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Flavonoids in Herbs : Biological Fates and Potential Interactions with Xenobiotics

PEI-DAWN LEE CHAO[1]*, SU-LAN HSIU[1] AND YU-CHI HOU[2]

[1.] Department of Pharmacy, [2.] School of Chinese Medicine, China Medical College, Taichung, Taiwan 404, R. O. C.

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ABSTRACT

Flavonoids represent a major group of natural antioxidants. In recent years, flavonoids have attracted increasing interest due to their various beneficial pharmacological effects and additional abilities to modulate CYPs and P-glycoprotein (Pgp), the product of *mdr* (multidrug - resistance) genes. There is a very large amount of *in vitro* data of flavonoids, but very few reports of animal studies are available. Moreover, information concerning the biological fates of flavonoids is very limited. Therefore, whether published *in vitro* data are predictive of *in vivo* effects need further discussion. On the other hand, flavonoids may activate or inhibit CYPs and Pgp, which may be beneficial in detoxication, in chemoprevention, or in drug resistance suppression. The aim of this review is to give an overview of the research reports on the biological fates of flavonoids and their potential interactions with xenobiotics. The perspectives for future research on flavonoids in herbs will be suggested at the end of this article.

Keywords: Flavonoid, metabolism, pharmacokinetics, fate, interaction, CYP, Pgp

INTRODUCTION

Flavonoids represent a major group of natural antioxidants. The major sources of flavonoids include fruits (e.g. orange, grapefruit, apple, grape), vegetables (e.g. onion, kale, broccoli, green pepper, spinach, tomatoe), soybeans and herbs (e.g. *Sophora japonica, Citrus grandis, Hypericum perforatum*). Flavonoids are present in most plants with high concentrations found in fruit peels, leaves and flowers. Epidemiological studies have suggested a protective role of dietary flavonoids against coronary heart diseases and possibly cancer[1-5]. A variety of flavonoid products are either being actively developed or currently sold as dietary supplements and/or herbal remedies. In recent years, flavonoids have attracted increasing interests due to their various beneficial pharmacological effects including anti-inflammatory, anti-allergic[6], antiviral[7,8], anticancer[9-11] and antioxidation properties[12]. However, there is a very large amount of *in vitro* data of flavonoids, but very few available reports of animal studies. Furthermore, information concerning the biological fates of flavonoids is very limited. Therefore, whether the *in vitro* data are predictive of human effects is worthy of discussion .

In 1930, a flavonoid glycoside rutin was isolated from oranges and designated as vitamin P. Since then, a flurry of research on flavonoids began and resulted in more than 4,000 flavonoids being identified. Flavonoids are primarily present as glycosides in nature. Information on the absorption, distribution, metabolism, and excretion of flavonoid glycosides in animals is limited and therefore, the biological fates of flavonoids in herbs have not been fully understood [13,14]. On the other hand, flavonoids were found to modulate CYPs and P-glycoprotein (Pgp), the product of *mdr* (multidrug-resistance) genes, which may be beneficial in detoxication, in chemoprevention or in drug resistance suppression. The aim of this review is to give an overview of the research reports on the biological fates of flavonoids and their potential interactions with xenobiotics.

I. *Biological Fates of Flavonoids*

(I) *Absorption of flavonoids*

Among flavonoids, quercetin and its glycosides are the most abundant in natural resources. In the past few years, there have been extensive studies on the absorption of quercetin and its glycosides in pure compounds or in diet[15-19]. On review of the literatures, controversies abound concerning which form of flavonoids is actually absorbed: glycoside, aglycone, or both forms. Hollman et al. compared the absorption of various forms of quercetin in human volunteers[18]. Their results reported that both quercetin and its glycosides could be absorbed and the absorption from onion (52%) was greater than that from quercetin aglycone (24%). The absorption from rutin, a quercetin rutinoside, was the poorest (17%) in healthy ileostomy subjects[19]. However, Walle et al. did not detect any quercetin glucosides in the ileostomy fluid; whereas substantial amount of quercetin aglycone was identified, suggesting that quercetin glucosides were hydrolyzed to quercetin in the small intestine and then absorbed[20].

