REVIEW ARTICLE

Accepted 4 April 2001
Revised 1 March 2001
Received 13 September 2000
Indian J. Pharm. Sci., 2001, 63(3) 187-195

Bioflavonoids - Their Pharmacokinetics and Interaction with Cytochrome P_{450} Isozymes and P-Glycoprotein

M. SRIPAL REDDY, K. RAJ NARAYANA, M.R. CHALUVADI AND D.R. KRISHNA*
Drug Metabolism and Clinical Pharmacokinetics Division
University College of Pharmaceutical Sciences
Kakatiya University, Warangal-506 009.

Bioflavonoids have a variety of biological effects in various mammalian cell systems both *in vitro* and *in vivo*. There are very few reports on their pharmacokinetics following administration in pure forms. Bioflavonoids have been implicated in quit a few drug interactions. These interactions seem to involve Cytochrome P_{450} and/or P-glycoprotein. In this review the available details on pharmacokinetics of various bioflavonoids in animals and human and the influence on Cytochrome P_{450} and P-glycoprotein have been presented. Further, the pharmacokinetic parameters like C_{max}, T_{max}, $T_{1/2}$ and AUC of bioflavonoids and the effect of dose on these parameters have been discussed. The available information on bioflavonoids biotransformations, such as methylation, sulfo- or glucuro-conjugations by different transferases in liver, has been reported. Different metabolites of quercetin (a widely investigated molecule), their metabolic pathways, clearance and volume of distribution of different bioflavonoids have been cited. Bioflavonoids have been reported to interact with cytochrome P_{450} isozymes particularly with 3A4 series and therefore, may alter the disposition of the concurrently administered drugs. P-glycoprotein, an important membrane protein, is produced as a result of mdr1 gene expression and is responsible for development of cytotoxic drug resistance in cancer. It has been reported that P-glycoprotein activity seems to be modulated by bioflavonoids. The reports on modulation of P-glycoprotein by bioflavonoids using cell line models have been reviewed and presented.

Bioflavonoids (BF) are a group of polyphenolic compounds, which are widely distributed through out the plant kingdom, and consist of about 3000 varieties[1]. The basic structures of various BF (Fig.1) with their different functional groups are represented in Table 1. They have a variety of biological effects on various mammalian cell systems, *in vitro* as well as *in vivo*[2,3] and have been shown to inhibit the growth of various cancer cell line *in vitro* and reduce tumor progression in experimental animals[4]. Absorption, distribution, metabolism and excretion of various BF compound in experimental animals and human have been studied using BF rich diets like onions, apples and tea. BF appear to influence Cytochrome P_{450}(CYP) mediated metabolism of some drugs. Some of them have been reported to modulate P-glycoprotein (P-gp) activity, thus affecting the efflux of drugs and other xenobiotics from the cell.

* For Correspondence

PHARMACOKINETICS OF BIOFLAVONOIDS

Absorption:

Understanding the absorption of BF is an important unsolved problem to judge their many alleged health effects. Indeed, it is often stated that BF present in foods cannot be absorbed from the intestine because they are bound to sugars as glycosides[5]. Bioavailability and absorption kinetics differed widely between sources, a major difference between these sources is the type of glycoside. However, it cannot be ruled out that the differences

