Pharmacological Activities of Flavonoids: A Review

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ABSTRACT
Flavonoids belong to a group of polyphenolic compounds, which are classified as flavones, flavanones, catechins and anthocyanins. Flavonoids of different classes have several pharmacological activities. Flavonoids possess pharmacological and biochemical effects, which inhibit a number of enzymes such as aldose reductase, cycloxygenase, Ca\textsuperscript{2+}-ATPase, xanthine oxidase, phosphodiesterase, and lipoxygenase. They also have a regulatory role on different hormones like androgens, estrogens and thyroids. In the view of their wide pharmacological and biological actions, they seem to have great therapeutic potential.

KEYWORDS: Flavonoids; biochemistry; pharmacology; therapeutic potential.

Introduction
Flavonoids are a group of polyphenolic compounds, which are widely distributed throughout the plant kingdom and about 3000 varieties of flavonoids are known (Kuhnau, 1976). Many have low toxicity in mammals and some of them are widely used in medicine for maintenance of capillary integrity (Cesarone et al., 1992). Flavonoids exhibit several biological effects such as anti-hepatotoxic, anti-inflammatory and anti-ulcer activity (Bors et al., 1980; Colerige et al., 1980). They also inhibit enzymes such as aldose reductase, cycloxygenase, Ca\textsuperscript{2+}-ATPase, xanthine oxidase, phosphodiesterase and lipoxygenase. They are potent antioxidants and have free radical scavenging abilities. Many have antiallergic, antiviral actions and some of them provide protection against cardiovascular mortality (Clack et al., 1950; Hertog et al., 1993). They have been shown to inhibit the growth of various cancer cell lines in vitro, and reduce tumor development in experimental animals (Mori et al., 1988). Flavonoids can be divided into various classes on the basis of their molecular structure (Rice-Evans et al., 1996). The four main groups of flavonoids are listed in Table 1, together with the examples and the food source in which they are present. Chemical structures of selected flavonoids are shown in Figure 1. The flavones are characterized by a planar structure because of a double bond in the central aromatic ring.

Pharmacological effects of flavonoids
Antiatherosclerotic effects. Because of their antioxidative properties, flavonoids are likely to have a major influence on the vascular system. Oxygen radicals can oxidize LDLs, which injures the endothelial wall and thereby promotes atherosclerotic changes. A few clinical studies have pointed out that flavonoid intake protects against coronary heart disease (Hertog et al., 1995; Hertog et al., 1993). Hertog et al., 1995 stated that the flavonoids in regularly consumed foods might reduce the risk of death from coronary heart disease in elderly men. Furthermore, a Japanese study reported an inverse correlation between flavonoid intake and total plasma cholesterol concentrations (Arai et al., 2000). Oxidative stress and vascular damage are postulated to play a key role in dementia, and the intake of red wine is reported to prevent the development of dementia (Orgogozo et al., 1997). The intake of flavonoids appears inversely related to the risk of dementia (Commenges et al., 2000).

Anti-inflammatory effects. Cyclooxygenase and lipoxygenase play an important role as inflammatory mediators. They are involved in the release of arachidonic acid, which is a starting point for a general inflammatory response. Selected phenolic compounds were shown to inhibit the cyclooxygenase and 5-lipoxygenase pathways (Ferrandiz et al., 1991; Ferrandiz et al., 1990; Laughton et al., 1991).