Flavonoid glycosides (e.g. rutin, naringin, hesperidin, baicalin, daidazin and phellamurin whose structures are shown in Figure 1) are generally hydrophilic in nature and thus cannot be transported across membranes by passive dif-

* Author for correspondence. Tel:886-4-22053366-1905; Fax:886-4-22031028; E-mail address: pdlee@mail.cmc.edu.tw

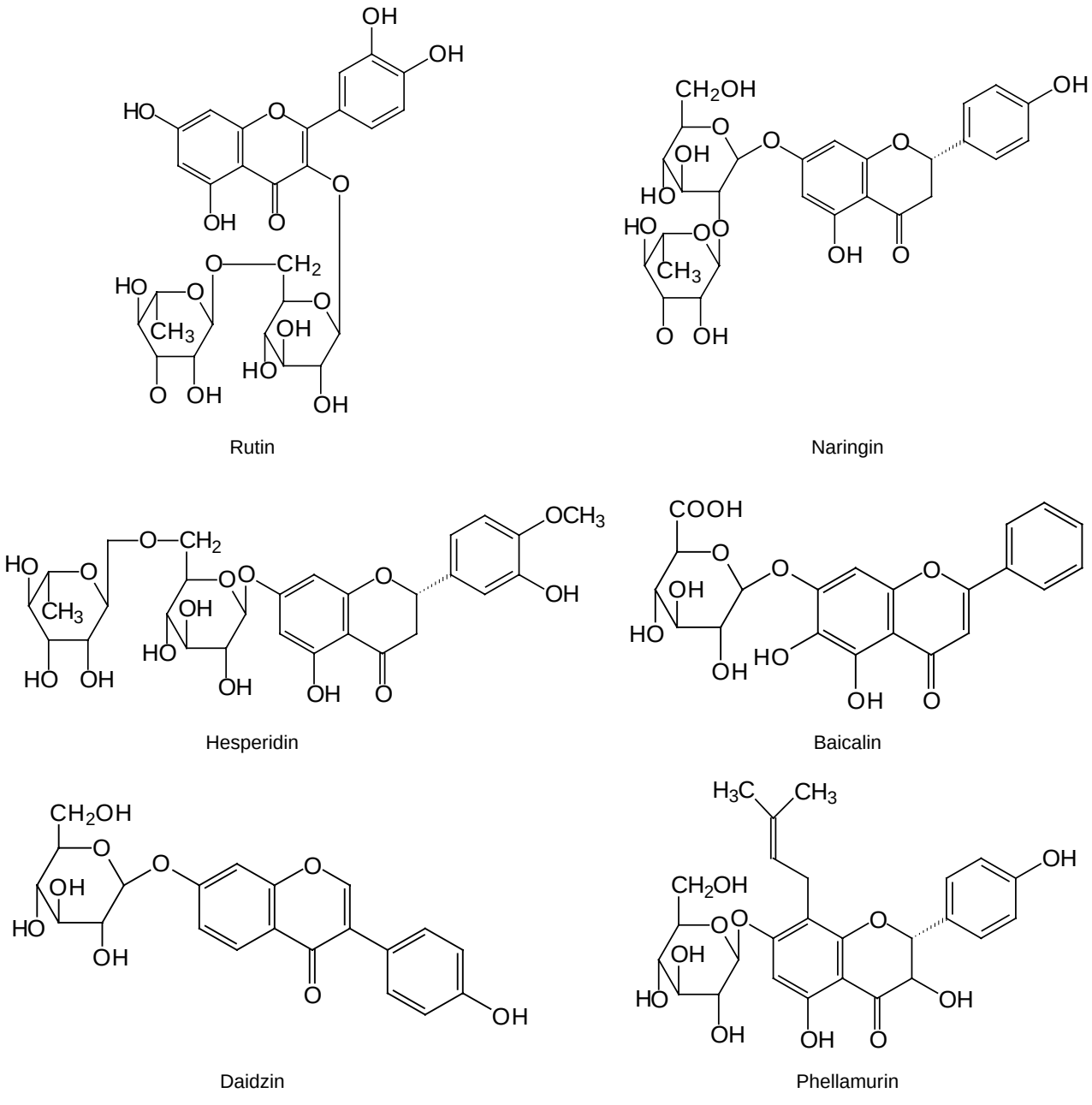


Figure 1. Chemical structures of flavonoid glycosides

fusion. The absorption of quercetin glucoside's parent form led to a speculation that it was transported across gut wall by the intestinal sodium-glucose transporter[19]. Upon hydrolysis by the enzymes released by enterobacteria, the sugar moiety of flavonoid glycosides were cleaved and resulted in more lipophilic aglycones, which become permeable through the gut wall. Studies showed that quercetin glucosides from onions were absorbed more efficiently than those from apples or quercetin glycoside supplements. This can be explained as the attached sugar moiety on the flavonoid glycosides affected the rate of hydrolysis of glycosides and thus the absorption of their aglycones[21]. Morand et al. reported that the nature of glycosylation greatly influences the efficiency of quercetin absorption in rats[22]. Quercetin 3-glucoside can be absorbed in the small intestine and the plasma level of its glucuronides/sulfates was three times higher than quercetin itself. This fact can be explained by the higher water solubility of quercetin 3-glucoside than quercetin. Olthof et al. suggested that the quercetin glucosides were rapidly absorbed in humans irrespective of the position of the glucose moiety[23]. However, the absorption of rutin, a quercetin glycoside containing a 3-glucose-rhamnose moiety, was even lower than its aglycone quercetin. This might be ascribed to the steric hindrance of 3-glucose-rhamnose moiety to enzymolysis. In contrast, 3-rhamnose moiety could not be absorbed in the small intestine, indicating the lack of rhamnosidase activity in rats.

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(II) *Determination of flavonoids and their conjugated metabolites in body fluids*

