Review article

Application and properties of selected flavanones

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Abstract: *Flavanones, secondary plant metabolites, are one of the main group of flavanoids. They are widely spread in nature in many plants. The large diversity of structural structure of flavanones and controlled methods of modifying their molecules have a huge impact on biological activity. The present review will summarize the current knowledge about occurrence, obtaining by chemical synthesis, application and bioactivity of flavanones. Also, they are received from specific chemical synthesis. Flavanones have a great biological activity. Derivatives of flavanone have many different properties such as anti-inflammatory, anticancer, antioxidant, antimicrobial or hepatoprotective activities. These natural polyphenolic compounds are used in cosmetology, pharmacy and medicine. The demand and usage on them increases.*

Keywords: *flavanones, flavonoids, secondary plant metabolites, biological activity.*

Introduction

Nowadays, there is a fashion for a healthy lifestyle related to dietary food replacing fatty foods with light and tasty plant-derived products rich in polyphenols, and thus flavonoids and flavanones [1]. Phenolic secondary metabolites present in plant-derived food exact beneficial effects in the prevention of cardiovascular disease or cancer [2]. These secondary metabolites have many interesting and valuable properties such as antioxidant [3], antiviral [4], antifungal [5], antiinflammatory [6], antitumor [7], antimicrobial [8] activities. Polyphenols may be classified into different groups. One of the largest groups of them are flavonoids [9]. Recently, the most-described and growing class of flavonoids are flavanones. In the last few decades, studies on flavanones, such as naringenin, hesperitin and their natural and synthetic derivatives, have disclosed many interesting results regarding their new application possibilities in medicine and cosmetology [10, 11, 12, 13].

In this review, the diversity, biological activities and various applications of natural and synthetic flavanone derivatives will be presented.

Characteristic of flavanones

Flavanones are the main precursors of flavonoids like flavones, isoflavones or flavanols. Flavanone is one of the chemically modified metabolic form of flavonoids. Bioavailability and bioactivity of flavanones depend on their chemical modification. They are important natural compounds with significant activities and various aromatic constituents. Flavanones have a huge potential in cancer chemotheraphy, cardiovascular diseases and many others.

Structure and occurrence of flavanones

Flavanones can be divided into two groups – natural and synthetic compounds. The main core of these molecules is flavanone (Fig. 1).

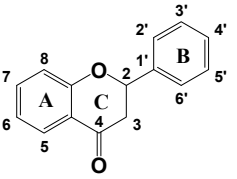

Figure 1. Chemical structure of flavanone

The flavanone class comprises a wide range of compounds with substitutions at the A- or B-ring, e.g., hydroxy, methoxy, methylenedioxy, O- and C-glycosyl, C-methyl, C-benzyl, C-hydroxymethyl, C-formyl, C-isoprenyl substituents (including furano or dihydrofurano rings), conjugations to stilbene, anastatin, phenolic acid, and diarylheptanoid moieties. Several examples are presented in Fig. 2 [14, 15, 16].

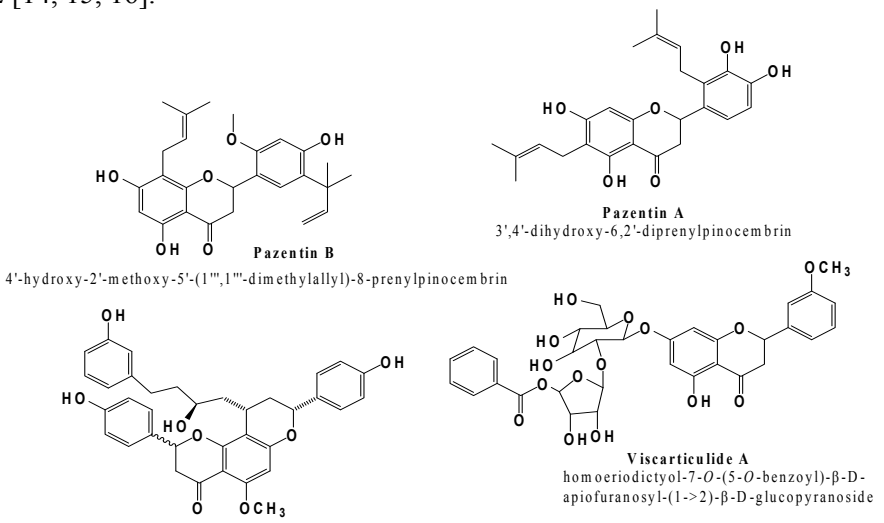

Figure 2. Chemical structure of several natural flavanones [14, 15, 16]

