FLAVONOIDS: DISTRIBUTION, CHEMISTRY AND PHARMACOLOGICAL ROLE IN HEALTH AND DISEASE

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Introduction

Flavonoids: Occurrence and distribution

The flavonoids are one of the most widespread groups of plant substances (1). They are ubiquitous in vascular plants and occur in the root, bark, leaf, fruit, flower, pollen and seeds(1-6). About 2% of the total carbon photosynthesised are converted to Flavonoids which in turn contribute to the myriad bright colours in plant tissues (3,7). These compounds are the largest group of plant phenols and more than 4000 types have been isolated and identified in vascular plants (1).

Role in plants

In plants, apart from contributing to the colour, the flavonoids act in concert with growth hormones and influence the morphogenesis as well as sex determination (8). They are also actively involved in the respiration and photosynthesis processes (1, 3, 4, 8). They are the antioxidants for ascorbate (universal component in plants) (1,8). In addition, these compounds exert allelopathic effects, enzyme inhibition, disease resistance / antifungal properties as well as UV protection especially in epidermal cells (1, 3, 8).

Flavonoids are not synthesised by animals but their presence in some animals such as the scent glands of the Canadian beaver and in the wings and bodies of butterflies are through diet (1). Fruits and vegetables contain flavonoids up to several hundred milligrams (9). The outer skin of onions (*Allium cepa*) contain up to 2.5 - 6.5 mg /100g of the flavonoid quercetin, whilst the celery tubers contain 9 mg/100 g fresh weight of flavone glycosides (9).

Generally in man, the daily dietary intake of flavonoids has been estimated to be 1 - 2 g / day which arise mostly through the intake of coffee, tea, bear, wine, cereals, vegetables, fruits, cocoa and peanuts (9,10).

Basic structure and classification

Polyphenols including the flavonoids were originally described as 'Vitamin P' by Szent Gyorgi *et.al* (11) in 1936. Geissman and Hinneiner (6) first described flavonoids as having the 2-phenylchromone (flavone) structure (Fig. 1) in 1952. Currently, it is widely excepted that the flavonoids are benzo-γ-pyrone (Fig. 2) derivatives, which exist as aglycone (without sugar) or glycoside (with sugar) forms. The benzo-γ-pyrone derivatives can be divided into at least 8 major classes namely; flavanone, flavonol, isoflavone, isoflavonol, flavanol, chalcone, flavone and anthocyanidine (12). Table 1 shows the different classes, representative flavonoids, and the corresponding source .

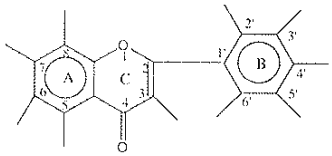

Figure 1. Flavone

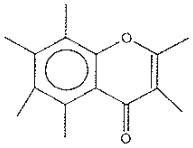

Figure 2. Benzo-γ-pyrone

The hydroxylation pattern, substitution (eg. methoxylation and isoprenylation), degree of polymerization and the types of conjugated groups (eg. glycosylation, sulfation and malonylation) vary within each class of flavonoid (1,12). Naturally occurring flavonoids are often hydroxylated in positions 3,5,7,3', 4' and 5' (Fig. 1). Methyl groups as well as sugar

Table 1. Flavonoid class and distribution (13-18)

Class	Flavonoid	Major Food Source
Anthocyanidine	oenin, cyanidin	cherries and grapes
Flavonol	quercetin, kaempferol	onions, broccoli, apples, tea, leek berries, grapes, red wine
Flavone	luteolin, apigenin	lemon, olive, celery, red pepper, celery, parsley
Flavonone	naringenin, taxifolin	citrus fruits, peel of citrus fruit
Flavanol	condensed tannin, catechin, epicatechin, epigallocatechin	green tea, black tea, red wine
Isoflavone & Isoflavonol	genistein, daidzein	soya beans and legumes
Chalcone	phloretin, butein	(not available)

substituents such as L-rhamnose, D-glucose, gluco-rhamnose, galactose and arabinose can be incorporated into the flavonoid molecule (usually at positions 3 or 7) (Fig. 1) via glycosidic lingkage (1,12).

Metabolism in animals and humans.

The absorption and the metabolism of flavonoids in humans has hardly been studied. Several extensive animal studies show that flavonoids are partly absorbed into the intestine (19-25). Only the aglycones (free flavonoids without a sugar molecule) are readily absorbed through the gut wall. (20). However, most dietary flavonoids are bound to sugars (glycoside form) and the intestinal wall does not contain nor secretes the relevant enzymes for the hydrolysis of the glycosidic bond of the flavonoids (26). Hydrolysis of the flavonoid glycosidic bond only occurs in the colon, aided by the micro-organisms(26). A recent human study has shown that the absorption of orally administered quercetin aglycone was 24%, quercetin glycoside from onions was 52% and pure quercetin rutinoside was 17% (27). The plasma quercetin levels in humans who eat onions regularly have been found to be 200 ng/ml (28). Subsequent to absorption, it is known from animal studies that the compounds are primarily broken down in the liver and the resulting metabolites are excreted as glucuronide conjugates and ring-scission phenolic products into the urine and faeces (19-23). However, the significance of these findings for humans is unclear as there is a great possibility for species variations in secondary metabolism (13).