Since the standards of flavonoid conjugated metabolites are not available, they were determined as their aglycones after hydrolysis by β-glucuronidase/sulfatase. Because flavonoid aglycones (e.g. quercetin, naringenin, hesperetin, baicalein, daidzein and neophellamuretin whose structures are shown in Figure 2) are prone to oxidation, the optimum quantitation methods for the conjugated metabolites of individual flavonoid in serum and urine were established in our laboratory[24-29]. In literatures, a mixed enzyme containing predominately β-glucuronidase and a little sulfatase was commonly used for the hydrolysis of glucuronides/sulfates of flavonoids in serum. Recently, it was gradually realized that more sulfates of flavonoid than glucuronides were present in the body fluids[29]. Therefore, separate hydrolysis of body fluids using glucuronidase and sulfatase, respectively, would be more appropriate in order to measure the sulfates and glucuronides more accurately. Regarding the optimum condition for enzymolysis, ascorbic acid was usually added to protect the flavonoid aglycones from oxidation. In addition, the optimum time for hydrolysis was investigated by time course study. The time needed for enzymolysis of various flavonoid conjugates was rather different. In general, it took less time for the hydrolysis of sulfates relative to the correspondent glucuronides. For example, baicalein glucuronides needed 7 h, whereas the sulfates needed only 2 h[29]. Daidzein glucuronides needed 14 h, whereas the sulfates needed only 2 h.

The HPLC analysis system used for the determination of aglycones was established for various flavonoids in our laboratory. In general, the mobile phase needs to be acidified with acetic acid or phosphoric acid in order to obtain peaks on chromatogram in better shapes[24-29].

(III) *Metabolism and distribution of common flavonoids*

Naringin is a major flavonoid constituent of the fruits of *Citrus aurantium*, and *C. grandis*, *etc*. The fates of naringin and naringenin were investigated in rabbits by oral administration of naringin and naringenin, respectively. In

