The Pharmacological Actions of Grapefruit Extracts: Naringin and Naringinin

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ABSTRACT

The grapefruit extract components, naringin and its aglycone naringinin, are commonly used health supplements; they exert a variety of pharmacological actions. This article attempts to review their pharmacokinetics, pharmacological actions and their uses in various managements, including effect on cardiovascular system; effect on skeletal system; effect on smooth muscle; effect on gastric intestinal system; effect on endocrine system; effect against tumour; protection against toxins in chemotherapy drugs and the environment; antioxidant effect; drug interactions; antiinflammatory effect and the newly discovered osteogenic and antibacterial actions.

Keywords: antioxidant effect, antibacterial effect, anti-inflammatory effect, drug interactions, osteogenic effect

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INTRODUCTION

Naringin is a flavonoid compound found in grapefruit and other citrus fruit, naringin gives grapefruit its characteristic bitter flavor. With its aglycone naringinin, they are commonly used health supplements; they exert a variety of pharmacological actions. For example, it may be instrumental in inhibiting cancer-causing compounds and thus may have potential chemotherapeutic value. On the other hand, studies have also shown that naringin interferes with enzymatic activity in the intestines and, thus, with the breakdown of certain drugs, resulting in higher blood levels of the drug. In order to summarize their actions on health, a MEDLINE search covering the period 1977-2008 was performed to identify review articles, studies, and case reports referencing the biological properties of naringin and naringinin. The studies are divided into the following sections:

- Pharmacokinetics
- Effects on cardiovascular system
- Effects on skeletal system
- Effects on smooth muscle
- Effects on gastric intestinal system
- Effects on endocrine system
- Effects against tumor
- Protection against toxins in chemotherapy drugs and the environment
- Antioxidant effects
- Antimicrobial effects
- Drug interactions
- Antiinflammatory effects
- Other effects

The studies in each section were arranged chronologically so that the research development can be followed and each of them were separated in individual paragraph, were started with aim/method, then the major results and end with conclusion for easy reference.

PHARMACOKINETICS

Disposition of citrus flavonoids was evaluated after single oral doses of pure compounds (500 mg naringin and 500 mg hesperidin) and after multiple doses of combined grapefruit juice and orange juice and of once-daily grapefruit (Ameer et al. 1996). Cumulative urinary recovery indicated low bioavailability (< 25%) of naringin and hesperidin. The aglycones naringenin and hesperitin were detected in urine and plasma. Conclusion: Absorbed citrus flavanones may undergo glucuronidation before urinary excretion.
Naringenin was administered intravenously and orally to rabbits, and naringin was administered orally. The concentration of naringenin in serum prior to and after enzymatic hydrolysis was determined by HPLC method (Hsiu et al. 2002). The absolute bioavailability of oral naringenin was only 4%, whereas after taking the conjugated naringenin into account, it increased to 8%. When naringin was administered orally, only little naringenin and predominantly its glucuronides/sulfates were circulating in the plasma. Conclusion: Extensive glucuronidation/sulfation of naringenin occurred during the first pass at gut wall.

Six healthy volunteers received orally 135 mg of each compound, hesperetin and naringin, under fasting conditions. Blood samples were collected at 14 different time points over a 12 h period. Urine was collected over 24 h, in five sequential timed intervals (Kanaze et al. 2007). Pharmacokinetic analysis showed that both hesperetin and naringenin were rapidly absorbed and their concentrations in plasma observed 20 min after dosing and reached a peak in 4.0 and 3.5 h, respectively. The mean peak plasma concentration (C(max)) for hesperetin and naringenin were 825.78 ± 741.63 ng/ml (2731.8±1358.4 nmol/l) and 2009.51±741.63 ng/ml and respectively. The mean AUC(0-infinity) values were 4846.20±1675.99 ng/ml h and 22.5 (2.74-99.23) min × μmol/l for naringenin and naringin, respectively. The elimination half-life for hesperetin was found to be 3.05±0.91 h and for naringenin 2.31±0.40 h, respectively. The mean values of the relative cumulative urinary excretion, as percentage of the administered dose, for hesperetin and naringenin, were found to be 3.26±0.44 and 5.81±0.81%, respectively. Conclusion: Oral administration of the flavanone aglycones, hesperetin and naringenin, lead to their rapid absorption as their conjugated forms. The cumulative urinary recovery data indicated low bioavailability for both flavanone aglycones, owing to extensive first-pass metabolism partly by cleavage of the C-ring by the enzymes of intestinal bacteria leading to degradation products such as phenolic acids.