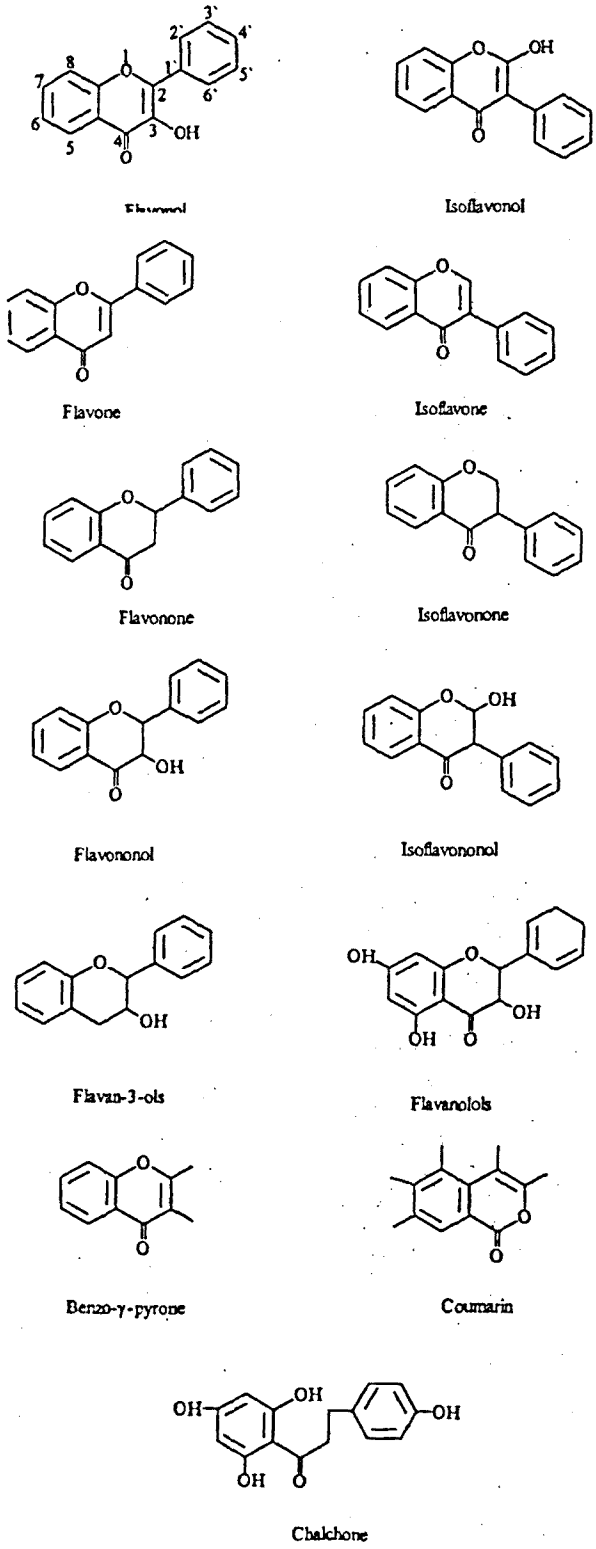

Fig. 1: Basic structures of various bioflavonoids and related compounds

between apples and onions in cell wall structures, location of glycosides in cells, or their binding to cell constituents also affects the liberation of quercetin from those foods in the gastrointestinal tract. Whatever is the absorption site (small intestine or caecum), it is important to determine whether quercetin could be transferred across the digestive mucosa either by purely passive process or by carrier mediated process. Hollman *et al.*,[6] studied absorption of quercetin from onions and of a major glycoside from tea, because onions and tea are the main dietary sources besides wine.[7] Onions contain quercetin mainly as glycosides, where as quercetin rutoside predominated in tea[8-10]. Quercetin glycosides from onions need to be liberated from food matrix before being absorbed. The absorption of quercetin aglycone would probably be greater than the quercetin rutoside within the gut[11]. Thus there is a predominant effect of the carbohydrate moiety on the absorption of quercetin and intestinal sugar carriers may also play a role in the absorption of BF. But in contrast, it was reported that the absorption of quercetin glycosides from onions (52%) is far better than that of the pure aglycone (24%)[12]. Manach *et al.*,[13] studied absorption of rutin and quercetin in rats and he noticed that there was a difference between these two in the rate of absorption from the gut and appearance of quercetin in blood plasma, when administered as rutin or quercetin. When rats are fed with rutin rich diet, quercetin metabolites could be found in plasma only after a significant breakdown of rutin to quercetin by the caecal microflora. Quercetin concentrations measured in caecal contents were lower in rats fed on rutin diet than in those fed with quercetin diet. Thus the possibilities of absorption of this flavonol appear to be greater with quercetin diet than with rutin diet. It implies that quercetin is available for digestive absorption within the small intestine and in the large bowel, where as, rutin has to be completely hydrolyzed to quercetin in colon before it is absorbed. Quercetin glycoside is actively absorbed from small intestine, where as quercetin rutoside is absorbed from colon after deglycosylation[59]. Hollman *et al.*,[15] showed that quercetin from onions, which contain only glycosides, was rapidly absorbed, whereas pure quercetin-3-rutinoside, the major species in tea, showed a markedly delayed absorption. The absorption rate from apples, which contain a variety of glycosides, was intermediate. Thus, these results point to a predominant role of the sugar moiety in the bioavailability and absorption of dietary quercetin in the human body. Uptake of ferulic

TABLE 1: FLAVNOIDS CLASSIFICATION AND SUBSTITUTION PATTERN

	3	5	7	2'	3'	4'	5'
Flavonols :							
Kempferol	OH	OH	OH	H	H	OH	H
Morin	OH	OH	OH	OH	H	OH	H
Rutin	O-R'	OH	OH	H	OH	OH	H
Myricetin	OH	OH	OH	H	OH	OH	OH
Quercetin	OH	OH	OH	H	OH	OH	H
Quercetrin	O-Rh	OH	OH	H	OH	OH	H
Myricitrin	O-Rh	OH	OH	H	OH	OH	OH
Spirenoside	OH	OH	OH	H	OH	O-Glu	H
Galangin	OH	OH	OH	H	H	H	H
Robinin	O-R'	OH	OH	H	H	OH	H
Kaempferide	OH	OH	OH	H	H	O-Me	H
Fisetin	OH	H	OH	H	OH	OH	H
Rhamnetin	OH	OH	O-Me	H	OH	OH	H
Flavonones :							
Hesperitin	H	OH	OH	H	OH	O-Me	H
Naringin	H	OH	O-R	H	H	OH	H
Naringenin	H	OH	OH	H	H	OH	H
Eriodictyol	H	OH	OH	H	OH	OH	H
Hesperidin	H	OH	O-Me	H	OH	O-Me	H
Pinocembrin	H	OH	OH	H	H	H	H
Likvirtin	H	H	OH	H	H	O-Glu	H
Flavones :							
Rhoifolin	H	OH	O-R'	H	H	OH	H
Apigenin	H	OH	OH	H	H	OH	H
Tangeretin	H	O-Me	O-Me	H	H	O-Me	H
Flavone	H	H	H	H	H	H	H
Baicalein	H	OH	OH	H	H	H	H
Luteolin	H	OH	OH	H	OH	OH	H
Chrysin	H	OH	OH	H	H	H	H
Techtochrysin	H	OH	O-Me	H	H	H	H
Diosmetin	H	OH	OH	H	OH	O-Me	H
Diosmin	H	OH	O-R'	H	OH	O-Me	H
Flavanolos :							
Silibinin	OH	OH	OH	H	H	-O-L-O-	
Silymarin	OH	OH	OH	H	H	-O-L-O-	
Taxifolin	OH	OH	OH	H	OH	OH	H
Pinobanksin	OH	OH	OH	H	H	H	H
Flavan-3-ols :							
Catechin	OH	OH	OH	H	OH	OH	H
Isoflavones :							
Genistein	–	OH	OH	H	H	OH	H
Daidzin	–	H	O-Glu	H	H	OH	H