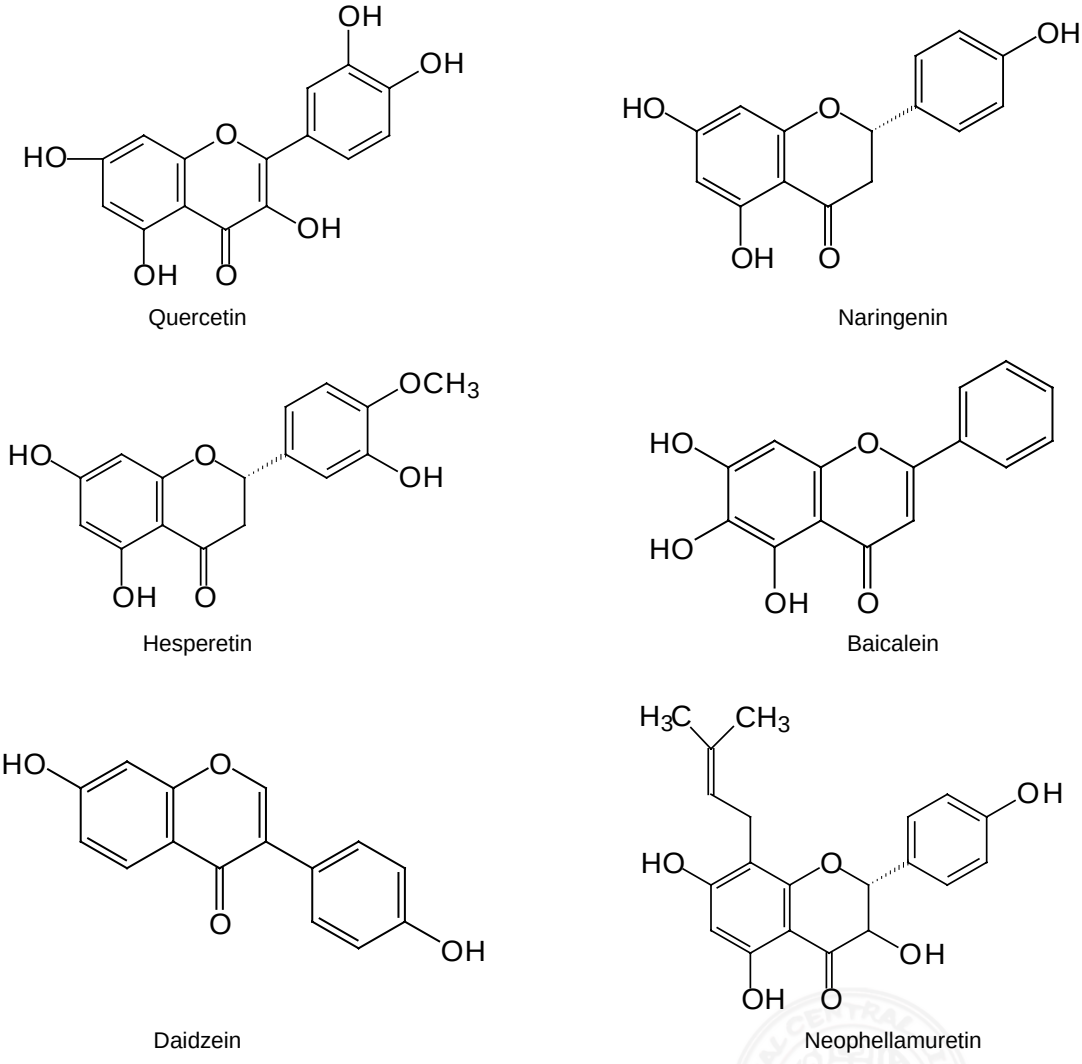


Figure 2. Chemical structures of flavonoid aglycones

addition, naringenin was administered intravenously in order to measure the absolute bioavailability of naringenin. The results showed that naringin was not absorbed *per se* and the major molecules circulating in blood were naringenin glucuronides/sulfates; whereas only a small amount of naringenin was present in the circulation[24]. When naringenin was administered orally, naringenin glucuronides/sulfates formed rapidly and present predominately in the bloodstream. However, the patterns of the serum profiles of naringenin glucuronides/sulfates were rather different between oral administrations of naringin and naringenin, indicating that the aglycone naringenin was absorbed more rapidly to result in much earlier T_{max} and higher C_{max} of its conjugated metabolites and eliminated faster.