In nature, flavanones occur in aglycone and glycosidic form. in every part of many higher plants from families such as *Compositae*, *Leguminosae* and *Rutaceae* [17]. However, the highest amounts of these compounds are present in citrus fruits like grapefruit, sweet and sour orange, tangelo [14].

Natural derivatives of flavanone

Natural derivatives of flavanone can be found in higher plants. Among flavanones the naringenin and hesperetin in the form of aglycone and glycoside are of particular interest because of their high prevalence in foods. A discussion about natural derivatives based on current literature is presented below.

Naringenin

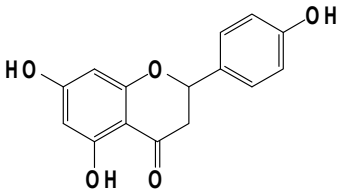

Figure 3. Structure of naringenin

Naringenin (5,7,4'-trihydroxyflavanone) (Fig. 3) is a hydroxyl derivative of flavanone. Naringenin can be found in the aglycone (naingenin) and glycosidic forms (naringin and narirutin). This flavanone occur in high concentration in citrus fruits (oranges, grapefruits, tangerines and tangelo [18]), mature peach seeds and in low concentration in tomatoes and their products. The naringenin chalcone occurs in higher quantity in tomato peel than naringenin [14]. Naringenin reduces cholesterol and exhibits the anticancer, antiinflammatory, antiulcer, diastolic, estrogenic, protective skin activities [18, 19, 20, 21].

Naringenin exerts anti-estrogenic activity in the presence of ERα receptors, whereas in the presence of ERβ receptors present a similar effect to 17 β-estradiol. Naringenin inhibits the aromatase and 17 β-hydroxysteroid dehydrogenase (17 β-HSD) activity in very high degree. Also, naringenin has antiproliferative activity against a number of human tumor cell lines including MCF-7 [18, 22, 23, 24].

Naringenin reduces total cholesterol and weaker high-density lipoprotein level (HDL). For example naringenin, in compare with rutin and nicotinic acid, decreases in a large extent the HDL level [18, 25, 26, 27].

Apolipoprotein in the liver (apoB-Lp) is a substrate of a number of hyperlipoproteinemias, including hyperlipidemia and hypercholesterolemia. Overproduction of apoB-Lp causes atherosclerotic changes in the peripheral and cerebral vessels. Naringenin reduces the secretion of apolipoprotein (apoB) and selectively increases its degradation in hepatocytes [26]. In addition, this flavanoe inhibits the synthesis of cholesterol esters by inhibiting the expression and activity of cholesterol acyltransferase (ACAT), an enzyme catalyzing its esterification. Naringenin also has anti-aggregatory activity due to the inhibition

of phosphodiesterases of cyclic nucleotides in the platelets, thus preventing atherosclerosis [18, 26, 28].

Naringenin has an effect on intestinal cramps but compared to chrysin, its activity is smaller [18, 29, 30].

Histamine is one of the factors that influence on the gastric acid secretion. Its excessive production and release causes peptic ulcer disease. Naringenin shows the antihistamine effect, inhibiting histamine decarboxylase and stabilizing mast cells [18, 31].

Bae, Han and Kim [32] presented that naringenin is a weak inhibitor of the bacterial enzyme urease and prevents the growth of *Helicobacter pylori*.

Naringenin due to the lack of a double bond and having only one -OH group at the B-ring shows the weaker antioxidant activity [18, 29, 33, 34].

Naringenin containing three hydroxyl groups reduces Cu^{2+} ions more strongly than apigenin. Both chemical compounds containing three hydroxyl groups [35]. Moreover, flavanones and isoflavones, in contrast to flavones and flavonols, do not form chelates with Cu^{2+} and Fe^{3+} ions [18, 29, 35].