-O-Me = Methoxy, -O-GLU = Glucosyl, --O-R' = Alkoxy, -O-L-O = Selane.

acid form dietary sources, such as tomatos, suggests that ferulic acid is more bioavailable than individual dietary BF and phenolics so far studied[16]. Hyperfolin pharamacokinetics was linear up to 600mg of the extract and plasma concentration curves in volunteers fit well in an open two-compartmental model[15]. After oral administration, absorption of quercetin ranged from 0-50% of the dose. Bioavailability of quercetin from both apples and of pure quercetin rhamnoside was 30% when compared to onions[18]. After 50 mg/kg administration of quercetin to the pigs, the oral bioavailabilty of free quercetin is 0.54%, quercetin in the form of conjugate is 8.6% and in the form of metabolite is 17%. Rutin was absorbed more slowly than quercetin because, the caecal microflora must hydrolyze it first, whereas, quercetin was absorbed from the small intestine[13,19]. But Staffeldt *et al.*,[20] reported that humans absorb appereciable amounts of quercetin and the absorption is enhanced by conjugation with glucose. Quercetin, apigenin, chrysoeriol and isorhamanetin aglycone could be detected neither in the GI lumen after 12 h nor in the kidneys at any time, but traces were found in the liver at 1.5 and 12 h[21].

Distribution:

Limited data is available on the distribution of BF. For this reason and because of the wide range in the solubility of BF, predictions of the rate of absorption from intestine and penetration through skin and mucous surface are difficult to make[13,18]. Larger amount of orally taken BF would probably be delivered, more or less directly to the liver, which decompose them. So far little is known about the affinity of BF for plasma proteins, but due to the low polarity of many aglycones, especially of those that are strongly methylated, they would probably be bound to serum albumin[22]. Hollman *et al.*,[23] showed that quercetin is found in the circulation after consumption of major dietary sources of quercetin and quercetin-3-rutinoside like apple, onions and tea. Synthetic BF like 3-methyl-4',6-dihydroxyl-3',5'-dibromo-flavone and 3-methyl-4',6-dihyroxyl-3',5'-diiodo-flavone are thyroxine (T_4) analogs. They disappear very quickly from plasma and enter into the tissues. T_4 content calculated, as percentage in the liver is much higher than that of the BF, this means that in the liver, many binding sites exist for T_4, but not for BF[24]. After i.v. injection of quercetin in two studies, the elimination half-lives were 2.4 and 0.7 h, the volume of distribution at steady state was 92.6 and 6.21 and the total body clearance was 34.6 and 28.1 1/h respectively[18]. Quercetin has a strong affinity for proteins and provides no direct protective effect during LDL oxidation[25]. After oral ingestion of 300 g of fried onions the T_{max} values of quercetin-4'-glucoside was 1.3 h and for isorhamnetin-4'-glucoside was 1.8h[26]. During long term dosing of hypericum extract (3X300 mg/day), a steady state was reached after 4 days for hypericin and pseudohypericin. The AUC values increased in nonlinear manner with increase in dose. The mean maximal and minimal plasma levels during the steady-state treatment were 8.5 and 5.3 ng/ml respectively for hypericin and 5.8 and 3.7 ng/ml respectively for pseudohypericin[27].

Metabolism:

The two major sites of BF metabolism are the liver and colonic flora. The capacities of flavonol biotransformations, such as catechol-O-methyl trasferase or various transferases catalyzing sulfo- or glucuro- conjugations, are particularly active in the liver for the metabolism of dietary BF[28]. The bacterial ring fission of BF occurs in the colon, the subsequent degradation products, phenolic acids, can be absorbed and are found in urine of animals[19]. However, the existence of a conjugation activity in the intestinal wall could not be ruled out. Manach et *al.*,[29] investigated that, about 80% of circulating plasma quercetin units are present as methoxy-derivative (isorhamnetin) and flavonol metabolites are circulating in plasma as conjugated derivatives[29]. Liver exhibits the capacity to O-methylate quercetin on its 4'-hydroxyl (tamarixetin), since this metabolite is found in relatively high concentrations in the bile. Conjugation and/or methylation, which probably play a role in lowering the relativity of quercetin which arises from the presence of two-OH on the β-ring, or the presence of -OH in 3 and 5 positions at the vicinity of the 4-oxo group. Between 12th and 24th h after the beginning of the meal, slight changes in plasma quercetin metabolites were observed in adapted rats, thus, elimination of these compounds might be compensated for by some digestive absorption still occurring during this period. However, quercetin is probably present mainly in conjugated forms, extensively bound to albumin and the actual antioxidant property of these forms is still uncertain and possibly less than that of the free forms[30]. Hertog *et al.*,[31] measured the sum of free quercetin, quercetin glycosides, and any glucuronides, sulfates in plasma and urine, which are found by conjugation in the liver or the small intestine. Fuhu *et al.*,[32] showed that the naringenin formed from naringin,

