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FLAVONOIDS – SMALL MOLECULES, HIGH HOPES

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Abstract: This brief review takes a look at flavonoids, a wide class of polyphenols, which are regarded as plant secondary metabolites. Their roles in plants are diverse and little understood. They can act as growth hormone modulators, phytoalexins, they offer UV protection, contribute to pollen viability and can function as signaling molecules in establishing symbiotic relationships. Flavonoids were also found to have a range of beneficial effects for the human body. Their anticancer, antioxidant, anti-inflammatory and cardioprotective activity, as well as their antibacterial, antiviral and antihelmintic properties make them promising candidates for the design of new drugs.

***Keywords*:** flavonoids, anti-inflammatory, anticancer, antimicrobial, cardioprotective

1. Introduction

Since the dawn of civilization, humans have used the healing properties of plants. Tea, tinctures and salves have been used for millennia to treat various affections, ranging from simple headaches to skin diseases,

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wounds and inflammations. Enveloped at first in magic and mysticism, pharmacy has now evolved into a separate field of science. However, despite all the progress made so far, scientists still turn to nature when they look for new compounds with biological activity.

Flavonoids are a very diverse class of plant secondary metabolites. Williams *et al.* estimated in 2004 that around 9000 different flavonoids had been isolated from plant sources at that time.[1]

The term *flavonoid* derives from the Latin word *flavus*, which means yellow, these compounds often being responsible for the pigmentation of the flower petals. Some of the first recorded experiments involving flavonoids were performed by Robert Boyle, who described in 1664 in his book „*Experiments and Considerations Touching Colours*" the effects that the variation of pH had on the color of plant pigments.[2]

Nowadays, scientists have found that apart from contributing to the colour of flowers, flavonoids play roles in plant growth, reproduction and defense. Moreover, due to their wide range of beneficial interactions with the human body, flavonoids are considered to be promising antiproliferative, antiinflammatory, antibacterial, antiviral and cardioprotective drug candidates. This paper is not meant to be a comperhensive review of flavonoid properties, but instead aims to instill into the reader the importance of flavonoids for life as we know it.

2. Structure

Structurally, flavonoids comprise of a C_6-C_3-C_6 backbone – two benzene rings bound together by a chain of three carbon atoms. Most flavonoids are phenyl benzopyran derivatives. If the phenyl moiety is attached to the C2 atom of the benzopyran core, the compounds are called flavonoids (I), if it is attached to the C3 atom, they are called isoflavonoids

(II) and finally, if the phenyl is attached to the C4 atom, they derivatives are called neoflavonoids (III) (Figure 1).

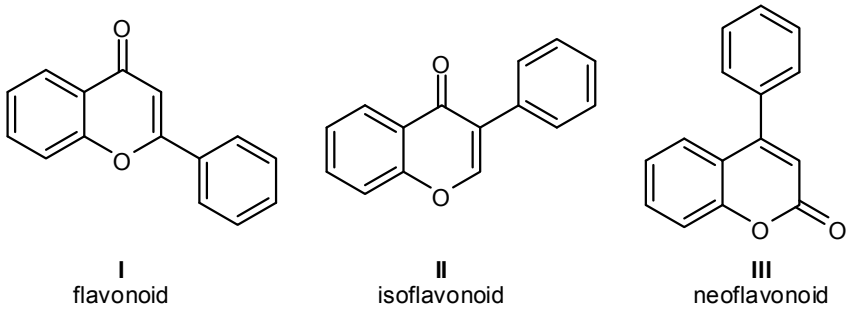


Figure 1. The three main classes of flavonoids.

Each of these three classes is further divided into subclasses. For instance, according to whether the C2-C3 bond is a double bond or a single bond and/or the carbonyl group is reduced to an alcohol or methylene group and/or there is a hydroxyl bound to the C3 atom, flavonoids (I) are split into flavones, flavanones, flavonols, flavanols and flavans (Ia-f) (Figure 2).