This inhibition reduces the release of arachidonic acid (Yoshimoto et al., 1983). Quercetin inhibits both cyclooxygenase and lipoxygenase activities, thus diminishing the formation of these inflammatory metabolites (Robak and Gryglewski, 1996; Kim et al., 1998). Another anti-inflammatory feature is that flavonoids also inhibit eicosanoid biosynthesis (Formica and Regelson, 1995; Damas et al., 1985). Eicosanoids, such as prostaglandins, are involved in various immunologic responses (Moroney et al., 1988). Flavonoids also inhibit both cytosolic and membrane tyrosine kinase (Formica et al., 1995). Integral membrane proteins, such as tyrosine 3-monooxygenase
kinase, are involved in a variety of functions, such as enzyme catalysis, transport across membranes, and transduction of signals that function as receptors of hormones and growth factors, and energy transfer in ATP synthesis. Inhibition of these proteins results in inhibition of uncontrolled cell growth and proliferation. Tyrosine kinase substrates seem to play key roles in the signal transduction pathway that regulates cell proliferation. Another anti-inflammatory property of flavonoids is their suggested ability to inhibit neutrophil degranulation. This is a direct way to diminish the release of arachidonic acid by neutrophils and other immune cells (Hoult et al., 1994; Tordera et al., 1994).

**TABLE 1**

Main groups of flavonoids, the individual compounds, and food sources.

<table>
<thead>
<tr>
<th>Group</th>
<th>Compound</th>
<th>Food sources</th>
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<tbody>
<tr>
<td>Flavones</td>
<td>Apigenin</td>
<td>Apple skins</td>
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<td></td>
<td>Chrysins</td>
<td>Berries</td>
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<td></td>
<td>Kaempferol</td>
<td>Broccoli</td>
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<td></td>
<td>Luteolin</td>
<td>Celery</td>
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<td></td>
<td>Myricetin</td>
<td>Fruit peels</td>
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<td></td>
<td>Quercetin</td>
<td>Lettuce</td>
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<td></td>
<td>Rutin</td>
<td>Cranberries</td>
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<td>Silibin</td>
<td>Grapes</td>
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<td>Olives</td>
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<td></td>
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<td>Parsley</td>
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<td></td>
<td></td>
<td>Tea</td>
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<tr>
<td>Flavanones</td>
<td>Fisetin</td>
<td>Citrus fruit</td>
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<td></td>
<td>Hesperetin</td>
<td>Citrus peel</td>
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<td></td>
<td>Narigin</td>
<td>Citrus peel</td>
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<tr>
<td></td>
<td>Naringenin</td>
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<tr>
<td></td>
<td>Taxifolin</td>
<td>Strawberries</td>
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<td></td>
<td></td>
<td>Tea</td>
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<tr>
<td></td>
<td></td>
<td>Fruit peels with</td>
</tr>
<tr>
<td>Catechins</td>
<td>Catechin</td>
<td>Red wine</td>
</tr>
<tr>
<td>Anthocyanins</td>
<td>Cyanidin</td>
<td>Berries</td>
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<td></td>
<td>Delphinidin</td>
<td>Cherries</td>
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<td></td>
<td>Epicatechin</td>
<td>Tea</td>
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<td></td>
<td>Epigallocatechin gallocate</td>
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<td></td>
<td>Malvidin</td>
<td>Grapes</td>
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<td></td>
<td>Pelargonidin</td>
<td>Raspberries</td>
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<td></td>
<td>Peonidin</td>
<td>Red grapes</td>
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<td></td>
<td>Petunidin</td>
<td>Red wine</td>
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<td>Dark pigments</td>
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**Antitumor effects.** Antioxidant systems are frequently inadequate, and damage from reactive oxygen species is proposed to be involved in carcinogenesis (Hoult et al., 1994; Tordera et al., 1994). Reactive oxygen species can damage DNA, and the division of cells with unrepaired or misrepaired damage leads to mutations. Reactive oxygen species can interfere directly with cell signaling and growth. The cellular damage caused by reactive oxygen species can induce mitosis, increasing the risk that damaged DNA will lead to mutations, and can increase the exposure of DNA to mutagens. It has been stated that flavonoids, such as apigenin, fisetin and luteolin are stated to be potent inhibitors of cell proliferation (Fotsis et al., 1997). Quercetin and apigenin inhibited melanoma growth and influenced the invasive and metastatic potential in mice (Caltagirone et al., 2000). Flavonoids inhibit angiogenesis, which is regulated by a variety of endogenous angiogenic and angiostatic factors (Fotsis et al., 1997). Pathologic, unregulated angiogenesis occurs in cancer (Fan et al., 1995). Angiogenesis inhibitors can interfere with various steps in angiogenesis, such as the proliferation and migration of endothelial cells and lumen formation. Flavonoids seem to play an important role among the known angiogenesis inhibitors, (Fotsis et al., 1997; Paper, 1998). However, the mechanism behind the antiangiogenic effect of flavonoids is unclear. A possible mechanism could be the inhibition of protein kinases (Oikawa et al., 1992). These enzymes are implicated to play an important role in signal transduction and are known for their effects on angiogenesis.