Hesperidin is a major flavonoid constituent of the fruits of *Citrus reticulata*. The fates of hesperidin and hesperetin were investigated in rabbits. The results indicated that hesperidin was not absorbed *per se*. The major molecule circulating in the bloodstream was hesperetin glucuronides/sulfates[26]. Another flavanone glycoside phellamurin, a major constituent of *Phellodendron wilsoni*, was orally administered to rats. The parent form, phellamurin, was not absorbed, whereas the major molecules circulating in the bloodstream were the glucuronides/sulfates of its aglycone neophellamuretin, which emerged rapidly after the dosage was administered[27]. These metabolites were immediately distributed to the brain, indicating that they can cross the blood brain barrier[28].

Another rat study investigated the absorption of baicalein and baicalin, a glucuronide of baicalein, which were flavonoid constituents of Scutellariae Radix. The results indicated that the patterns of the serum profiles of baicalein glucuronides/sulfates were rather different between baicalin and baicalein, suggesting that the aglycone baicalein was absorbed more rapidly to result in much earlier T_{max} and higher C_{max} of its conjugated metabolites and eliminated faster than baicalin[30].

When flavonoid aglycones (e.g. quercein, morin, naringenin and hesperetin) were intravenously administered to rabbits, they were metabolized very rapidly and intensively. The major metabolites were their conjugated metabolites, e.g. sulfates and glucuronides[24-26]. Specifically , the conjugated metabolites of quercetin showed much higher serum levels than its parent form since the first blood sampling time at 5 min after dose administration .

After oral intake, deglycosylation of flavonoid glycosides has been proposed as the first stage of metabolism in the gastrointestinal tract. Day et al. used human small intestine and liver cell-free extracts to investigate whether there is glucosidase activity toward flavonoid glycosides[31]. Some but not all flavonoid glycosides were hydrolyzed by the small intestine and liver cell-free extracts.

Flavonoids may undergo reactions such as hydroxylation, methylation and reductions. Conjugation reactions with sulfate and/or glucuronic acid seem to be the most common pathway for flavonoid metabolism. Recently, sulfation metabolism was found to be more prominent than the glucuronidation pathway for quercetin, morin, naringenin, hesperetin, daidzein and baicalein in our laboratory. The conjugated metabolites of flavonoids are still believed to possess antioxidation ability *in vivo*, although may be weaker than the aglycone parent forms.

Based on the comparisons of the biological fates between the flavonoid glycosides and their corresponding aglycones, glycosides served like a sustained-released natural prodrugs of their aglycones. The advantages of flavonoid glycosides include their high abundance in herbs and good water solubility making them valuable resources of antioxidants.

(IV) *Bacterial degradation of flavonoids*

The gastrointestinal metabolism of flavonoids has been reported to be dependent on intestinal microflora[32-36]. The microflora residing in the intestine can release enzymes to gradually hydrolyze the glycosides into aglycones, which are absorbable by the intestine. The aglycones that are not absorbed in the small intestine can thereafter be degraded by colonic microflora into phenolic acids. From human feces, two phenotypically different types of bacteria utilizing quercetin-3-glucoside as carbon and energy source were isolated[35]. Isolates of one type were identified as strains of *Enterococcus casseliflavus*. They utilized the sugar moiety of the glycoside, but did not degrade the aglycone further. The second type of isolate was identified as *Eubacterium ramulus*. This organism was capable of degrading the aromatic ring system by detachment of the A ring from the residual flavonoid molecules and the opening of the heterocyclic C ring. 3,4-Dihydroxybenzaldehyde, phloroglucinol and ethanol were detected in small amounts as breakdown products of quercetin-3-glucoside. Another *in vitro* fermentation study using human faecal flora indicated that rutin, naringin and naringin were completely metabolized within the 72 h fermentation period[36].