indicated that enteral bacteria play an important role in this metabolic pathway. In addition there was a lag time for BF to appear in urine, which is to be expected if naringenin formation requires enteral micro-organisms to cleave the sugar moiety from naringin. The absorbed naringin may also be transformed to naringenin by gut wall or hepatic enzymes as an alternative source of the aglycone recovered in the urine. Naringenin is rapidly and almost completely glucuronidated, presumably at the first (gut wall or hepatic) pass. The higher amount of BF present in the liver will induce hepatic enzymes, such as those involved in the glucuronidation[33]. This would lead to an increased metabolism of BF itself. It has been shown that the most substantial metabolic pathway of natural BF in mammals is conjugation with glucuronide and sulfate [34,35]. Naringenin, hesperetin, chrysin, apigenin, tangeretin, kempferol, galangin and tamarixetin were all metabolized extensively by induced rat liver microsomes but only to minor extent by uninduced microsomes[36]. Catechin was present as both a sulfate conjugate and a conjugate containing both glucuronide and sulfate residuces,3'-O-methyl catechin was present primarily as a glucuronide conjugate[14]. The BF 5,6 - benzoflavone, flavone and quercetin have the biphasic effect of stimulating mouse hepatic microsomal parathion oxidation at a concentration of 1 μM and inhibiting activity when increased to 100 μM[37]. Rutin, hesperidin, naringin and poncerin were transforned to their aglycones by the intestinal microflora producing α-rhamnosidase, β-glucosidase, and baicalin, puerarin and daidzin were transformed to their aglycone by the bacteria producing β-glucuronidase, α-glycosidase and β-glycosidase, respectively[38]. The two major sites of the BF metabolism are the liver and the colonic flora. The subsequent degradation products, phenolic acids, can be absorbed and are found in the urine of the animals[19]. The common dietary constituents, quercetin, fisetin, galangin, myricetin, kemferol, chrysin and apigenin, were potent inhibitors of p-form phenolsulfotransferases (PST) mediated sulfation, with IC_{50} values < μ1 M. Curcumin, genistein and ellagic acid were also inhibitors of p-form PST, with IC_{50} values 0.38-34.8 μM. This suggests the potential for clinically important drug interactions, as well as possible role of BF as chemo-protective agents in sulfation-inducted carcinogensis[39]. Quercetin was rapidly O-methylated by either porcine liver or hamster kidney catechol-O-methyltransferase, with K_m values 6.1 and 6.9 μM and V_{max} values 14,870 and 200 pmol/mg of protein per minute, respectively. The rapid metabolic inactivation of mutagenic BF, quercetin catalyzed by catechol-O-methyltrasferase may be a major reason for the lack of their carcinogenic activities *in vivo*[40].

Excretion:

After oral administration of grape fruit juice, monomethoxy- and dimethoxy-BF of naringenin, hesperitin and four related flavonones were absorbed and may undergo glucuronidation before urinary excretion. Cumulative urinary recovery indicates low bioavailability (<25%) of naringenin and hesperidin[41]. Quercetin pharmacokinetics were described by a first-order two compartmental model with median $t_{1/2}$ (α) of 6 min and median $t_{1/2}$ (β) of 43 min. The median estimated clearance of 0.28 l/min/m^2 and median volume of distribution at steady state was 3.7 l/m^2 [42]. Excretion in the urine, as a proportion of intake was 17% for isorhamnetin-4'-O-β-glucoside and 0.2% for quercetin-4'-O-β-glucoside after 300 g consumption of fried onions[26]. The elimination half-life of quercetin was 28 h following the ingestion of onions and 23 h for apples[18]. The rate of elimination of quercetin metabolites seems very low, and high plasma concentrations are easily maintained with a regular supply of quercetin or rutin in the diet[43]. Glucuronidation is the major mechanism of hepatic flavopiridal biotransformation. Metabolites are mainly excreted into bile but also release into the systemic circulation[44]. The pharmacokinetic parameters of various flavonoids are given in the Table 2 and the putative metabolic pathways of one of the widely studied flavonoid, quercetin is represented in Fig. 2.

BIOFLAVONOIDS - EFFECT ON CYTOCHROME P_{450}:

BF interact with Cytochrome P_{450} (CYP) specifically CYP 1 A and 3 A series, which will change the disposition of the concurrently administered drugs. The CYP 1A isozymes were found to be the main enzymes inducted in the BF hydroxylation, whereas others seems to be involed in BF demethylation[45]. Glangin is sequentially transforned to kempferol and then to quercetin by a mechanism dependant on CYP[46]. Interactions of acacetin, diosmetin, eriodictyl, hesperetin, homoeriodictyl and naringenin with human CYP were studied. Acacetin and diosmetin were potent inhibitors of ethoxyresorufin-O-dealkylase (EROD), naringenin was potent inhibitor of CYP IA EROD activity and hesperetin was O-demethylated by both CYP IAI and IBI to eriodictyl[47].