Naringenin reduces the neurotoxic effect induced by the β-amyloid peptide. In research on mice with amnesia activated by scopolamine, naringenin slowed the memory loss process [36, 37].

Naringenin stimulates the blood circulation of the retina. In studies conducted in rats, positive effects were found in recuperation of the retina after induction of its ischemia. A similar experiment was carried out on rabbits, comparing the healing effects of flavonoids differing in the number of hydroxyl groups per molecule. It was found that compounds with 3 hydroxyl groups, such as naringenin, increase the blood supply to the eyeball most intensively by stimulating blood flow in the blood vessels.

Hesperetin

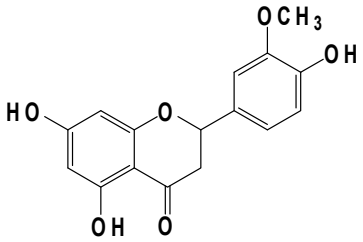

Figure 4. Structure of hesperetin

Hesperetin (4'-methoxy-5,7,3'-trihydroxyflavanone) belongs to flavanones (Fig. 4). Hesperetin in the form of glycoside (hesperidin) is the dominant flavonoid in lemons, limes, oranges, tangerine and tangor species of citrus fruits. Another glycoside of hesperetin is neohesperidin [14].

Hesperetin is a cholesterol-lowering flavanone. The flavanone reduces the mass of cholesterol ester and inhibits the secretion of apolipoprotein B (ApoB) to 80% [38].

This compound also demonstrates antioxidant, antiallergic, hypolipidemic, anticoagulant, angioprotective (protecting blood vessels), anticancer, anti-inflammatory and antifungal activity. Hesperetin may be helpful in the treatment of hypertension due to its properties. Moreover, hesperetin has antifungal activity [11, 14, 39].

In studies investigating the efficacy of flavanones obtained from citrus residues to prevent patulin contamination (PAT), the results showed that hesperetin and other flavanones are effective in controlling PAT and completely inhibiting PAT accumulation in *A. terreus* [40]. Hesperetin, like naringenin, has a protective effect on the skin. Miller and others examined effects of citrus flavanones naringenin (NAR) and hesperetin (HES) on the status of antioxidants in the liver and the composition of the phospholipid membrane in 24-month-old rats. Both flavanones did not affect liver histology but reduced the levels of alanine aminotransferase and aspartate aminotransferase in serum [41].

Recent studies showed that flavonoids might have beneficial neuropharmacological effects including antidepressant and anticonvulsant properties. Hesperetin may also effectively protect neurons from damages induced by oxidative or nitrosative stress. Citrus flavanones also have antidepressant effects through mechanisms that differ from conventional antidepressants [39].

Hesperetin reduces intracellular replication of viruses including herpes virus type 1, poliovirus type 1, parainfluenza virus type 3 and respiratory syncytial virus [42].

Hesperetin in clinical use is restricted due to its poor water solubility. Additionally, folate receptor is overexpressed in various cancer cells. Therefore, the chitosan folate hesperetin nanoparticles (CFH) were synthesized by covalently conjugating folic acid with chitosan molecules. The size of CFH nanoparticles is about 450 nm, which is advantageous in the case of passive targeting of the tumor cell, especially due to leaky tumor vascularization. The test results confirm that hesperetin induces apoptotic cell death in HCT15 cells and CFH increase the Bax and Bad expression levels to induce apoptosis [43].

Other natural flavanones

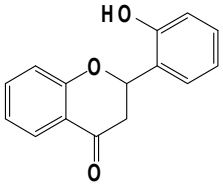

Figure 5. Structure of 2'-hydroxyflavanone

2'-hydroxyflavanone (Fig. 5) is another representative of flavanones. This compound was isolated from *Mimosa pudica* (L.) whole plant and was found to exhibit anti-inflammatory effects in vitro [44]. 2'-hydroxyflavanone derivatives were synthesized from the alkylation at 2'-OH position of 2'-hydroxyflavanone

and examined against pro-inflammatory mediators (TNF-α, 1L-1β and NO) *in vitr*o and *in vivo* models. Scheme of synthesis is presented in Fig. 6 [45].