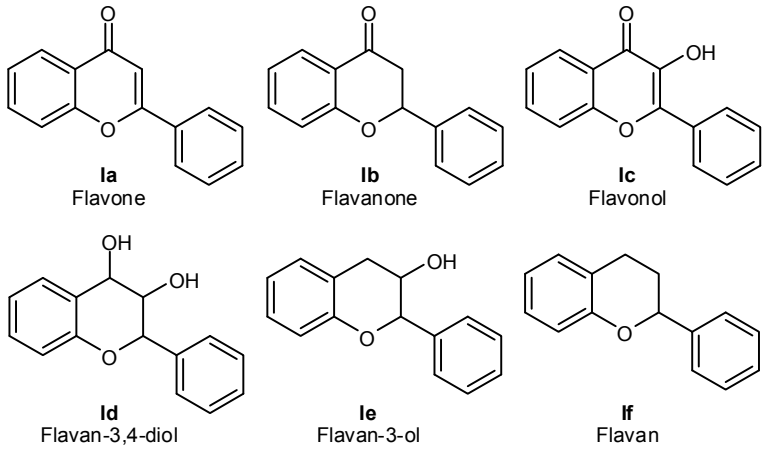


Figure 2. The main subclasses of flavonoids.

Isoflavonoids are also divided into isoflavones, isoflavanones, isoflavanols and isoflavans. 3-Arylcoumarins are isoflavonoids with a double bond between the C3-C4 atoms and a carbonyl group at the C2 atom. If the carbonyl group is missing, the C3-C4 unsaturated derivatives are called isoflavenes (Figure 3, structures IIa and IIb). Furthermore, some isoflavonoids have four condensed rings, due to favorable substitution patterns (Figure 3, structure IIc).

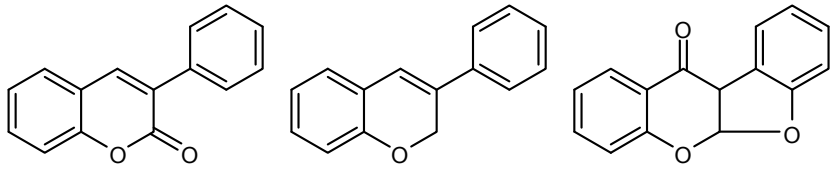


Figure 3. The general structure of 3-arylcoumarins (IIa) and isoflav-3-enes (IIb); a four-ring isoflavonoid, coumaronochromone (IIc).

As far as neoflavonoids are concerned, if there is a double bond between C3-C4 and a carbonyl group at the C2 position, the derivatives are called 4-arylcoumarins (Figure 4, IIIa). If the double bond is missing, then they are called 3,4-dihydro-4-arylcoumarins (Figure 4, IIIb). If the carbonyl group is missing, then they are callen neoflavenes (Figure 4, IIIc).

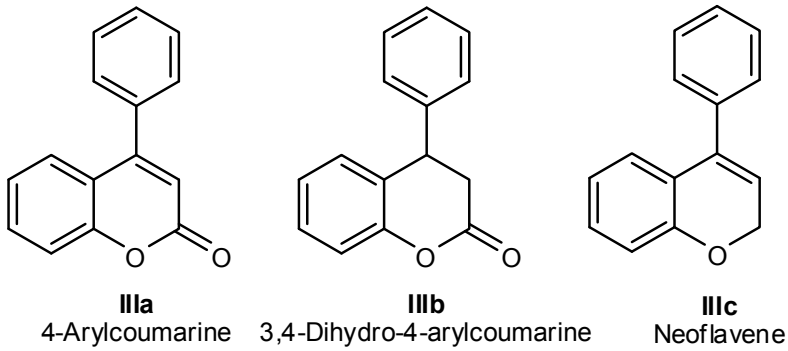
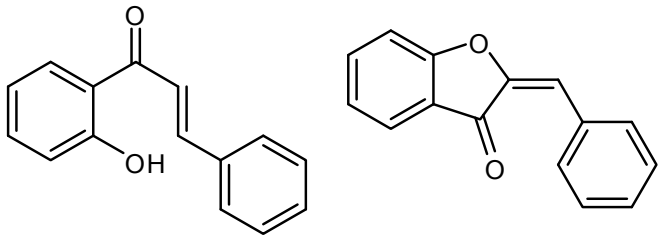


Figure 4. The three main subclasses of neoflavonoids.