Ten healthy beagles were administered 70 mg citrus flavonoids as a grapefruit extract contained in capsules, while two additional dogs were used as controls and given an excipient (Mata-Bilbao Mde et al. 2007). Naringin reached its maximum plasma concentration at around 80 min, whereas naringenin and naringenin glucuronide reached their maximum plasma concentrations at around 20 and 30 min, respectively. Maximum plasma concentrations of naringin, naringenin, and naringenin glucuronide (medians and ranges) were 0.24 (0.05-2.08), 0.021 (0.001-0.3) and 0.09 (0.034-0.36) ng/ml for naringenin glucuronide. The median and range values for mean residence time were 3.3 (1.5-9.3), 2.8 (0.8-11.2) and 8.0 (2.3-13.1) h for naringin, naringenin and naringenin glucuronide, respectively. Conclusion: The results of this study demonstrate the absorption of grapefruit flavonones via the presence of their metabolites in plasma.

**EFFECTS ON CARDIOVASCULAR SYSTEM**

The effect on hematocrits of adding grapefruit to the daily diet was determined using 36 human subjects (12 F, 24 M) over a 42-day study (Robbins et al. 1988). The hematocrits ranged from 36.5 to 55.8% at the start and 38.8% to 49.2% at the end of the study. Conclusion: Ingestion of grapefruit lowers elevated hematocrits in human subjects.

The cholesterol-lowering effects of tangerine peel extract or a mixture of citrus bioflavonoids. The effects of the citrus bioflavonoid naringin were tested by using it as a supplement in a high-cholesterol diet (Shin et al. 1999). The combination of the inhibited HMG-CoA reductase (-24.4%) and ACAT (-20.2%) activities as a result of naringin supplementation could account for the decrease of fecal neutral sterols. Conclusion: Hypocholesterolemic effect of naringin was more potent when dietary vitamin E level is low. Conclusion: Interactive effect of naringin and vitamin E on cholesterol biosynthesis. This study evaluated the effect of naringin on blood lipid levels and aortic fatty streaks, and its action mechanism in hypercholesterolemic rabbits (Choe et al. 2001).

The susceptibility of LDL to in vitro oxidation was assessed. LDL oxidation were monitored by change in 234-absorbance in the presence of pure flavonoids (Naderi et al. 2003). Genistein, morin and naringin have stronger inhibitory activity against LDL oxidation than biochanin A or apigenin. Conclusion: Flavonoids prevent in vitro LDL oxidation and probably would be important to prevent atherosclerosis.

The effect of naringin on hypercholesterolemic subjects was studied. A hypercholesterolemic group (n = 30) and healthy control group (n = 30) were established (Jung et al. 2003). Naringin supplementation was found to lower the plasma total cholesterol by 14% and low-density lipoprotein cholesterol concentrations by 17%, apolipoprotein B levels were significantly lowered, erythrocyte superoxide dismutase and catalase activities were significantly increased. Conclusion: Naringin may play an important role in lowering plasma cholesterol and regulating the antioxidant capacity in hypercholesterolemic subjects.

The lipid lowering and antioxidative capacity of naringin was evaluated in LDL receptor knockout (LDLR-KO) mice fed a cholesterol (0.1 g/100 g) diet (Kim et al. 2004). The hepatic HMG-CoA reductase activity was significantly lower in the naringin and lovastatin supplemented groups than in the control group, the superoxide dismutase, catalase, and glutathione reductase activities were all significantly higher in the naringin-supplemented group than in the control group. Conclusion: Naringin lowers the plasma cholesterol level via the inhibition of hepatic HMG-CoA reductase activity and improve the activities of hepatic antioxidant enzymes against oxidative stress.

Effects of flavonoids to improve retinal function recovery after ischemic insult were studied. Electrotetrophography
was used to measure the b-wave recovery as an indication of retinal function recovery (Chiou and Xu 2004). Narin- genin, hesperetin, and rutin were found to produce marked positive effects on b-wave recovery, whereas naringin, hes- peridin, and quercetin showed poor recovery of b-wave after ischemic insult of the retina. Conclusion: Flavonoids that showed strong increase of ocular blood flow also showed marked increase of retinal function recovery.