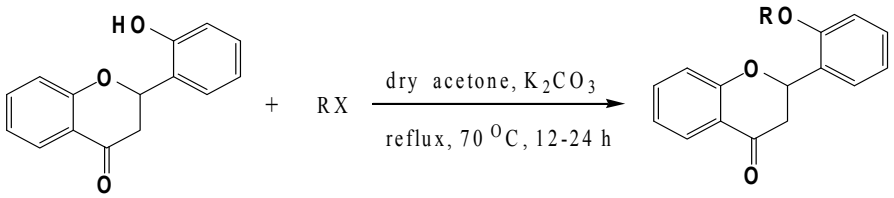

Figure 6. Synthetic scheme of synthesis 2'hydroxyflavanone derivatives [45]

These derivatives showed inhibition of lipopolysaccharide (LPS), pro-inflammatory mediators and comparable anti-inflammatory activity with ibuprofen in carrageenan-induced rat paw edema assay [45].

Two prenylated flavanones, pazentin A (3',4'-dihydroxy-6,2'-diprenylpinocembrin) and pazentin B (4'-hydroxy-2'-methoxy-5'-(1''',1'''-dimethylallyl)-6-prenylpinocembrin) (Fig. 2) and four derivatives of Pazentin A and B (Fig. 7 and Fig. 8) were isolated from *Dalea pazensis Rusby* by the benzene extraction of the roots. The compounds were evaluated *in vitro* for their inhibition on mushroom tyrosinase enzyme and activity on melanogenesis in B16 murine melanoma cells. This information obtained may be relevant to the knowledge of the structure-activity relationship for these flavanones in order to investigate the rational design of skin whitening agents [15].

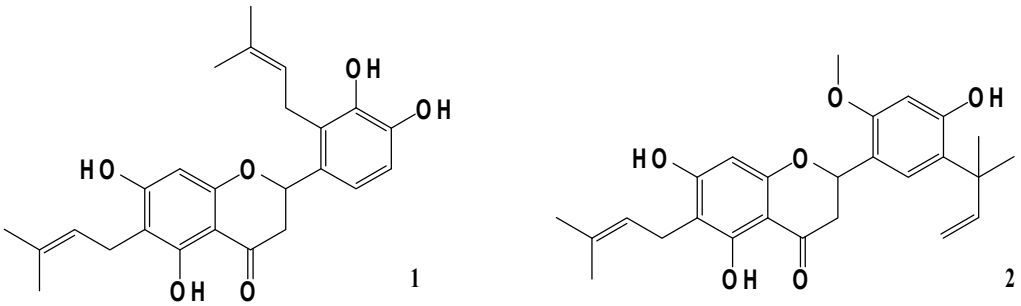

Figure 7. Structures of Pazentin A and Pazentin B derivatives [15]

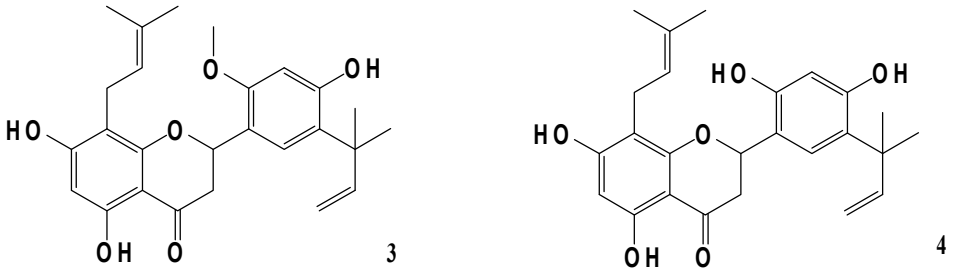

Figure 8. Structures of Pazentin A and Pazentin B derivatives [15]

Synthetic flavanones

Synthetic flavanones can be obtained through various syntheses. For example 2'-hydroxyflavanone and 2'-O-alkylated derivatives of 2'-hydroxyflavanone were prepared by using alkylating reagents in acetone [45], flavanone and thiosemicarbazide reacted in the hot ethanol (EtOH) or in DMSO environment [46], the synthesis of hesperidin (3',5,7-trihydroxy-4'-methoxy-flavanonees-7-rhamnoglucoside) using sulfuric acid (VI) H_2SO_4 in anhydrous methanol (CH_3OH) [47]. Derivatives of flavanones can be also synthesized from 2-hydroxybenzoic acids [34]. The general scheme of synthesis of flavanone with primary amine was presented in the Fig. 9.