**Antithrombogenic effects.** Platelet aggregation contributes to both the development of atherosclerosis and acute platelet thrombus formation, followed by embolization of stenosed arteries. Activated platelets adhering to vascular endothelium generate lipid peroxides and oxygen free radicals, which inhibit the endothelial formation of prostacyclin and nitrous oxide. It was shown in the 1960s that tea pigments can reduce blood coagulability, increase fibrinolysis, and prevent platelet adhesion and aggregation (Lou et al., 1989). Selected flavonoids, such as quercetin, kaempferol, and myricetin were shown to be effective inhibitors of platelet aggregation in dogs and monkeys (Osman et al., 1998). Flavonols are particularly antithrombotic because they directly scavenge free radicals, thereby maintaining proper concentrations of endothelial prostacyclin and nitric oxide (Gryglewski et al., 1987). Flavonoids are powerful antithrombotic agents *in vitro* and *in vivo* because of their inhibition of the activity of cyclooxygenase and lipoxygenase pathways (Alcaraz and Ferrandiz, 1987). It is well known that arachidonic acid, which is released in inflammatory conditions, is metabolized by platelets to form prostaglandin, endoperoxides, and thromboxane A2, leading to platelet activation and aggregation (Tzeng et al., 1991). The main antiaggregatory effect of flavonoids is thought to be by inhibition of thromboxane A2 formation. Flavonoids affect arachidonic acid metabolism in different ways. Some flavonoids specifically block cyclooxygenase or lipoxygenase, whereas others block both enzymes (Landolfi et al., 1984). *In vitro* studies showed that flavonoids bind to platelet membranes and may therefore have an accumulative effect over time (Van Wauwe and Goossens, 1983).

**Antiosteoporotic effects.** In an English study, bone mineral density was compared between older women who consumed tea and those who did not. Women in the study who drank tea had higher bone mineral density measurements than did those who did not drink tea. The flavonoids in tea might be responsible for the prevention of osteoporosis (Hegarty et al., 2000).
Antiviral effects. Wang et al (1998) has shown an antiviral activity of flavonoids. Herpes simplex, parainfluenza, respiratory syncytial and adenovirus were affected by flavonoids. Quercetin was reported to exhibit both antinfecitive and antireplicative abilities. The interaction of flavonoids with the different stages in the replication cycle of viruses was previously described (Kaul et al., 1985). Flavonoids in their glycone form seem to be more inhibitory on rotavirus infectivity than are flavonoids in their aglycone form (Bae et al., 2000). Because of the worldwide spread of HIV since the 1980s, investigations of the antiviral activity of flavonoids have mainly focused on HIV. Most of these studies focused on the inhibitory activity of reverse transcriptase, or RNA-directed DNA polymerase (Huang et al., 1997), but antintegrase and antiprotease activities were also described (Middleton, 1998). Again, flavonoids have mainly been studied in in vitro experiments; therefore, no clear contribution of flavonoids to the treatment of HIV-infected patients has yet been shown (Vlietinck et al., 1998).

Antibacterial Activity. Antibacterial activity has been displayed by a number of flavonoids. Most of the flavonones having no sugar moiety showed antimicrobial activities, whereas none of the flavonols and flavonolignans tested showed inhibitory activity on the microorganisms (Wild and Fosel, 1969).