The protective effect of naringin against the damage inflicted by ROS during renal I/R was investigated in Sprague-Dawley rats using histopathological and biochemical parameters (Singh and Chopra 2004). Pretreatment of animals with naringin markedly attenuated renal dysfunction, morphological alterations, reduced elevated TBARS levels and restored the depleted renal antioxidant enzymes. Conclusion: Reactive oxygen species (ROS) play a causal role in renal ischemia/reperfusion (I/R) induced renal injury and naringin exert renoprotective effects probably by the radical scavenging and antioxidant activities.

To confirm the hypcholesterolemic role of naringin, male rabbits were fed 0.5% high-cholesterol diet or high-cholesterol diet supplemented with either 0.05% naringin or 0.03% lovastatin for 8 weeks (Jeon et al. 2004). The naringin and lovastatin significantly lowered plasma total- and LDL-cholesterol and hepatic lipids levels, while significantly increasing the HDL-C/total-C ratio compared to the control group. Conclusion: Both naringin and lovastatin contributed to hypocholesterolemic action. Naringin seemed to preserve tissue morphology from damage induced by high cholesterol diet.

The potential vasorelaxant, antioxidant and cyclic nucleotide PDE inhibitory effects of the citrus-fruit flavonoids naringin and (+/-)-naringenin were comparatively studied (Orallo et al. 2005). (+/-)-naringenin relaxed, in a concentration-dependent manner, the contractions elicited by phenylephrine (PHE, 1 μM) or by a high extracellular KCl concentration (60 mM) in intact rat aortic rings. Conclusion: The vasorelaxant effects of (+/-)-naringenin seem to be basically related to the inhibition of phosphodiesterase (PDE), PDE4 and PDE5 activities.

Patients with stage I hypertension, the antihypertensive effect of juice of the so-called sweetie fruit (a hybrid between grapefruit and pummelo) with and without high flavonoid content were studied (Reshef et al. 2005). The high-flavonoid (HF) sweetie juice was more effective than LF sweetie juice in reducing diastolic blood pressure. Conclusion: The active ingredients associated with the antihypertensive effect of sweetie juice are the flavonoids naringin and hesperidin.

The effect of the flavonoids hesperidin and naringin on glucose and lipid regulation in C57BL/6J-db/db mice was studied (Jung et al. 2006). Hesperidin and naringin effectively lowered the plasma free fatty acid and plasma and hepatic triglyceride levels, and simultaneously reduced the hepatic fatty acid oxidation and carnitine palmitoyl transferase activity. Conclusion: Hesperidin and naringin are beneficial for improving hyperlipidemia and hyperglycemia in type-2 diabetic animals.

The protective effect of naringin in isoproterenol (ISO)-induced myocardial infarction (MI) in rats was studied (Rajadurai and Prince 2006). Pretreatment with narin- genin significantly decreased the levels of total, ester, and free cholesterol, triglycerides, and free fatty acids in serum and heart and increased phospholipids in heart. Conclusion: Na- ringin has a lipid-lowering effect in ISO-induced MI rats.

The cardioprotective potential of naringin on lipid per- oxides, enzymatic and nonenzymatic antioxidants and histopathological findings in ISO-induced MI in rats were evaluated (Rajadurai and Prince 2006). Oral administration of na- ringin to ISO-induced rats showed a significant decrease in the levels of lipid peroxidative products and improved the antioxidant status. Histopathological findings of the myocardial tissue showed the protective role of naringin in ISO- induced rats. Conclusion: Naringin possesses antilipoper- oxidative and antioxidant activity in experimentally induced cardiac toxicity.

The preventive role of naringin on cardiac troponin T (cTnT), lactate dehydrogenase (LDH)-isoenzyme, cardiac marker enzymes, electrocardiographic (ECG)-patterns and lysosomal enzymes in ISO-induced MI in male Wistar rats were investigated (Rajadurai and Prince 2007). Pretreatment with naringin positively altered the levels of cTnT, intensity of bands of the LDH1 and LDH2-isoenzyme and the activi- ties of cardiac marker enzymes, ECG-patterns and lysosomal hydrolases in ISO-induced rats. Conclusion: Naringin possess cardioprotective effect in ISO-induced MI in rats.