Not all flavonoids are benzopyran derivatives. These are called minor flavonoids and are split into two main categories: chalcones, lacking the oxygen-containing ring (Figure 5, structure IV) and aurones, bearing a benzofuran core (Figure 5, structure V).



IV
2'-Hydroxychalcone

V
Aurone

Figure 5. The general structure of chalcones and aurones.

3. Flavonoids and plants

Although they are considered to be secondary metabolites, flavonoids were shown to be involved in many biological processes that take place in plants. They can act as auxin modulators,[3] contribute to plant protection,[4] affect pollen viability[5] and help establish symbiotic relationships with bacteria.[6]

3.1. Flavonoids and auxins

Auxins are a class of plant hormones that play a crucial role in the growth and development of plants. Amongst the most abundant auxins is indole-3-acetic acid (IAA). This was shown by Luo *et al.* to be in direct relationship with the flavonoid content in the skin of grape berries.[7] Treatment of grape berries with IAA lead to an increase in the content of skin flavonoids of 5-10% within 24 h. When instead of IAA, an auxin inhibitor, 1-*N*-naphthylphthalamic acid (NAP) was used, the skin flavonoid content decreased by 10-20% after 24 h. Determination of chalcone

synthase (CHS), an enzyme involved in flavonoid biosynthesis, showed that the production of the protein was induced by treatment of the berries with IAA. On the other hand, treatment of grape berries with the flavonoid quercetin lead to a decrease in indole-3-acetic acid oxidase (IAO) activity by 7-45%, suggesting that higher flavonoid levels lead to a decrease in IAA levels.

In order for auxins to exert their function, they need to be transported from the sites of synthesis to the distal parts of the plant. The presence of flavonoids leads to a decrease in polar auxit transport (PAT) within the plant. In a study performed on *Arabidopsis thaliana* mutants, Yin *et al.* managed to identify a flavonoid diglycoside, kaempferol 3-O-rhamnoside-7-O-rhamnoside, as a potent PAT inhibitor.[8] Plants lacking the flavonoid 3-O-glucosyltransferase UGT78D2 produced larger amounts of kaempferol 3-O-rhamnoside-7-O-rhamnoside which led to reduced PAT, which in turn led to reduced plant height and loss of apical dominance (increased branching). By blocking the biosynthesis of flavonoids, however, normal growth could be restored.

In another study performed on *Arabidopsis thaliana* mutants, Peer *et al.* showed that the expression of the PIN protein-responsible genes varied with the content of flavonoids.[9] PIN proteins are responsible for the transport of auxins across cell membranes. By analyzing wild-type plants, as well as mutants that lacked flavonoids (*tt4*) and mutants that produced an excess of kaempferol and quercetin (*tt3*), the authors found that the PIN expression differed for the *tt4* and *tt3* mutants. However, treatment of the *tt4* mutants with naringenin, a kaempferol precursor, restored the PIN expression to wild-type levels.

3.2. Flavonoids and plant protection

A great number of plant-pathogens, from viruses to bacteria, fungi and insects, are present in nature. In response, plants synthesize phytoalexins, compounds used as a means of defense. Some flavonoids are also used for this purpose. One such example is sakuranetin, a flavanone present in rice. Hasegawa *et al.* estimated the amounts of sakuranetin present in blast infected susceptible and resistant rice plants and determined the antifungal properties of the flavanone.[10] The authors have found that sakuranetin production in resistant plants started two days after infection, as opposed to three days for blast fungus-susceptible plants. After four days, the amount of sakuranetin in the leaves of both resistant and susceptible plants was about the same. However, the concentration of sakuranetin in the fungal induced lesions was estimated to be 0.3 mM for the resistant plants, as opposed to only 0.2 μM for the susceptible plants. When the antifungal properties of sakuranetin were determined *in vitro*, the authors found that a concentration of 0.1 mM flavanone inhibited the growth of blast fungus mycellium by 36% after 5 days, whereas a concentration of 0.3 mM flavanone inhibited the growth of blast fungus mycellium by 50% after 5 days, suggesting that sakuranetin plays a role in defending rice plants against blast fungus.