(V) *Excretion of flavonoid conjugates into bile and urine*

The sulfates and glucuronides of flavonoids are ionized under physiological pH and very soluble in water; therefore, they are readily excreted by animals into bile and urine. When excreted into bile, the conjugated metabolites are passed into the duodenum and metabolized by enterobacteria, which hydrolyzes the sulfates/glucuronides and further fragments the flavonoids aglycones into aromatic acids. The resulting metabolites may be reabsorbed and enter an enterohepatic circulation to result in a second peak of serum profile. The structure of flavonoid conjugates determines the extent of biliary excretion and enterohepatic circulation. The half-life of elimination also can be prolonged and the plasma levels of quercetin metabolites have been detected up to 24 h after flavonoid consumption, indicating a possible build-up of quercetin metabolites in plasma after repeated intake of onion[37].

Urinary excretion of the metabolites of flavonoid gly-

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cosides in Citrus Aurantium Fructus and Scutellariae Radix were investigated in humans[38-40]. The variation of urinary excretion of flavonoid metabolites among individuals is very large. The urinary recovery of flavonoid metabolites from Scutellariae Radix decoction was predominantly as sulfates and glucuronides of baicalein and wogonin. The amount of baicalein sulfates was much more than the glucuronides, whereas the amounts of sulfates and glucuronides of wogonin were comparable. Previous studies have shown that the urinary excretion of flavonoid conjugated metabolites, based on the fraction of intake, can vary from trace to 24.6% depending on the source and structure of flavonoids[38].

II. *Potential Flavonoid-xenobiotic Interactions*

(I) *Modulation of CYPs by flavonoids*

Flavonoids exert a highly specific effect on crucial regulatory enzymes and receptors in organisms. Among the proteins that interact with flavonoids, cytochromes P450 (CYPs), key enzymes involved in the metabolism of xenobiotics (e. g. pharmaceuticals, carcinogens), play a prominent role [41]. Flavonoids influence these enzymes in several ways including the induction of the expression of several CYPs and modulate (inhibit or stimulate) their metabolic activity. Therefore, the interactions of flavonoids with CYPs give rise to several important issues. Flavonoids might dramatically affect the plasma concentration of pharmaceuticals resulting in either overdose or loss of their therapeutic effects. The other important issue is the involvement of flavonoids in the process of carcinogenesis. Flavonoids might enhance activation of carcinogens via induction of specific CYPs, which would be detrimental[42, 43]. On the other hand, inhibition of CYPs involved in carcinogen activation and scavenging reactive species formed from carcinogens by CYP-mediated reactions can be beneficial properties of various flavonoids.

Induction of CYP activity by flavonoids proceeds via various mechanisms including direct stimulation of gene expression through a specific receptor and/or CYP protein, or mRNA stabilization[44, 45]. Certain flavonoids induce CYPs via binding to aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor[46, 47]. This mechanism is associated with the enhanced activity of CYP1 family enzymes including CYP1A1, 1A2 and 1B1 that are responsible for the activation of carcinogens such as benzo[a]pyrene, 7,12-dimethyl benzo[a]anthracene and aflatoxin B1[48].

The inhibition of gene expression of CYP1 family enzymes through blocking AhR plays an important role in the chemopreventive properties of flavonoids. For instance, quercetin, one of the most popular natural flavonoids, binds as an antagonist to AhR and inhibits the CYP1A1 mRNA transcription and protein expression which resulted in reduced benzo[a]pyrene-DNA adduct formation[49, 50]. However, flavonoids act more often as AhR agonists to induce CPY1A1 and CYP1A2 activities[51,52].

The mutagenicity of 2-amino-3-methylimidazo[4,5-f]quinoline in the Ames test strain *Salmonella typhimurium* TA98 was inhibited by flavonoids with distinct structure-antimutagenicity relationships, and this effect correlated with inhibition of various CYP isozymes[53-55]. However, it appears that most flavonoids are unlikely to reach the plasma levels necessary to cause an antimutagenic effect[48].

Synthetic and naturally occurring flavonoids are effective inhibitors of four CYP metabolizing xenobiotics: CYP1A1, 1A2, 1B1 and 3A4. While specific activities of CYP1A1 and 1B1 were solely inhibited by tested flavonoids, certain metabolic activities of CYP3A4 and 1A2 were also stimulated by some flavonoids[54,55]. From available data on flavonoid-CYP interactions, the general conclusion could be drawn that flavonoids possessing hydroxyl groups inhibit CYP activity, whereas those lacking hydroxyl groups can stimulate the enzyme activity. In another study, quercetin inhibited metabolism of aryl hydrocarbons while stimulating the activity of cDNA expressed human CYP1A2[56]. Thus, flavonoids can either inhibit or activate human CYPs depending upon their structures, concentration, and experimental conditions.