Naringin was investigated for its differential effects on hepatic cholesterol regulation when supplemented for 3 weeks and 6 weeks in Sprague-Dawley rats (Kim et al. 2006). Supplementation with naringin did not exhibit a hypolipidemic effect when given with a HFHC diet. Narin- gin can, however, be beneficial for lowering hepatic choles- terol biosynthesis and levels of plasma lipids in this animal model. Conclusion: Naringin time-dependently lowers hepatic cholesterol biosynthesis and plasma cholesterol in rats fed high-fat and high-cholesterol diet.

The preventive role of naringin on heart weight, blood glucose, total proteins, albumin/globulin (A/G) ratio, serum uric acid, serum iron, plasma iron binding capacity and membrane bound enzymes and glycoproteins such as he- xosome, hexosamine, fucose and sialic acid in ISO-induced MI in rats and in vitro free radical scavenging assay were studied (Rajadurai and Prince 2007). Pretreatment with narin- genin exhibited a significant effect and altered these biochemical parameters positively in ISO-induced rats. Naringin also scavenges 1,1-diphenyl-2-picrylhydrazyl, 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid) and nitric oxide radicals in vitro. Conclusion: Naringin has cardioprotective role in ISO-induced MI in rats.

The preventive role of naringin on mitochondrial en- zymes in ISO-induced MI in male albino Wistar rats was stu-died (Rajadurai and Prince 2007). Oral pretreatment with naringin to ISO-induced rats daily for a period of 56 days significantly minimized the alterations in all the bio-chemical parameters and restored the normal mitochondrial function. Transmission electron microscopic observations also correlated with these biochemical findings.

Rajadurai and Prince (2009) evaluated the preventive role of naringin on mitochondrial lipid peroxides, anti-oxidants and lipids in ISO-induced MI in male Wistar rats. Oral pretreatment with naringin (10, 20 and 40 mg/kg) to ISO-induced rats daily for a period of 56 days significantly decreased the levels of mitochondrial lipid peroxides with a significant increase in the activities/levels of mitochondrial antioxidants and significantly minimized the alterations in the mitochondrial lipid levels in ISO-induced rats. Conclu- sion: naringin prevents alterations in mitochondrial lipid peroxides, antioxidants and lipids in ISO-induced MI in rats.

**EFFECTS ON SKELETAL SYSTEM**

The influence of dietary bioflavonoid (rutin [R], quercetin [Q], and naringin [N]) supplementation on physiological molar crestal alveolar bone (CAB)-cemento-enamel junction (CEJ) distances in young male albino rats was studied (Wood 2004). The N group demonstrated the lowest CAB-C Ej distance, followed by the R and Q groups (P <.001-.05), except in the mandibular lingual region, where the Q group had a lower CAB-CEJ distance than the N and R groups (P <.05). The control group showed the largest CAB-CEJ dis- tances. Conclusion: Rutin, quercetin, and naringin sup- plementation reduce molar crestal alveolar bone-cemento- enamel junction distance in young rats.

The amount of new bone produced by naringin in col- lagen matrix to that produced by bone grafts and collagen matrix in rabbits was compared (Wong and Rabie 2006). A total of 284 and 490% more new bone was present in de- fects grafted with naringin in collagen matrix than those
grafted with bone and collagen, respectively. Conclusion: Naringin in collagen matrix have the effect of increasing new bone formation locally and can be used as a bone graft material.

The effect of naringin, which was also a HMG-CoA reductase inhibitor, was studied in UMR 106 osteoblastic cell line in vitro (Wong and Rabie 2006). Naringin significantly increased bone cell activities in vitro. Conclusion: Besides statin, this provided another example of HMG-CoA reductase inhibition that increases the bone cell activities.

The osteoblastic activity of extracts of Drynaria fortunei (Kunze) J. Sm. rhizome was asayed in the UMR106 cell line cultured in vitro (Li et al. 2006). The ethanol extract, and its ethyl acetate and n-butanol fractions exhibited stimulating activity. Conclusion: Two active constituents were isolated and identified as naringin and neoeucoritin.