Due to their polyphenolic nature, flavonoids are also believed to play a role in the defense of plants against harmful ultra violet (UV) radiation. Götz *et al.* found that the concentration of quercetin in *Arabidopsis thaliana* after a 14 day exposure to UV-B radiation with wavelengths above 295 nm more than doubled when compared to plants that received UV-B radiation with wavelengths above 360 nm.[11]

3.3. Other roles of flavonoids in plants

Some plants require flavonoids for proper pollen development. Taylor *et al*. studied *Petunia* plants and found that mutants that could not produce flavonoids were self-sterile.[12] The pollen grains themselves were viable, however, the lack of flavonoids prevented germination and tube growth. Other studies[13] showed that adding exogenous flavonoids to the pollen could correct the problem. However, Ylstra *et al.* proved that not all plants require flavonoids for proper pollen development.[14] Pollen coming from mutant *Arabidopsis* plants was found to germinate and grow tubes despite the lack of flavonoids.

Flavonoids are also used by plants as signaling molecules when trying to establish symbiotic relationships with nitrogen fixing bacteria present in the soil. For this purpose, certain flavonoids are produced and secreted into the soil. Once the bacteria pick up their presence, they in turn produce compounds called Nod factors. Once the plant detects the Nod factors, it initiates nodule formation. Many *Leguminosae* undergo nodule formation, including soybean plants, which form symbiotic relationships with *Sinorhizobium fredii*.[15]

4. Flavonoids and mammals

Through plants, flavonoids make their way into animal bodies. Here, they are believed to display a wide range of beneficial effects and there is an ever-increasing amount of evidence to backup this belief.

4.1. Flavonoids as antioxidant, anti-inflammatory and cardioprotective agents

Due to their polyphenolic nature, flavonoids display antioxidant properties. Fu *et al.* recently isolated six flavonoids, four chalcones and two isoflavonoids, from licorice, a natural sweetener.[16] *In vitro* tests against $ABTS^{\cdot+}$ revealed that three out of the six tested compounds displayed higher radical scavenging activity when compared to ascorbic acid. Moreover, five out of the six tested flavonoids were found to inhibit lipid peroxidation at lower concentrations than butylated hydroxytoluene (BHT). *In vivo* tests performed on macrophage rat cells showed that all four tested chalcones inhibited the formation of reactive oxygen species (ROS) at concentrations ranging between 0.3 and 10 μM.

Lemmens *et al.* found that 7-mono-O-(β-hydroxyethyl)-rutoside, a semi-syhtnetic flavonoid, offers protection to human umbilical vein endothelial cells in concentrations as low as 60 nM.[17] The effect was found to be instantaneous and was attributed to its ability to directly scavenge radicals. Oxidative stress was induced to endothelial cells by addition of H_2O_2. Once inside the cells, H_2O_2 can react with Fe, resulting in the formation of OH hydroxyl radicals. The authors concluded that, because the tested flavonoid has the ability to chelate Fe ions, it is present at the OH hydroxyl radicals generation site, thus being able to neutralize them as soon as they form.

Apart from their antioxidant activity, some flavonoids also display anti-inflammatory properties. Fu *et al.*[16] found that out of the six flavonoids extracted from licorice, five of them inhibited the production of nitric oxide, interleukin-6 and prostaglandin E2 in bacterial lipopolysaccharide (LPS) induced murine macrophage cells. Again, the four tested chalcones proved

to be the most potent anti-inflammatory agents out of the six tested flavonoids.

Kang *et al*.[18] found that three flavonoids isolated from bitter oranges, namely nobiletin, naringin and hesperidin, also displayed anti-inflammatory properties when administered to LPS-stimulated murine macrophage cells. Moreover, the anti-inflammatory activity was attributed to their ability to block the nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signalling pathways, thus inhibiting the formation of pro-inflammatory agents.

The intake of flavonoids through dietary sources has long been associated with a decreased risk of coronary heart disease. A study performed on 805 men aged 65-84, over a period of five years, suggests that a daily intake of over 30 mg of flavonoids decreases the risk of myocardial infarction by approximately 50% when compared to a daily intake of under 20 mg of flavonoids.[19] 5-Hydroxy substituted flavonoids, such as apigenin and naringenin, were found to have cardioprotective properties against ischaemia/reperfusion induced injury in rats.[20] Naringenin was found to protect the hearts of one year old rats against ischaemia/reperfusion injury by activating the mitochondrial large conductance calcium-activated potassium channel.[21]

4.2. Flavonoids and cancer

The American Cancer Society estimates that about one third of the cancer deaths that occur every year in the United States can be attributed to bad nutrition and lack of physical activity.[22] There is a general consensus that a diet rich in fruits and vegetables can help prevent the onset of cancer

and indeed, many studies have shown that dietary flavonoids have anticancer properties.