(II) *Modulation of P-glycoprotein by flavonoids*

Cancer cell resistance to chemotherapy is often mediated by overexpression of P-glycoprotein (Pgp), a plasma membrane ABC (ATP-binding cassette) transporter, which extrudes cytotoxic drugs at the expense of ATP hydrolysis. On the other hand, Pgp in normal tissues may serve as a cellular defense mechanism against naturally occurring xenobiotics. A series of flavonoids commonly found in plants was tested for their ability to modulate adriamycin accumulation and efflux in Pgp-expressing HCT-15 colon cells[57]. Many flavonoids in the micromolar range inhibited the accumulation of adriamycin, i.e. quercetin, kaempferol and galangin. Flavonoid-induced stimulation of efflux was rapid and was blocked by the multidrug - resistant reversal agents verapamil, vinblastine, and quinidine. Quercetin showed partial protection against adriamycin-induced cell growth inhibition. It was concluded that certain favonoids may acutely up-regulate the apparent activity of Pgp. In another study, the effects of flavonols on Pgp activity were studied in rat hepatocytes by assessing the transmembrane transport of Pgp substrates like Rhodamine-123 and doxorubicin[58]. The results indicated that flavonols, reported to strongly up-regulate the apparent activity of Pgp in cancer cell lines, may modulate differently the transport of putative Pgp substrates in normal rat hepatocytes. Moreover, quercetin and genistein potentiate the effects of adriamycin and daunorubicin, respectively, in a multidrug-resistant MCF-7 human breast-cancer cell line[59,60]. Another study used cultured mouse brain capillary endothelial cells (MBEC4 cells) to investigate the effect of quercetin[61]. The result indicated that low concentrations of quercetin activated the activity of Pgp, whereas high concentrations of quercetin inhibited Pgp[62]. Due to the potential importance of Pgp in cellular defense

against environmental carcinogens[63,64], there is accumulated evidence on cancer chemopreventive properties of flavonoids from experiments with cell lines.

Recently, it has been reported that prenylated flavonoids bind with high affinity, and strongly inhibit drug interactions and nucleotide hydrolysis. As such, they constitute promising potential modulators of multidrug resistance[65]. The *in vitro* everted gut studies by our group indicated that phellamurin, a prenylated flavonoid glycoside, significantly inhibited the function of intestinal Pgp. Nevertheless, animal studies using rats showed that it markedly decreased the blood level of cyclosporin, a substrate for CYP3A4 and Pgp[66]. The *in vivo* effects of quercetin on the fate of cyclosporin have been investigated in rats and pigs[67]. Likewise, the *in vivo* results that quercetin greatly inhibited cyclosporin absorption was found contradictory to its *in vitro* effect of inhibition on intestinal Pgp. Apparently, the *in vitro* data on Pgp are not necessarily predictive of the *in vivo* effects of flavonoids.

(III) *Modulation on multidrug resistance protein (MRP) by flavonoids*

The membrane protein mediating the ATP-dependent transport of lipophilic substances conjugated to glutathione, glucuronate, or sulfate, have been identified as members of the multidrug resistance protein (MRP) family[68]. A soybean isoflavone genistein was found as an inhibitor on the basis of its effect on drug accumulation in MRP1-overexpressing cells[69]. More studies concerning the effects of flavonoids on MRP are needed in the future.

(IV) *Flavonoid-drug interactions*

Since the first report dealing with the grapefruit juice-drug interaction was published in 1989, increasing attention has been focused on flavonoid-drug interactions. The *Citrus* flavanone naringin was proved not to be the causative agent in grapefruit juice[70]. Subsequently, the minor flavonoid constituents, naringenin and quercetin. were investigated for their effects on CYP3A4, Pgp and MRP. They were found as potent inhibitors of CYP3A4[71,72] and modulator of Pgp[60,67]. The *in vivo* results that marked a decrease of cyclosporin absorption caused by the coadministration of quercetin indicated that the potent inhibition of CYP3A4 by quercetin was not in agreement with the *in vivo* effect.