Effect of naringin and naringenin on colon cell proliferation in rats was used to assess whether naringin has similar bioactivity against osteoporosis in vitro (Wei et al. 2007). A blood test showed that naringin-treated rats experienced significantly lower activity of serum alkaline phosphatase and had higher femur bone mineral density, compared to untreated rats. Conclusion: These outcomes suggest that naringin offer a potential in the management of osteoporosis in vitro.

Naringin was shown to enhance alkaline phosphatase activity, osteocalcin level, osteopontin synthesis and cell proliferation in primary cultured osteoblasts. Naringin increased mRNA and protein levels of BMP-2 using Western blot, ELISA and RT-PCR assay (Wu et al. 2008). In addition, naringin also prevented the decreasing of BMP-2 and bone loss inducing by ovariectomy in vivo. Conclusion: naringin increase BMP-2 expression and enhance osteogenic response via the phosphoinositide 3-kinase (PI3K), Akt, c-Fos/ c-Jun and AP-1-dependent signaling pathway.

EFFECTS ON SMOOTH MUSCLE

Effect of naringin and naringenin on contractions induced by noradrenaline in rat vas deferens was studied (Herrera and Marhuenda 1993). Naringin significantly increased contractions induced by noradrenaline in rat vas deferens. Naringenin increased the contractile effect of noradrenaline and was dose dependent. Conclusion: Naringin and naringenin increased contractions induced by noradrenaline in rat vas deferens.

The potency, structure-activity relationship, and mechanism of vasorelaxation of flavonoids: fisetin, rutin, quercetin, flavones: chrysin, flavone, baicalein; flavanones: naringenin, naringin; isoflavones: daidzein and flavanes: epigallo catechins was examined in the isolated rat aorta (Ajay et al. 2003). Most of the flavonoids tested showed concentration dependent relaxant effects against K+ (80 mM) and norepinephrine (PE, 0.1 μM)-induced contractions with a greater inhibition of the responses to the α1-adrenoceptor agonist. Conclusion: Relaxant effects of flavonoids on vascular smooth muscle of the isolated rat thoracic aorta.

The mechanical and electrophysiological effects of (+)-naringenin were investigated in vascular smooth muscle cells (Saponara et al. 2006). (+/-)-Naringenin induced concentration-dependent relaxation in endothelium-denuded rat aortic rings. Conclusion: The vasorelaxant effect of the naturally-occurring flavonoid (+/-)-naringenin on endothelium-denuded vessels was due to the activation of BK(Ca) channels in myocytes.

EFFECTS ON GASTRIC INTESTINAL SYSTEM

The gastric anti-ulcer activity of a specific histidine decarboxylase inhibitor naringenin, has been studied on the various types of ulcers experimentally induced in rats, viz., pylorus-ligated (Shay method) and restraint ulcers, and on the gastric mucosal damage induced by aspirin, phenylbutazone or reserpine (Parmar 1983). Naringenin possessed significant anti-ulcer activity in all these models, manifesting a dose-dependent anti-ulcer effect. Conclusion: Naringenin, a specific histidine decarboxylase inhibitor, has gastric anti-ulcer activity.

To determine the gastroprotective properties of naringin and the involvement of endogenous prostaglandins in mucosal injury produced by absolute ethanol (Martin et al. 1994). Oral pretreatment with the highest dose of naringin (400 mg/kg), 60 min before absolute ethanol was the most effective antiulcer treatment. Conclusion: Naringin has a ‘cytoprotective’ effect against ethanol injury in the rat, but this property appears to be mediated by non-prostaglandin-dependent mechanisms.

Whether specific flavonoids induce cell migration in colon epithelial cells either wild type or heterozygous for Apc genotype was studied (Fenton and Hord 2004). Naringin and hesperidin induced the greatest migratory response in IMCE cells at 1 microM and induced migration greater than untreated control cells. Conclusion: Flavonoids promote cell migration in nontumorigenic colon epithelial cells differing in Apc genotype.

EFFECTS ON ENDOCRINE SYSTEM

A structure-activity study of 13 commonly consumed flavonoids was conducted to evaluate inhibition of thyroid peroxidase (TPO), the enzyme that catalyzes thyroid hormone biosynthesis (Divi and Doerge 1996). Inhibition by the more potent fisetin, kaempferol, naringenin, and quercetin, was consistent with mechanism-based inactivation of TPO as previously observed for resorcinol and derivatives. Myricetin and naringin inhibited TPO by different mechanisms. Conclusion: Dietary flavonoids inhibit thyroid peroxidase.