TABLE 2: PHARMACOKINETICS OF SOME SELECTED BIOFLAVONOIDS

Bioflavonoids	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2(K)}$ (h)	$t_{1/2(2)}$ (h)	MRT (h)	V (l)	CL (L)	$Css_{(max)}$ (ng/ml)	$Css_{(min)}$ (ng/ml)
Quercetin (64 mg orally)	196	2.9	0.87 #6min *2.4 *0.7	16.8 #43min	-	#3.7 *92.6 *6.2	*34.6 *28.1 #0.28	-	-
Hyperfolin (14.8 mg orally)	150	3.5	-	9	12	-	-	-	-
Hypericin (1.5 mg orally)	1.5	2-2.6	24.8-26.5	-	-	-	-	&8.5	&5.3
Pseudohypericin (0.526 mg orally)	2.7	0.3-1.1	16.3-36	-	-	-	-	&8.5	&3.7

* i.v. injection of quercetin glycosides of two studies; #300g oral treatment of fried onions, and 3x300 mg/day oral administration of hypericum extract; C_{max} = Maximum Concentration of drug in plasma; T_{max} = Time of drug to reach peak concentration; $t_{1/2}$ = Elimination half-life; MRT = Mean Residence Time: V=Volume of distribution; CL = Systemic clearance; C_{ss} = Steady state concentration.

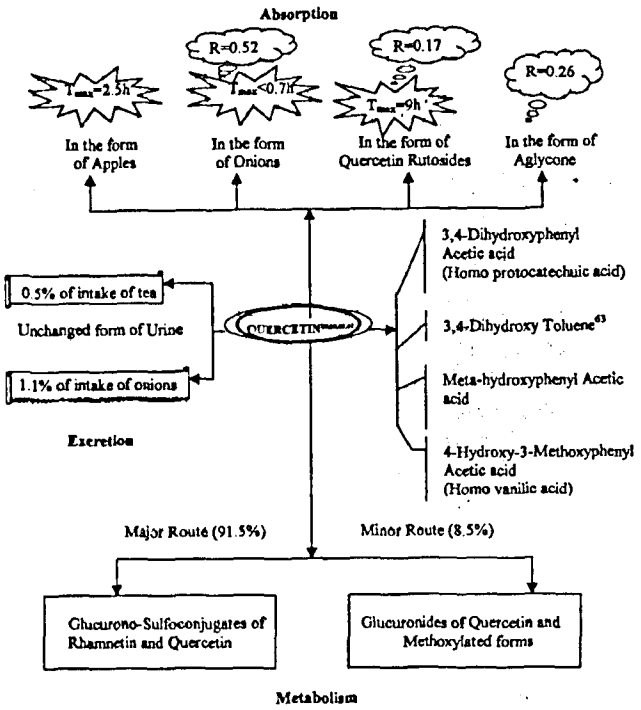

Fig. 2: Putative metabolic pathway of Quercetin

A series of ten structurally related BF were evaluated for their effect on methoxyresorufin-O-demethylase (MROD) activity in human liver microsomes. All compounds inhibited CYP 1A1 mediated activity, galangin was the most potent inhibitor followed by 3-hydroxyflavone and flavones[36]. Flavones inhibit CYP 1A2 (IC_{50} = 0.066μM) more strongly than CYP 1A1 (IC_{50} = 0.14μM). Four hydroxylated flavone derivatives (3-hydroxy, 5-hydroxy, 7-hydroxy and 3,7 -dihydroxyflavone) were also potent inhibitors of CYP 1A1 (IC_{50}<0.1μM) and CYP 1A2 (IC_{50}<0.3 μM). The inhibition by galangin of the MROD activity of CYP 1A2 was mixed type, with a K_i value of 0.008 μM, and it shows 5-fold selectivity in its inhibition of CYP 1A2 over 1A1[48]. Rat CYP 1A1 is the most among all the Cytochrome P_{450}'s studied, the one that plays the major role in the transformation of kempferol into quercetin[49], which is time dependant and contribute to mutagenesis by kempferol[50]. BF that are present in the citrus fruits such as naringenin, quercetin and kempferol interact with the metabolism of drugs such as 17-β-estradiol and other steroids that are extensively metabolized through the CYP 3A4 or closely related CYP isozymes. After administration of grape fruit juice, peak estrone (between 2-6 h after tablet intake) concentrations increased significantly[51]. Compounds of grape fruit juice inhibit CYP 3A4 mediated saquinavir metabolism in Caco-2 cell monolayer[19].

BIOFLAVONOIDS-EFFECT ON P-GLYCOPROTEIN (P-gp)

Structure:

Resistance to chemotherapy in cancer cells is mainly mediated by over expression of P-glycoprotein (P-gp), a plasma membrane ATP-binding cassette (ABC) transporter that extrudes cytotoxic drugs at the expense

of ATP hydrolysis. P-gp consists of two homologous halves each containing a transmembrane domain and a cytotoxic nucleotide-binding domain (NBD) which consists of two consensus walker motifs, A and B, involved in ATP binding and hydrolysis. The protein also contains a S-signature characteristic of ABC transporters. Since the trasporter has extraordinary broad substrate specificity, its cellular funtion has been described as a "hydrophobic vacuum cleaner".

Interestingly, BF also binds to NBDs with high affinity. Their binding site partly overlaps both the ATP - binding site and the steroid-interacting regions. Therefore BF constitute a new promising class of bifunctional modulator of P-gp[52], Fig. 3.