Biological and pharmacological effects of flavonoids

Pharmacological effects of flavonoids were observed as early as 1936 by Rusynyak and Szent Gyorgi (11). Scorbutic guinea pigs were restored to healthy state when fed with flavonoids whilst, vitamin C alone was not able to do so. The flavonoids which were known as vitamin P then was used in the treatment of capillary fragility (29). Many of these compounds are also found to occur as active components in folk medicines (30). Recent interests in the biological and pharmacological effects and their application in health and disease have increased tremendously. Most of the flavonoids exert their beneficial effects through their ability to scavenge free radicals, inhibit enzymes, chelate ions, mimic hormones and thus competitively bind to the corresponding receptors and various other unknown mode of action (31-45).

The flavonoids are known to affect RNA, DNA, and protein synthesis, anti inflammatory and anti allergic activity, collagen biosynthesis, mutagenicity and carcinogenicity, inhibit key enzymes such as ATPase, aldose reductase, glutathione-S-transferase, iodothyronine deiodinase, NADH oxidase, xanthine oxidase, pp60 kinase, uterine peroxidase hyaluronidase, tyrosine kinase and etc., involved in lipid peroxidation phenomena and various other biological systems (31-45).

The most understood mechanism of flavonoids is their capacity as antioxidants. (43). The so called antioxidant properties of flavonoids may arise as a result of its high propensity to electron transfer, ion chelation and direct scavenging of reactive oxygen species (ROS) or reactive nitrogen species (RNS) (42,43). There is increasing evidence that DNA damage caused by free radicals, ROS and RNS have strong implications in carcinogenesis (42). Various studies showed that flavonoids have anticarcinogenic properties (46). Quercetin, one of the most potent antioxidant flavonoid potentiates the growth inhibitory activity of adriamycin (ADR) in MCF-7 ADR-resistant human breast cancer cells (multidrug resistant breast tumor cell) (47). The flavonoids naringenin and rutin protected the UVB induced template plasmid DNA damage (48).

The isoflavones genistein and daidzein (rich in soya) were able to prevent UVA and UVB or peroxyl-radical induced lipid peroxidation (13). These compounds are also able to compete with the oestrogen receptor in breast tumour cell thus inhibiting the mitogenic actions of oestrogen (13). Genistein inhibits tumour cell proliferation and angiogenesis (13). The flavonoid luteolin has been shown to have radioprotective (gamma ray) effect in mice, believed to be attributed to the hydroxyl radical scavenging potency in a direct or endogenous enzyme mediated mechanism (49). Apigenin is able to inhibit the proliferation of B104 rat neuronal cell, arresting at G2-M phase and induce morphological differentiation.The differentiation process resumed when the apigenin was removed from the culture system (50).

The oxidative damage to LDL is considered to be an important stage in the development of atherosclerosis (13). Numerous drugs and dietary components have been reported to prevent the human LDL oxidative modification (51). The flavonoids in red wine, namely catechin, epicatechin, quercetin, resveratoral, anthocyanins and procyanidines were presumed to be responsible for the protective effects on coronary heart diseases (10, 13). A red wine extract (minus the alcohol) inhibited the oxidation of LDL and also reduced the thrombotic phenomena (10). Genistein in soya has been suggested as an anti atherogenic agent (13). *In vitro* studies have shown that this compound is a potent tyrosine kinase inhibitor(13). Thus it may block the actions of the various growth factors such as fibroblast growth factor and platelet derived growth factor (PDGF) which are implicated in the smooth-muscle cell proliferation that forms part of the atherosclerotic process (13).

Numerous flavonoids have been demonstrated to be effective against the toxic actions of snake bite. Their mode of action appeared to be through the inhibition of hyaluronidase (spreading factor) contained in the venom (36). Several plant extracts have also been claimed to have antivenom properties and flavonoids were found to be the active component (36).

The potent inhibitors of cAMP dependent phosphodiesterase in cell free systems, namely quercetin and fisetin potentiated the beta adrenoreceptor agonist mediated lipolysis in isolated rat adipocytes (38). Some flavonoids were reported to be able to exert anti inflammatory action via the inhibition of the key enzymes, cyclooxygenase and lipoxygenase (52). Ipriflavone has been used in humans in the control of otosclerotic bone remodelling disturbance. In vitro studies have shown that quercetin inhibits bone resorption induced by prostaglandin E2 (PGE2) (53). Numerous reports have demonstrated the anti viral, anti microbial as well as anti fungal effects of plant extracts and flavonoids (54,55).

Conclusions

The natural occurrence of flavonoids in plants, their myriad pharmacological effects and the fact that they are dietary compounds has made it a well sought after avenue for the development of potential new therapeutics. To date, several thousand reports have shown the benefits of flavonoids in health and disease. There are numerous problems that need to be recognised and addressed before these compounds could be used as therapeutics.

The solubility of flavonoids in aqueous solution and the absorption through the gut has to be given due consideration as most flavonoids have poor solublility in aqueous solution. One has to bear in mind that the *in vitro* experiments show the direct effect of flavonoid on the system studied whilst these compounds may be subjected to extensive alterations in the in vivo system. One way to overcome this problem would be to target the flavonoid of interest to the desired location in the body. The ideal vehicle and the method as well as the feasibility of this process need to be studied extensively. The ideal dose which is safe for consumption needs to be established. Several reports have indicated that above a certain concentration, some of the antioxidant flavonoids may become prooxidants (56). In addition the accumulation of the flavonoid metabolites in the body may cause nephropathic damage (57). One has to bear in mind that the protective effects of flavonoids in their natural form (obtained through diet) far outweigh their capacity as therapeutics. The use of flavonoids as dietary supplements has already been practised in many countries including Malaysia. However, the necessity for this is questionable. The best and the most effective way to maintain health and prevent disease is to consume flavonoids and other micronutrients in their natural form. So, eat fresh fruits, vegetables, nuts and grains and lead a disease-free life.

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