This study reports on some environmental chemicals with estrogenic activity (xenoestrogens) and their binding interaction for human plasma sex-hormone binding globulin (hSHBG) (Découch et al. 1999). The flavonoid phytoestrogens genistein and naringenin were also identified as hSHBG ligands, whereas their glucoside derivatives, genisin and naringin, had no binding activity for hSHBG. Conclusion: Naringin interacts with human sex hormone-binding globulin.

Several flavonoids, such as rutin, kaempferol, quercetin, apigenin, naringin, morin and biochanin A were selected to determine their antioxidant effects on in vitro insulin, hemoglobin and albumin glycosylation (Asgary et al. 2002). Biochanin A, the best inhibitor of insulin and hemoglobin glycosylation, inhibits their glycosylation 100 and 60%, respectively. Glycosylation of albumin was inhibited 100% by both biochanin A and apigenin. Conclusion: Plants containing flavonoids may have preventive effects in diabetic complications.

The effect of citrus bioflavonoids on blood glucose level, hepatic glucose-regulating enzymes activities, hepatic glycogen concentration, and plasma insulin levels was studied, and assessed the relations between plasma leptin and body weight, blood glucose, and plasma insulin (Jung et al. 2004). Hesperidin and naringin supplementation significantly reduced blood glucose compared with the control group. Naringenin also markedly lowered the activity of hepatic glucose-6-phosphatase and phosphomonozyrate carboxykinase compared with the control group. Conclusion: Hesperidin and naringin prevent the progression of hyperglycemia, by increasing hepatic glycolysis and glycogen concentration and/or by lowering hepatic gluconeogenesis.

The effect of various doses of naringin was studied on streptozotocin (STZ)-induced hyperglycaemic rats to evaluate the possible hypoglycaemic and antioxidant activity of naringin in diabetes (Ali and El Kader 2004). Exogenous administration of naringin to hyperglycaemic rats causes a dose-dependent decrease of the glucose level, an increase of the insulin concentration, a decrease of the H2O2 and TBARS levels, as well as the increase of the total antioxidant status. Conclusion: Naringin provided a significant amelioration of hypoglycaemic and antioxidant activity in STZ-induced diabetic rats.

Using purified intestinal brush border membrane vesi-
cles and everted intestinal sleeves, glucose uptake in intesti-
tine was studied with naringin and naringin (Li et al. 2006).
Naringin, but not naringin, significantly inhibited glucose uptake in the intestine. Conclusion: Inhibition of in-
testinal glucose uptake and renal glucose reabsorption ex-
plains, the antihyperglycemic action of naringin and its
derivatives.

The combined protective role of low dose of naringin (15 mg kg-1) and vitamin C (25 mg kg-1) and high dose of naringin (30 mg kg-1) and vitamin C (50 mg kg-1) on strep-
tozotocin (STZ)-induced toxicity was studied in male Wis-
tar rats (Punithavathi et al. 2008). Oral administration of high doses of naringin (30 mg kg-1) and vitamin C (50 mg kg-1) to diabetic rats for a period of 21 days normalized all the above-mentioned biochemical parameters. Conclusion: The antihyperglycemic and antioxidative effects of naringin and vitamin C in STZ-induced type II diabetes mellitus in rats.

EFFECTS AGAINST TUMOUR

Two citrus flavonoids, hesperetin and naringenin, and four noncitrus flavonoids, baicalin, galangin, genistein, and quercetin, were tested singly and in one-to-one combina-
tions for their effects on proliferation and growth of a human breast carcinoma cell line, MDA-MB-435. These com-
ponents, were tested for their ability to inhibit development of mammary tumors in female Sprague-Dawley rats (So et al. 1996). IC50 values for the one-to-one combinations ranged from 4.7 micrograms/ml (quercetin + hesperetin, quercetin + naringenin) to 22.5 micrograms/ml (naringenin + hesperetin). Rats given orange juice had a smaller tumor burden than controls, although they grew better than any of the other groups. Conclusion: Citrus flavonoids are effective inhibitors of human breast cancer cell proliferation in vitro, especially when paired with quercetin.