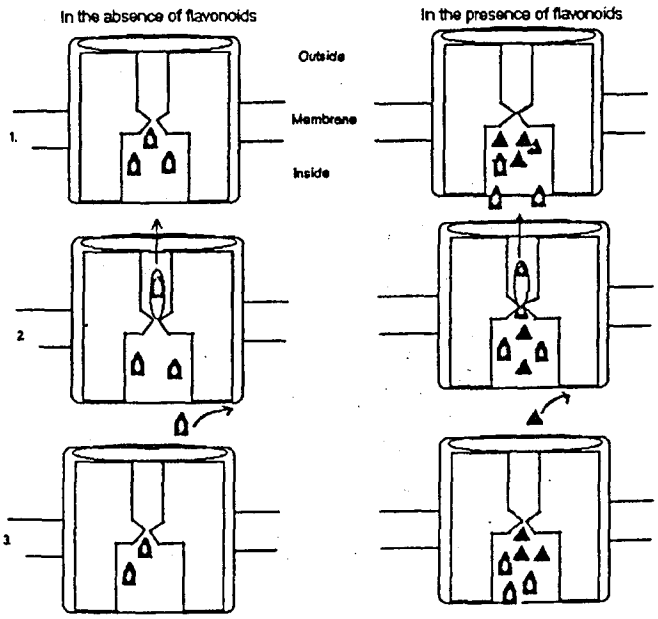

Fig. 3: Model of P-Glycoprotein mediated of Quercetin. The three stages on the left depict the outward transport of a drug in the absence of a Bioflavonoid and, on the right, in the presence of a Bioflavonoid, such as quercetin (Δ). 1: Both the drug and the Bioflavonoid can occupy the transport site. 2 : The hydrolysis of ATP then drives a conformational change in the transporter with release of the substrate at the external surface. 3 : The transporter returns to the substrate-binding conformation

Modulation of P-gp:

Multi-drug resistance due to P-gp is a seriousimpediment to successful chemotherapy of cancer. Numerous compounds are known to inhibit the drug exporting function of P-gp. Understanding the mechanisms of action of these chemosensitizers is made difficult by the complexity of the *in vivo* cell systems usually employed. Quercetin inhibits P-gp-mediated Hoechst 33342 efflux and enhanced accumulation, as measured by flow cytometry, by using multi-drug resistance CHRC5 cells, mainly by inhibiting the ATPase activity of P-gp required for transport. The ATPase domain of P-gp may be an attractive target for new chemo sensitizing agents[53]. The C-terminal NBD-2 of a P-gp like transporter, encoded by the mdr1 gene in *Leishmania tropica* and involved in parasite multi-drug resistance (MDR), was over expressed in *Escherichia coli* as a hexahistidine tagged protein and purified. Different classes of BF have different affinities: flavone>flavonone>isoflavone>glucurorhamnosyl-flavone>chromone. The results suggest that flavone's inhibition of both daunomycin efflux and parasitic growth in the presence of the drug correlates to direct binding of the compound to cytosolic domain of the P-gp-like transporter[54]. Flavones (apigenin) bound more strongly than flavonones (naringenin) isoflavones (genistein), or glycosylated derivatives (rutin) to hexahistidine tagged C - terminal NBD (H6 - NBD2) from mouse P-gp. Interestingly these BF are the classes of modulators with bifunctional interactions at vicinal ATP - binding site and steroid-interacting region within a cytosolic domain of P-gp[55]. Genistein, quercetin and daidzein were known to increase the acccumulation of daunorubicin, whereas, decreased accumulation of Rhodamine -123 (Rh-123) in multi-drug resistance protein (MRP) - mediated MDR cell lines. The depolarization of the membrance potential caused by genistein might be involved in the acceleration of the efflux of Rh - 123 measured in the MRP - over expressing cell lines[56]. Dietary BF are reported to strongly up regulate the apparent activity of P-gp modulating activity, on etoposide's absorption. The addition of natural rodent diet or quercetin increased etoposide absorption in everted sacs of jejunum or ileum, in comparison to those added with artificial rodent diet[57]. Cytotoxic BF such as sophoraflavone, kurarinone (GS08), norkurarional (GS 11), kurarinol (GS12) and kushenol-K which are isolated from *Sophora flavescens* at nontoxic concentrations, could not affect the cytotoxicity of paclitaxel, a well known P-gp substrate and also had no effect on the accumulation of rhodamine -123 in all cells tested at 10 μM. So P-gp had no effect on the cytotoxicity of the BF, and the BF had no effect on the action of P-gp. Grape fruit juice

components modulate to limited extent P-gp mediated saquinavir transport on Caco-2 cell monolayers[19].

CONCLUSIONS

Absorption:

The extent of oral absorption of flavonoids varies from species to species. There is predominant affect of carbohydrate moiety on the absorption and intestinal sugar carriers also play a role in the absorption. BF present in foods like onions, apples, tea, wine etc, absorb to a less extent from GIT when compared to the administration of pure form (Except the report by Hollman *et al.*,[12]) because they are present as glycosides in fruits or vegetables. Many glycosides are to be hydrolyzed to aglycones in colon micro flora before getting absorbed.

Distribution and Elimination:

Limited data is available on the distribution of BF. Because of the wide range in the solubility of BF, it is difficult to predict their affinity for plasma proteins, but probably they are bound to serum albumin because of their low polarity. BF are mainly metabolized in liver and micro flora of the colon. Biotransformations like methylations and sulfo- or glucuro - conjugations usually take palce in the liver. Ring fission and subsequent degradation occurs in the colon by bacterial enzymatic action. Mainly glucuronide metabolites were found in the urine and bile after administration of BF. The rate of elimination of quercetin metabolites is low with higher elimination half - life.