In recent years, there is a growing increase in the sale of a herbal antidepressant, St. John's wort. However, important interactions between St. John's wort and many drugs have been described[73]. Concomitant use of St. John's wort with CYP3A eliminated medicines e.g. cyclosporin might bring about a subtherapeutic level that could result in acute heart transplant rejections[74]. Although not all investigations yielded the same results, most agreed that *Hypericum* extracts activated CYP3A4[75-78]. Although induction of CYP3A4 isozymes could explain a majority of interactions, such an effect would not explain all the drug interactions. Plasma digoxin concentrations, for example, are decreased through the induction of intestinal Pgp and there is evidence that St. John's wort could induce intestinal Pgp in rats and humans[79]. St. John's wort consists of the leaves and flowering tops of *Hypericum perforatum*. The alcoholic extracts contain 0.1-0.3% hypericin, 2-4% flavonoids (e.g. quercetin, ruin, kaempferol, luteolin, apigenin and quercitrin) and up to 6% hyperforin. From the results of *in vivo* interaction studies using flavonoids (e.g. phellamurin, quercetin) as precipitant drug[66,67], the content of flavonoids in St. John's wort might be responsible for the interaction with CYP 3A4/Pgp substrates, e.g. cyclosporin.

CONCLUSIONS

Flavonoids are a "gold mine" for human health[79]. The biological fates of flavonoids are still not clear. In general, oral intake of either the flavonoid glycosides or aglycones mainly present in the circulation as their conjugated metabolites of the aglycone, predominately as sulfates. It is suggested that the conjugated metabolites of flavonoids be more focused for *in vitro* studies to evaluate the *in vivo* activities of flavonoids.

Flavonoids have a potential to cause interactions with xenobiotics. To understand the pharmacokintics of a "precipitant drug" is very important for elucidating the mechanism of interaction with an "object drug". The significant role of the conjugated metabolites of flavonoids for interaction with xenobiotics is speculated. The direct *in vitro* effects of the sulfates/glucuronides on the modulation of CYPs, Pgp and MRPs are worthy of investigation. For the visualization of multidrug resistance *in vivo*, the use of single photon emission tomography (SPET) and positron emission tomography (PET) are feasible to study the functionality of Pgp and MRP transporters (80). Modulation of CYPs, Pgp and MRP by flavonoids may be beneficial in detoxication, in chemoprevention or in drug resistance suppression.

Because flavonoids are very common constituents in various herbs, it is proposed that herbs represent a potential and possibly an overlooked cause for drug interaction. Medications whose absorption and metabolism are mediated by CYPs, Pgp, and/or MRP should require close monitoring when coadministered with flavonoid-containing herbs or dietary supplements.

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中草藥黃酮類：生物體內之命運及與外源物之交互作用

李珮端[1*]　徐素蘭[1]　侯鈺琪[2]

1. 中國醫藥學院　藥學系
2. 中國醫藥學院　中醫系
台中市學士路91號

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摘　要

黃酮化合物是天然抗氧化物中主要的一類。近幾年來，黃酮類因其具多種優越之藥理活性，同時亦因它們可調控CYPs、P-glcoprotein（多重藥物抗藥性基因之產物）而備受矚目。目前已有相當多相關之體外試驗文獻，但卻僅有少數體內試驗報告，有關黃酮類於生物體內命運之相關報告亦極為有限，因此黃酮化合物的體外試驗結果，是否可直接推論體內效應，是一值得探討的問題。另外，黃酮類可能活化或抑制CYPs、Pgp，因而造成對其他外源物體內命運之影響，此種作用未來或可應用於解毒、化學預防或克服藥物抗藥性等方面。本文主要係回顧有關黃酮類於生物體內之命運及其與外源物交互作用之相關文獻，並對有關中草藥黃酮類之未來研究提出建議。

關鍵詞：黃酮類、代謝、動力學、交互作用、細胞色素、P-醣蛋白