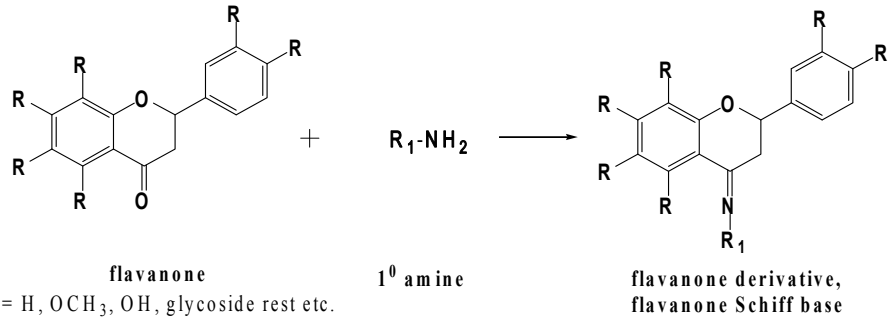

Figure 9. General scheme of synthesis of flavanone Schiff bases

Farrerol (Fig. 10) isolated from *Cyrtomium devexiscapulae* and *Cyrtomium laetevirens* is a flavanone-type-compound and may have potential anti-hypertension and anti-atherosclerosis application [48].

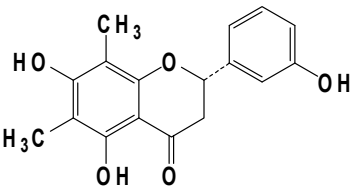

Figure 10. Structure of Farrerol

New flavanone derivatives of farrerol were synthesized by a typical synthetic method with using nitration reaction. Some of the synthesized compounds exhibited promising anti-tumor, cytoprotective and anti-vegetation activities [49].

Benzyl-1,2,3-triazolyl hesperetin derivatives were obtained by azide-alkyne cycloaddition with using hesperidin (Fig. 11). This generate semi-synthetic natural product derivatives utilizing copper-catalyzed. All final reaction components were analyzed in terms of DPPH (2,2,-diphenyl-1-picrylhydrazyl) and ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid) scavenging effects, cancerous cell inhibitory effects against cervical (HeLa and CaSki) and ovarian (SK-OV-3) cancer cell lines. Molecules bearing electron donating (ED) groups demonstrated

scavenging activities both for DPPH and ABTS radicals and inhibiting property against cervical cancer cell lines (CaSki). Whereas molecules holding electron withdrawing groups (EWD) presented better results against cervical cancer cell lines (HeLa). Both EWD and ED based molecules exercised similar action against ovarian cancer cell line [47].

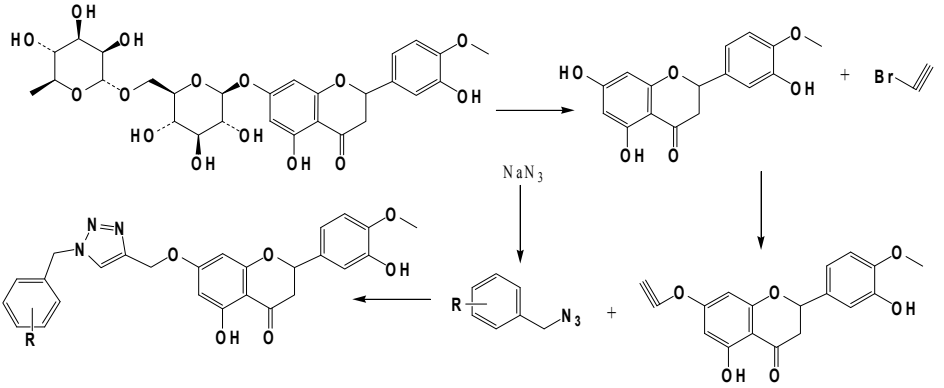

Figure 11. Synthesis of substituted benzyl-1,2,3-triazolyl hesperetin derivatives