Effect on CYP and P-gp:

BF interacts with CYP isozymes viz., CYP 1A2 and 3A4 and alter the extent of metabolism of many drugs *in vitro* and *in vivo*. Several reports are available on interaction of BF with the CYPs in rat and human liver microsomes. CYP 1A2 is more strongly affected by flavones than CYP 1A1.

A membrane protein P-gp, which transports drugs or xenobiotics from the cell, modulates MDR in chemotherapy. BF are bifunctional modulators of the action of P-gp either by binding to the NBD or through ATPase domain. Flavones have the highest affinity for ATPase domain when compared to other classes of BF. Certain BF are cytotoxic and do not have any interaction with P-gp.

REFERENCES

1. Kuhnau, **J. World Res. Nut. Diet**, 1976, 24, 117.
2. Bors, W., Heller, W., Michel, C. and Saran, M., **Methods Enzymol.**, 1990, 186, 343.
3. Colerige Smith, P.D., Thomas, P., Scurr, J.H, and Dormandy, J.A., **Brit. Med.J.**, 1980, 296, 1726.
4. Mori, A., Nishinoc, Enoki, N. and Tavata, S. **Phytochemistry**, 1988, 27, 1017.
5. Kuhnau, **J. World Rev. Nutr. Diet.**, 1976, 24, 117.
6. Hollman, P.C.H., Jeanne, H.M.D., Sonja, D.V.L., Marcel, J.B.M and Kasan, M.B., **Amer.J. Clin. Nutr.**, 1995, 62, 1276.
7. Hertoz, M.G.L., Hollman, P.C.H., Katan, M.B. and Kromhout, D., **Nutr. Cancer**, 1993, 20, 21.
8. Herrmannk. Z., **Lebensin Unters Forsch**, 1998, 186, 1.
9. Kiviranta, J., Huorinen, K. and Liltunen, R., **Acta Pharma. Fenn**, 1988, 97, 67.
10. Bailey, R.G., Mc Dowell, I. and Nursten, H.E., **J. Sci. Food Agric.**, 1990, 52, 509.
11. Mc Anlis, G.T., Mc Eneny, J., Pearce, J. and Young, I.S., **Eur. J. Clin. Nutr.**, 1999, 53, 92.
12. Hollman, P.C. and Katan, M.B., **Free Radical. Res.**, 1999, 31, S75.
13. Manach, C., Morand, C., Demigne, C., Taxier, O., Regert, F. and Remesy, C., **FEBS Letters**, 1997, 409, 12.
14. Graefe, U.E., Derendof, H. and Veit, M., **Int. J. Clin. Pharmacol. Ther.**, 1999, 37, 219.
15. Hollman, P.C., Bijsman, M.N., Van Gameren, Y., Cnossen, E.P., De Vries, J.H. and Katan, M.B., **Free Radical Res.**, 1999, 31, 569.
16. Biber, A., Fischer, H., Romer, A. and Chatterjee, S.S., **Pharmacopsychiatry**, 1998, 1, 36.
17. Bourne, L., Ganga, G., Baxter, D., Hugher, P. and Rice-Evans, C., **Free Radical Res.**, 2000, 32, 273.
18. Graefe, E.U., Derendrof, H. and Veit, M., **Int.J. Clin. Pharmacol. Ther.**, 1999, 5, 219.
19. Hollman, P.C. and Katan, M.B., **Arch. Toxicol. Suppl.**, 1998, 20, 237.
20. Staffeldt, B., Kerb, R., Brockmoller, J., Ploch, M. and Roots, I., **J. Geriatr. Psychiatry Neurol.**, 1994, 1, 47.
21. Pforte, H., Hempel, J. and Jacobasch, G., **Nahrung.**, 1999, 43, 205.
22. Schroder, J.P.V.E., Heide, D.V., Rokos, H., Kohrle, J. and Morreale, G.H., **Endocrinology**, 1997, 138, 78.
23. Hollman, P.C., Van Trijp, J.M., Buysman, M.N., Vander Gaag, M.S., Mengelers, M.J., De Vries, J.H. and Katan, M.B., **FEBS Letters**, 1997, 418, 152.
24. Metzer, J., Bekemeier, H., Schneidewind, E.M. and Wenzel, U., **Pharmazie**, 1979, 34, 185.
25. Aziz, A.A., Edwards, C.A., Lean, M.E. and Crozier, A., **Free Radical Res.**, 1998, 29, 257.
26. Griffitths, L.A. In; Herbone, J.B. and Mabry, T.J. Eds., the BF : Advances in research Chapman and Hall, London, 1982, 681.
27. Manach, C., Texier, O., Regerat, F., Agullo, G., Demigne, C. and Remesy, O., **J. Nutr. Biochem.**, 1996, 7, 375.

