Cancer Chemother Pharmacol (1995) 36: 448–450

LETTER TO THE EDITORS/REPLY

Mohamadi A. Sarkar

Quercetin not only inhibits P-glycoprotein efflux activity but also inhibits CYP3A isozymes

Accepted: 31 March 1995

Sir,

I have found the paper by Scambia et al. [1] describing the effect of quercetin, a plant-derived flavonoid, on the reversal of the multidrug resistance type 1(MDR1)-associated Adriamycin resistance in MCF-7 human breast-cancer cell lines to be very interesting. The authors have shown that quercetin and other flavonoid derivatives inhibit P-glycoprotein (Pgp) pump-efflux activity in a dose-dependent manner. Moreover, 10 m*M* of quercetin appears to reduce the expression of immunoreactive Pgp in MCF-7 Adriamycin-resistant (AdrR) cells. These results indicate that quercetin may be capable of reversing MDR and synergizing the inhibitory activity of Adriamycin on the growth of MCF-7 AdrR cells. The authors conclude by stating that quercetin and related flavonoids may have therapeutic application in cancer therapy, particularly when used in combination with other conventional cytotoxic drugs.

However, I would like to caution the authors and others considering the use of quercetin and other flavonoids for such therapeutic applications. Flavonoids have been well established as inhibitors of a very important class of cytochrome P-450 isozymes, the CYP3A subfamily (the CYP450 are phase I oxidative enzymes found mainly in the liver). The CYP3A isozymes not only are abundant in the liver but are also expressed at significant levels in the gastrointestinal mucosa [2]. The CYP3A family of enzymes account for up to 25% of the total hepatic CYP450 and mediate the metabolism of a large variety of compounds, including cyclosporin A, erythromycin, lidocaine, quinidine, midazolam, triazolam, lovastatin, and tamoxifen. Grapefruit juice, which contains several flavonoids, of which naringin is the most common one, has been reported to increase significantly the bioavailability of nifedipine [3], felodipine [4], nitrendipine [5], and other dihydropyridine calcium channel antagonists. Enhanced hemodynamic and adverse experiences have been observed in patients with borderline hypertension for some of these agents [3]. This interaction appears to occur due to inhibition of presystemic metabolism and subsequent metabolic steps in the liver. Therefore, inhibition of these isozymes by the flavonoids is probably the reason for the >3-fold increase in the peak serum concentration and the (Cmax) 2-fold increase in the area under the plasma concentration-time curve (AUC) reported for nisoldipine [6] and other dihydropyridines. In mechanistic in vitro studies with human liver microsomes, quercetin has been shown to be the most potent inhibitor of nifedipine and felodipine metabolism [7]. A 50-μmol/l concentration of quercetin inhibited approximately 70% of felodipine and 50% of nifedipine metabolism.

Most importantly, if therapeutic application of quercetin is considered, it would be given with cytotoxic agents, e.g., vinca alkaloids, etoposide, and teniposide, for tumors that are nonresponsive to these drugs. However, it has been reported that these cytotoxic agents could be metabolised by the CYP3A isozymes [8]. Therefore, it is possible that coadministration of quercetin (the most potent inhibitor of CYP3A isozymes) could inhibit the metabolism of these agents, thereby augmenting the hematologic toxicity due to accumulation of the parent compound.

Although the clinical significance of the inhibitory effects of quercetin have not been fully elucidated, it is clear that quercetin and other flavonoids should be used judiciously. Significant potential exists for drug interactions due to coadministration of quercetin with other drugs, such as dihydropyridines, that are metabolized by the CYP3A isozymes. Furthermore, inhibition of the CYP3A isozymes may also interfere with the metabolism of cytotoxic agents, the effect of which quercetin is supposed to enhance due to reversal of Pgp efflux.