Flavanone-metal ion complexes display biological activity in many assays measuring DNA binding, anti-tumor, antioxidant, anti-inflammatory, DNA intercalation and anti-coagulant activities. It is innonative and promising class which can act as selective cholinesterase inhibitors (ChEls). Group of scientists [50] synthesized new series of flavanone derivatives (hesperidin, hesperetin, naringin and naringenin) complexed with copper (II) or zinc (II) ions (Fig. 12) and evaluated their potential use as selective ChEls.

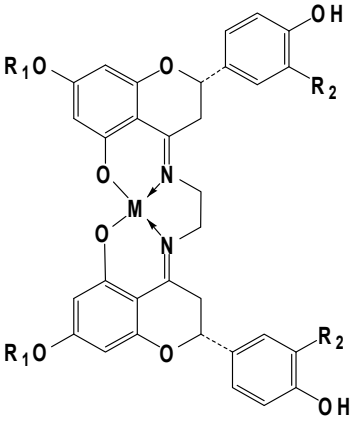

Figure 12. General structure of metal complexes with flavanone derivatives [50]

Flavanone-metal complexes showed good inhibitory capacity against the AChE (acetylcholinesterase) and BChE (butyrylcholinesterase), in contrast to pure flavanones and their imine derivatives.

Moreover, the flavanone-metal complexes showed exceptional inhibitory activity than galanthamine [50].

Flavanones can also be used in the treatment of mental illness. This is confirmed by recent studies by a group of researchers from China. They designed a series of new flavanone derivatives and tested their antipsychotic activity *in vitro* and *in vivo*. The assessment of biological activity showed that compounds 7a-7g (Fig. 13) reduced the activity of the dopamine receptor (D2) and inhibited neurological inflammation *in vitro* [51].

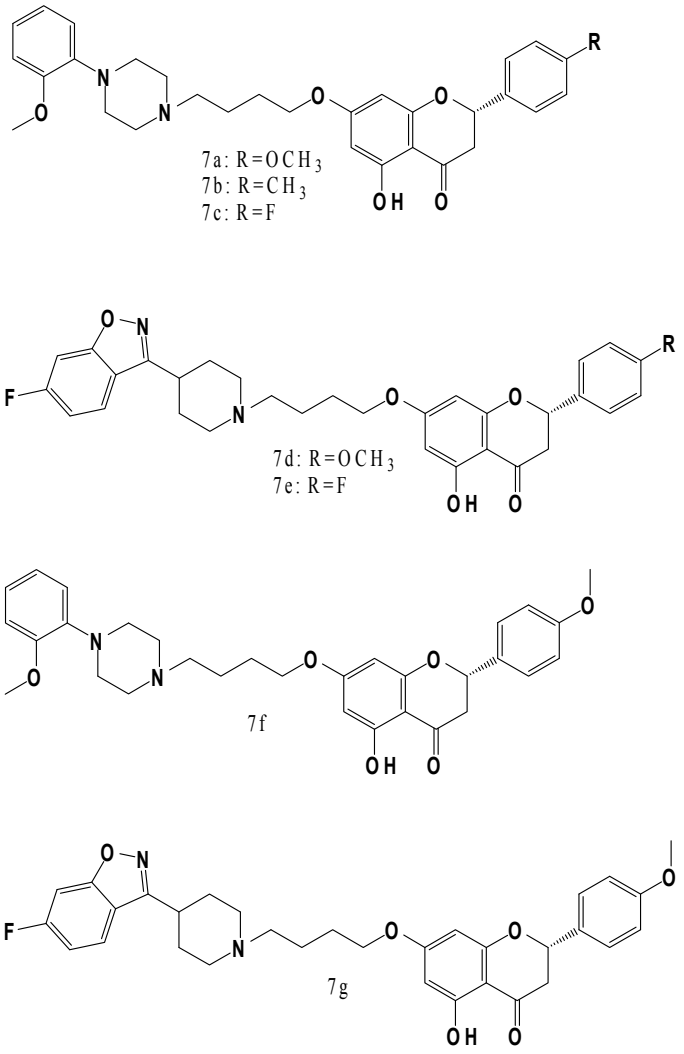

Figure 13. Structures of compounds 7a-7g [51]

Pinocembrin (5,7-dihydroxyflavanone) (Fig. 14) is one of the primary flavanones and biologically active constituent of honey. It has antimicrobial, antiinflammatory, anticancer and antioxidant potential. It has been reported about the antimicrobial efficacy of Pinocembrin and its derivatives [52].