28. Paintz, M. and Matzner, **J. Pharmazie,** 1979, 34, 839.
29. Manach, C., Morand, C., Texier, O., Favier, M.L., Agullo, G., Demignec, Regerat, F. and Remesy, C., **J. Nutr.,** 1995, 125, 1911.
30. Donovan, J.L., Bell, J.R., Kasim-Karakas, S., German, J.B., Walzem, R.L., Hansen, R.J. and Waterhouse, A.L., **J. Nutr.**, 1999, 129, 1662.
31. Hertog, M.G.L., Hollman, P.C.H and Venema, D.P., **J. Agr. Food Chem.,** 1992, 40, 1591.
32. Fuhu, U. and Kummert, A.L., **Clin. Pharmacol. Ther.,** 1995, 58, 365.
33. Gross, M., Pfeiffer, M., Martini, M., Campbell, D., Slavin, J. and Potter, J., **Cancer Epidemol. Biomarker Prev.,** 1996, 5, 711.
34. Ramos, S. and Sultatos, L.,**Toxicology,** 1998, 131, 155.
35. Graefe, E.U. and Veit, M., **Phytomedicine,** 1999, 6, 239.
36. Silva, I.D., Rodrigues, A.S., Gasper, J., Maia, R., Laires, A. Rueff, J., **Mutagenesis,** 1997, 12, 383.
37. Morand, C., Crespy, V., Manach, C., Besson, C., Demigne, C. and Remesy, C., **Amer. J. Physiol.,** 1998, 275, 212.
38. Doostdar, H., Burde, M.D. and Mayer, R.T., **Toxicology,** 2000, 144, 31.
39. Ameer, B., Weintraub, R.A., Johnson, J.V., Yost, R.A. and Rouseff, R.L., **Clin. Pharmacol. Ther.,** 1996, 60, 34.
40. Ferry, D.R., Smith, A., Malkhandi, J., Fyfe, D.W., de Takats, P.G., Anderson, S., Baker, J. and Kerr, D.J., **Clin.Cancer Res.,** 1996, 2, 659.
41. De Vries, J.H., Hollman, P.C., Meyboom, S., Buysman, M.N., Zock, P.L., Van Staveren, W.A. and Katan, M.B., **Amer. J. Clin. Nutr.,** 1998, 68, 60.
42. Jager, W., Zembsch, B., Wolschann, P., Pittenauer, E., Senderowicz, A.M., Sausville, E.A., Sedlacek, H.H., Graf, J. and Thalhammer, T., **Life Sci.,** 1998, 62, 1861.
43. Hollman, P.C., Van Trijp, J.M., Mengelers, M.J., De Vries, J.H. and Katan, M.B., **Cancer Lett.,** 1997, 114, 139.
44. Nielsen, S.E., Breinholt, V., Justesen, U., Cornett, C. and Dragsted, L.O., **Xenobiotica,** 1998, 28, 389.
45. Zhai, S., Dai, R., Friendman, F.K. and Vastal, R.E., **Drug Metab. Disposition,** 1998, 26, 989.
46. Zhai, S., Dai, R., Wei, X., Friendman, F.K. and Vestal, R.E., **Life Sci.,** 1998, 63, 119.
47. Eagling, V.A., Profit, L. and Black, J.D., **Brit. J. Clin. Pharmacol.,** 1999, 48, 543.
48. Silva, I.D., Rodrigues, A.S., Gasper, J., Maia, R., Laires, A. Rueff, **J.Teratogen. Carcin. Mut.,** 1996, 16, 229.
49. Schubert, W., Cullberg, G., Edger, B. and Hendner, T., **Maturitas,** 1994, 20, 155.
50. di Pietro, A., Dayan, G., Steinfels, E., Krell, T., Trompier, D., Baubichon-Cortay, H. and Jault, J., **Braz. Med. Biol.,** 1999, 32, 925.
51. Shapiro, A.B. and Ling. V., **Biochem. Pharmacol.,** 1997, 53, 587.
52. Perez-Victoria, J.M., Chiquero, M.J., Conseil, G., Dayan, G., Di pietro, A., Barron, D., Castanys, S and Gamarro, F., **Biochemistry,** 1999, 38, 1736.
53. Conseil, G., Baubichon-Cortay, H.Dayan, G., Jault, J.M., Barron, D. and Di Pietro, A., **Proc. Natl. Acad. Sci.,** 1998, 95, 9831.
54. Versantoort, C.H., Rhodes, T. and Twentyman, P.R., **Brit. J. Cancer,** 1996, 74, 1949.
55. Chieli, E., Romiti, N., Cervelli, F. and Tongiani. R., **Life Sci.,** 1995, 57, 1741.
56. Choi, S.U., Kim, K.M., Choi, E.J., Park, S.H., Lee, C.O., Jung, N.P., Yoon, S.K. and Ryu, S.Y., **Anticancer Res.,** 1999, 19, 2035.
57. Lo, Y.L. and Huang, J.D., ***In Vivo,*** 1999, 13, 51.
58. Hollman, P.C., Van Leeuwen, S.D., Mengelers, M.J., De Vries, J.H. and Katan, M.B., **Amer. J. Clin. Nutr.,** 1995, 62, 1276.
59. Ader, P., Wessmann, A. and Wolffram, S., **Free Radical Biol. Med.,** 2000, 28, 1056.
60. Hollman, P.C., Vd Gaag, M., Van Trijp, J.M., Mengelers, M.J., De Vries, J.H. and Katan, M.B., **Free Radical Biol. Med.,** 1996, 21, 703.
61. Kim, D.M., Jung E.A., Sohng, I.S., Han, J.A., Kim, T.M. and Han, M.J., **Arch Pharm. Res.,** 1998, 21, 17.
62. Zhu, B.T., Ezell, E.L. and Liehr, J.G., **J. Biol.Chem.,** 1994, 269, 292.
63. Silva, I.D., Rodrigues, A.S., Gaspar, J., Laires, A. and Rueff, J., **Mutat. Res.,** 1997, 393, 247.
64. Crespy, V., Morand, C., Besson, C., Demigne, C. and Remesy, C., **Amer. J. Physiol.** 1999, 277, G120.