M. A. Sarkar
West Virginia University, 9530 Health Sciences North Morgantown, WV 26506-9500, USA

References

1. Scambia G, Ranelletti FO, Panici PB, De Vincenzo R, Bonnano G, Ferrandina G, Piantelli M, Bussa S, Rumi C, Cianfriglia M, Mancuso S (1994) Quercetin potentiates the effect of Adriamycin in a multidrug-resistant MCF-7 human breast-cancer cell line: P-glycoprotein as a possible target. Cancer Chemother Pharmacol 34: 459–464
2. Kolars JC, Ren PS, Schuetz JD, Fang C, Watkins PB (1992) Identification of rifampin inducible P450IIIA4 (CYP3A4) in human small bowel enterocytes. J Clin Invest 90: 1871–1878
3. Bailey DG, Spence JD, Munoz C, Arnold JMO (1991) Interaction of citrus juices with felodopine and nifedipine. Lancet 337: 268–269
4. Edgar B, Bailey DG, Bergstrand R, Johnsson G, Regardh CG (1992) Acute effect of drinking grapefruit juice on the pharmacokinetics and dynamics of felodipine and its potential clinical relevance. Eur J Clin Pharmacol 42: 313–317
5. Soons PA, Vogels BAPM, Roosemalen MCM, et al. (1991) Grapefruit juice and cimetidine inhibit stereoselective metabolism of nitrendipine in man. Clin Pharmacol Ther 50: 394–403
6. Bailey DG, Malcolm J, Arnold O, Strong A, Munoz C, Spence DJ (1993) Effect of grapefruit juice and naringin on nisoldipine pharmacokinetics. Clin Pharmacol Ther 54: 589–594
7. Minisalco A, Lundahl J, Regardh, CG, Edgar B, Eriksksson UG (1992) Inhibition of dihydropyridine metabolism in rat and human liver microsomes by flavonoids found in grapefruit juice. J Pharmacol Exp Ther 261: 1195–1199
8. Zhou XJ, Xhou PX, Gautheir T, Placidi M, Maurel P, Rahmani R (1993) Human liver microsomal cytochrome P4503A isozymes mediated vindesine biotransformation – metabolic drug interactions. Biochem Pharmacol 45: 853–861

Reply

G. Scambia · F. O. Ranelletti · P. Benedetti-Panici
R. De Vincenzo · G. Bonanno · G. Ferrandina
M. Piantelli · S. Mancuso

Reply to the letter to the editors

Accepted: 31 March 1995

There have been numerous publications dealing with the ability of flavonoids to inhibit the activity of many different enzymes involved in important cellular processes, to list but a few, protein-tyrosine kinase [1], phosphodiesterases [2], adenosine triphosphatase (ATPase) [2], lipoxygenase [3], and reverse transcriptase [4]. The wide spectrum of activity of flavonoids has given rise to more than one question:

1. How do the flavonoids really work?
2. Which common trait might explain the pharmacological effect of this broad class of molecules?

As mentioned by Dr. Sarkar, "in vitro" studies have shown that quercetin inhibits dihydropyridine metabolism in rat and human liver microsomes at concentrations of 50 and 100 μM [5]. Moreover, other studies have shown that the flavonoids found in grapefruit juice inhibit cytochrome P-450, thereby increasing the bioavailability of felodipine and nifedipine [6]. In this case it is difficult, however, to predict the exact concentration of flavonoid expected after grapefruit juice intake [5]. Furthermore, a recent paper showed that there was no change in the hepatic level of cytochrome P-450 in mice after quercetin consumption [7].

In our experimental models [8], the concentrations of quercetin (1–10 μM) potentiating the effect of Adriamycin (ADR) on the growth of MCF-7 ADRr cells and reversing ADR resistance "in vitro" [probably by modulating P-glycoprotein (Pgp) activity] are 5- to 10-fold lower than those (50–100 μM) inhibiting 50% of CYP3A activity [5]. As far as flavonoid toxicity in human is concerned, a plasma concentration of 12 μM quercetin, which is similar to that effective "in vitro" in potentiating ADR activity, has been achieved by intravenous injection of 100 mg without the production of any apparent side effect [9]. It should also be noted that because of its scavenging and antiperoxidative activity, silybin, the main component of the flavonoid silymarin, is used as a hepatoprotector "in vivo" [10].

Quercetin enhances the detoxification process in the liver by reducing lipid peroxides and increasing glutathione-S-transferase activity [11]. Moreover, these effects of quercetin, together with its ability to inhibit cytocrome P-450, can interfere with the initiation and promotion phases of the carcinogenetic process and, thus, determining the chemopreventive potential of dietary bioflavonoids [3, 11, 12]. It is also noteworthy that in nude mice, quercetin-cisplatin (cis-DDP) combined treatment reduced tumor growth to a significantly greater degree than did cis-DDP alone, with no significant increase in toxicity being observed for the combined treatment as compared with treatment with cis-DDP alone [13].

We share Dr. Sarkar's opinion that therapeutic application of quercetin, particularly in combination with che-

G. Scambia · F. O. Ranelletti · P. Benedetti-Panici · R. De Vincenzo · G. Bonanno · G. Ferrandina · M. Piantelli · S. Mancuso (✉)
Istituto di Clinica Ostetrica e Ginecologica, Universita Cattolica del Sacro Cuore, Facoltá di Medicina e Chirurgia "Agostino Gemelli", Largo Agostino Gemelli 8, I-00168 Rome, Italy