Antifungal Activity. Flavonoids isolated from the peels of tangerine oranges and tested for fungistatic activity towards Deuterophoma tracheiphila showed promising activity. Chlorflavonin was the first chlorine-containing flavonoid type antifungal antibiotic produced by strains of Aspergillus candidus (Tencate et al., 1973). Biochemical effects of flavonoids

(i) On enzymes. Flavonoids are known to inhibit a number of enzymes such as aldose reductase (Jager et al., 1998), xanthine oxidase (Koch et al., 1992), phosphodiesterase (Alcaraz et al., 1987), Ca^{2+} A TPase (Scerola et al., 1984), lipo-oxygenase (Baumann et al., 1980) and cyclooxygenase (Varma and Kinosita, 1976). Flavonols like myricetin, quercetin and kaempferol inhibit the activity of the adenosine deaminase of endothelial cells, while flavones are inactive (Hayashi et al., 1993). Quercetin, myricetin and kaempferol are effective in antagonizing bradykinin responses (Nagai et al., 1992). Effects of luteolin and quercetin on inhibition of tyrosine kinase, on cell growth and metastasis (Bamard et al., 1993). They have inhibitory properties on the 5'-nucleotidase (5'-ribonucleotide phosphohydrolase) activity (Hur et al., 1994). Flavonoids inhibit intracellular Ca^{2+} elevation by reducing phospholipase-C activity (Beladi et al., 1987) and they possess potent inhibitory effects on several enzyme systems such as protein kinase-C, protein tyrosine kinase, phospholipase A2 and others (Musci et al., 1985). Flavonoids have high potencies and selectivities for inhibition of CYPI A isoenzymes (Melzig, 1996). Silymarin acts as a strong antioxidant by virtue of it’s ability to act as an acceptor of O_{2} or CCl_{3} radicals. By trapping O_{2} related free radicals, silymarin hinders their interaction with polyunsaturated fatty acid and abolishes the enhancement of lipid peroxidation. Some flavonoids are predominant inhibitors of either cyclooxygenase or lipoxygenase, others are equally effective against both enzymes (Calixto and Yunes, 1991; Huang et al., 1999).

(ii) On hormones. Flavonoids have also been shown to have regulatory activities on hormones by binding to 17 beta-hydroxy steroid dehydrogenases which regulates estrogen and androgen levels in humans, and to 3 beta-hydroxy steroid dehydrogenase, which regulates progestin and androgen levels in humans (Noro et al., 1983). Quercetin, myricetin, rutin, kaempferol affect the transport, metabolism, and action of thyroid hormones. Quercetin myricetin, rutin, kaempferol, galangin, spirenoside and robinin are potent nontoxic ITH deiodinase inhibitors in microsomal membranes, and intact rat hepatocytes. Myricetin, rutin, kaempferol are specific high affinity competitors for L- T4-binding to human TBPA, weaker antagonists in the T3-5'-deiodinase reaction, and very poor inhibitors of T3 binding to the nuclear T3 receptor.


Conclusion

Flavonoids have received much attention in the literature over the past 10 years and a variety of potential beneficial effects have been elucidated. The flavonoids as natural compounds have several great advantages over other therapeutic agents because many diets are rich in polyphenolics compounds and are consumed daily having a relatively long half-life with minimum side effects and is easily absorbed in the intestine after ingestion. However, most of the research is involved in vitro studies; therefore, it is difficult to draw definite conclusions about the usefulness of flavonoids in the diet. Currently, the intake of fruit, vegetables, and beverages (eg, tea and moderate amounts of red wine) containing flavonoids is recommended, although it is too early to make recommendations on daily flavonoid intakes.

References


Huang B, Fong WP and Yeung HW (1997). Anti-human immunodeficiency virus (anti-HIV) natural products with special

Fig. 1. Chemical structures of selected flavonoids.

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