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Reply

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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-

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motherapeutic agents, should be considered with caution. To this end it would be important to evaluate the possibility of reducing the therapeutic doses of cytotoxic agents used in combination with quercetin, given that this flavonoid may increase their bioavailability. What is more, the detoxifying activity of quercetin may even prove to reduce the cytotoxic side effects of chemotherapeutic agents.

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