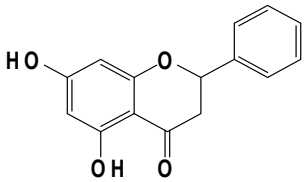

Figure 14. Chemical structure of Pinocembrin

A series of 5,7-dihydroxyflavanone derivatives (Fig. 15) were efficiently synthesized and their antimicrobial efficacy on Gram-negative and Gram-positive bacteria and yeast were evaluated. Among these compounds, most of the halogenated derivatives exhibited the best antimicrobial activity against Gram-positive bacteria (*Bacillus subtilis, Bacillus anthracis, Bacillus cereus, Staphylococcus aureus*), the Gram-negative bacterium *Vibrio cholerae* and the yeast *Saccharomyces cerevisiae* [52].

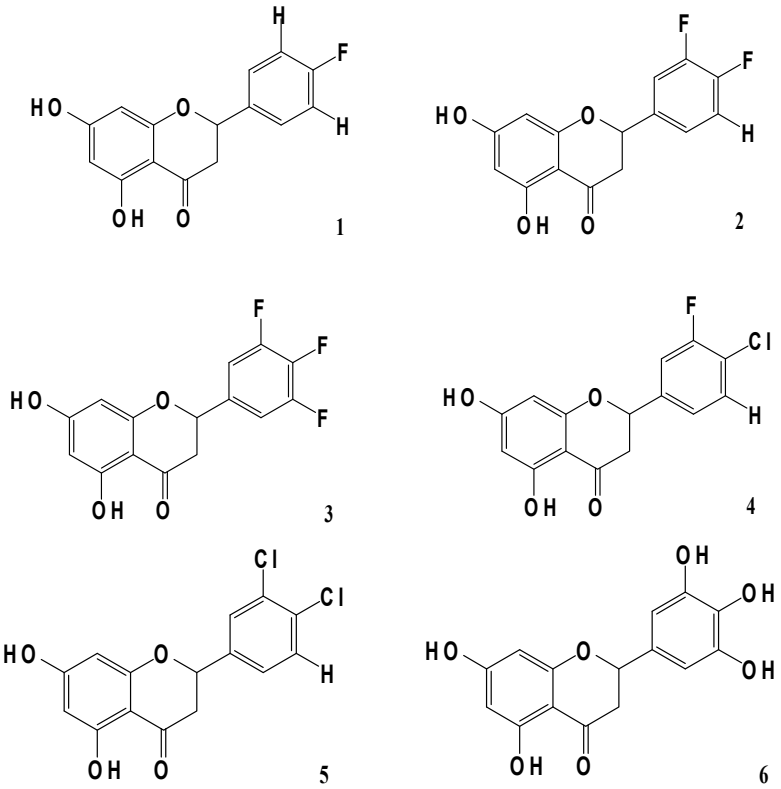

Figure 15. Chemical structures of Pinocembrin derivatives

This research suggests that halogenated flavanones might represent promising pharmacological candidates for further drug development.

Summary

Summarizing the topic, flavanones and its derivatives have many interesting and multifarious properties. Over a dozen years, knowledge of flavanones has increased. Extensive studies have been carried out on the bioavailability and bioactivity of flavanones. This group of flavonoids is very important in cosmetic and pharmaceutical industry. Derivatives of flavanone have a huge influence on diseases, development and metabolism in animals, plants and people.

In conclusion, it is more and more accepted that natural polyphenolic compounds such as flavanones used in the human diet can be helpful in combating many diseases. Expanding knowledge about the flavanones' health properties may contribute to an increase in demand for fruit and vegetables.

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