Cardio protective

Flavonoids are an essential component of food so it is also called 'Functional food' due to their antioxidant activity they have a good impact on the vascular system. In the cardiovascular system, flavonoids show antihypertensive, anti-atherosclerotic, antiplatelet activities and are potentially used in the treatment of myocardial ischemia [12]. In their work, demonstrated the cardio protective activity of different f lavonoids on the heart of Langendorff-perfused rat having ischemia discussed in their review that luteolin is one of the flavones and decreases blood pressure in spontaneously hypertensive rats and helps in the improvement of vascular relaxation in the aortic ring. Luteolin causes relaxation by stimulation of NO-dependent and independent mechanism in the endothelium, in which luteolin increases cAMP level by inhibiting phosphodiesterase enzyme so, accumulation of cAMP activates endothelial Nitric oxide synthetize and increases the level of nitric oxide in endothelial cells.

Anti-inflammatory

Inflammation is a biological response of our body that is common in various diseases like asthma, gout, arthritis, carcinoma, diabetes, multiple sclerosis, bacterial and viral infection, etc [13]. It is caused by the releases of various inflammatory mediators like prostaglandins, leukotrienes, histamines, serotonin, etc. These mediators are released due to the stimulation of signaling pathways which involves cyclooxygenase, and kinases, the anti-inflammatory activity of isolated compounds were assessed through the inhibition of nitric oxide formation, ten compounds were shown significant effect than the standard drug Dexamethasone synthesized different flavone derivatives and evaluated them against the production of nitric oxide and prostaglandins E_2, in which compound 3 g was more potent against both the mediators.

Antioxidant

Antioxidants can prevent the damage of the living tissues by preventing the oxidation of biomolecules which are taking place by a high level of free radicals in a living system [14]. This oxidation can lead to tissue damage, death of cells, and cause of various diseases like cancer, cardiovascular diseases, skin diseases, and inflammation, etc. Antioxidants act in two ways: prevention of oxidation and chain-breaking antioxidants. Various natural and synthetic derivatives flavones and flavonoids potentially act as antioxidants by both the mechanism reported the synthesis and antioxidant activity of flavones and chalcones. Compounds were tested for radical scavenging activity by four models, 1,1-Diphenyl-2-picrylhydrazyl radical assay, 2,2-azinobis (3-ethylbenzothiazoline-6-sulphonic acid), nitric oxide, and lipid peroxidation scavenging assays.

Anticancer

Cancer is one of the death-causing health hazards. Incidence and mortality of cancer are consistently rising universally. As per the survey of the International Agency on Cancer Research, There may be chances of 18.1 million new cancer cases and 9.6 million deaths in 2018. In literature, it comes to know that flavonoids can inhibit carcinogenesis *in vitro* and some shreds of evidence prove that flavonoids can do so *in vivo* also evaluated anticancer activity of 28 different derivatives of flavonoids on human acute myeloid leukemia cell line HL-60, and activity was compared against known anticancer agents. Eight compounds were shown inhibition of growth of HL-60 cell line with IC-50 value 10-940 ng/ml [15]. The flavonoid genistein was shown the highest activity which was almost equivalent to known anticancer agents.

Literature also shows that fermented soya milk contains a larger amount of genistein and daidzein as compared to unfermented milk, when the mixture of this fermented milk and isoflavone given to rat at seven-week of age it helps to inhibit mammary carcinogenesis which was induced by 2-amino-1-methyl-6-phenylimidazo [4,5-b] pyridine.

Enzyme inhibition

Flavonoids are found to be active at the inhibition of certain enzymes like topoisomerase, acetychloliestrase, xanthine oxidase, cyclooxygenase, aldehyde oxidase, and aromatase enzyme. Topoisomerase is an enzyme that can inhibit DNA metabolism, the agents which will be activated through the inhibition of this enzyme will potentially act as anti-cancer agents. There are so many compounds that are found to be topoisomerase inhibitors, quinoline derivatives, Flavonoids derivatives, metal complexes, fatty acid, etc. Angiotensin-converting enzyme inhibitors play their vital role in the regulation of blood pressure different Flavonoids for *in vitro* ACE inhibitor activity by fluorimetric method for which two concentrations were taken 100 µM and 500 µ. Luteolin was found highly active ACE inhibitors with an IC-50 value of 23 µM. Recently Flavonoids are reported to have aromatase enzyme inhibitory activity. The aromatase enzyme is responsible for the development of hormone-dependent breast tumors.

CONCLUSION

It is concluded that due to the over expression of aromatase enzyme in breast tissues, increases the level of estrogen through the conversion of androgen, Cancerous cell depends on estrogen for the growth and progression which leads to the development of estrogen-dependent breast tumor. Flavonoids have structural similarity with the natural substrate of the aromatase enzyme so it is easily recognized by the enzyme to bind with active amino acid residues in the binding pocket of enzymes. In their study reported the synthesis of methylated flavones and evaluated the compound against aromatase enzyme in which 7-methoxy flavones and 2,4-dihydroxy flavones were potent with an IC-50 value of 2-9 µM.

CONFLICT OF INTEREST

The authors have no conflict of interest.

ACKNOWLEDGMENT

The authors are grateful to the G H Raisoni group and University Department of Pharmaceutical Sciences, for supporting the authors for the completion of this mini review.

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