Chen *et. al*.[23] found that the flavonoid nobiletin, present in citrus fruits, can prevent angiogenesis in human ovarian cancer by decreasing the concentration of the vascular endothelial growth factor (VEGF). This is achieved by lowering the concentrations of hypoxia-inducible factor 1α (HIF-1α) and NF-κB, which act as VEGF regulators. The authors found that a concentration of 20 μM nobiletin was able to reduce the number of blood vessels in tumors by 34%, which in turn caused a 41% reduction in tumor size.

Srivastava *et. al*.[24] studied the effects of quercetin on leukemic, breast cancer and normal cells. The authors found that while the flavonid had little impact on normal cells, it induced apoptosis in the tested cancer cells. Moreover, administration of quercetin to tumor bearing mice led to a 5 fold increase in lifespan for 40% of the tested subjects, while at the same time, causing a significant reduction in tumor size. Shi *et. al*.[25] found similar apoptotic properties for apigenin in human bladder cancer, while Smith *et. al*.[26] found that fisetin induced apoptosis in breast cancer cells. Fisetin was also found to enhance the effects of other anti-tumor agents, such as cisplatin. A similar effect was observed by Luo *et. al*.[27] using kaempferol treated ovarian cancer cells.

4.3. Flavonoids as antiviral and antimicrobial agents

Song *et. al.* studied the effects of green tea catechins on various strains of influenza virus and found that (−)-epigallocatechin gallate (EGCG) and (−)-epicatechin gallate (ECG) effectively inhibit the replication of influenza A virus in MDCK cells.[28] The authors determined that the EC_{50} values

against the A/H1N1 and A/H3N2 subtypes are 28 μM and 22 μM for EGCG and 26 μM and 22 μM for ECG, respectively. Sithisarn *et. al.* found that biochanin A, an isoflavone, and baicalein, a flavone, have antiviral properties.[29] When tested against H5N1 influenza virus, the authors determined IC_{50} values of 18.7 μM and 8.9 μM and selectivity indexes of 5.82 and 5.60 for baicalein and biochanin A respectively.

Both natural and synthetic flavonoids have also been found to display antimicrobial properties. Thongnest *et. al.* has found that some prenylated flavonoids isolated from *Eriosema chinense* have inhibitory properties against Gram-positive bacteria.[30] Katerere *et. al.* isolated six flavonoids from three *Combretaceae* species and found them to be active against *Candida albicans*.[31] Mbaveng *et. al.* isolated several flavonoids from *Dorstenia barteri* and found that four of them displayed potent antimicrobial properties.[32] Arima *et. al.* showed that certain flavonoids together displayed better antibacterial properties when compared to those of each flavonoid alone,[33] while Fujita *et. al.* discovered a synergy effect between baicalein and tetracyclin against Methicillin-Resistant *Staphylococcus aureus*.[34]

Our group has synthesized and tested a series of 1,3-dithiolium bearing flavonoids against both Gram-positive and Gram-negative bacteria.[35-37] The results show that most of the tested compounds display potent antibacterial properties, with minimum inhibitory concentrations (MICs) of as low as 0.24 μg/mL. The synthetic flavonoids appear to target the microbial cell wall, while leaving the microbial DNA intact, however, more studies are required before a definitive mechanism of action can be established.[38]

Conclusions

Despite being regarded as secondary metabolites, flavonoids are involved in many aspects of plant biochemistry. Although their roles are not yet fully understood, the importance of flavonoids is underlined by the great number and structural diversity present in nature. Moreover, the scientific community is becoming more and more aware of the great potential that this class of compounds has when it comes to treating cancer, developing new antibiotics or new antiviral drugs. It is therefore without a doubt that the future of medicine will see this class of compounds play an important role in the development of new cures to century-old problems.

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