The antimutagenicity of the Citrus flavonoids naringin, hesperidin, nobiletin, and tangeretin against the mutagens benzo(a)pyrene, 2-aminofluorene, quercetin, and nitroqui-
noline N-oxide was investigated in the Salmonella/micro-
some assay (Calomme et al. 1996). Naringin and hesperidin showed a weak antimutagenic activity against benzo(a)py-
rene. Conclusion: The antimutagenic properties the Citrus
flavonoids, especially tangeretin and nobiletin, might pre-
vent cancer.

To investigate the possible relationship between intake of flavonoids-powerful dietary antioxidants that may also inhibit P450 enzymes-and lung cancer risk, we conducted a population-based, case-control study in Hawaii (Le Marchand et al. 1998). The authors found significant inverse associations between lung cancer risk and the main food sources of the flavonoids quercetin (onions and ap-
ples) and naringin (white grapefruit). Conclusion: Foods rich in certain flavonoids may protect against certain forms of lung cancer. Decreased bioactivation of carcinogens by inhibition of CYP1A1 should be explored.

Russo et al. (2000) investigated the free-radical scavenging
capability of bioflavonoids (rutin, catechin, and narin-
gin) and the effects of these polyphenols on xanthine oxida-
tive activity, spontaneous lipid peroxidation, and DNA cleavage. The bioflavonoids under examination showed a dose-dependent free-radical scavenging effect, a significant inhibition of xanthine oxidase activity, and an antiliperox-
iodative capacity. In addition, they showed a protective ef-
ficacy on DNA cleavage. Conclusion: Bioflavonoids as anti-
radicals, antioxidants and DNA cleavage protectors.

The effects of various flavonoids and carotenoids on Rhodamine 123 accumulation in MDR Colo 320 human colon cancer cells expressing MDR1/LRP were studied. The Colo 205 cell line was used as a drug-sensitive control (Ugocsai et al. 2005). Catechin, neohesperidin, naringin, ro-
binin, phloridzin, dihydrobenitin and sakuranetin, had only marginal effects on Rhodamine 123 accumulation. Conclu-
sion: The tested flavonoids were weak apoptosis inducers on multidrug-resistant (MDR) and parent cells.

The hypothesis that untreated and irradiated grapefruit as well as the isolated citrus compounds naringin and limo-
nin would protect against azoxymethane (AOM)-induced aberrant crypt foci (ACF) by suppressing proliferation and elevating apoptosis through anti-inflammatory activities was examined (Vamala et al. 2006). Lower levels of iNOS and COX-2 are associated with suppression of proli-
feration and upregulation of apoptosis, which may have contributed to a decrease in the number of high multiplicity ACF in rats provided with untreated grapefruit and limonin. Conclusion: Consumption of grapefruit or limonin may help to suppress colon cancer development.

Whether secondary plant constituents, i.e., flavonoids, tocochromelins, curcumin, and other substances regulate VEGF in human tumor cells in vitro was studied by measuring VEGF release by ELISA from MDA human breast cancer cells and, for comparison, U-343 and U-118 glioma cells (Schindler and Mentlein 2006). The rank order of VEGF inhibitory potency was naringin > rutin > a-tocopherol suc-
cinate > lovastatin > apigenin > genistein > a-tocopherol > or= kaempferol > y-tocopherol; chrysos and curcumin were inactive except at a concentration of 100 μmol/L. Glioma cells were similarly sensitive, with U343 more than U118, especially for α-TOS and tocopherols. Conclusion: Glyco-
side flavonoids of naringin, a constituent of citrus fruits, and rutin, a constituent of cranberries) induced the greatest response to treatment at the lowest concentration in MDA human breast cancer cells.

Six citrus flavonoids were tested for antineoplastic activ-
ity (Miller et al. 2008). The hamster cheek pouch model was utilized, and the solutions of the flavonoids (2.0-2.5%) and the solution of the carcinogen, 7,12-dimethylbenz[a]an-
thracene (0.5%), were applied topically to the pouches. The results with naringin and naringenin show that both of these flavonoids significantly lowered tumor number [5.00 (control group), 2.53 (naringin group), and 3.25 (naringenin group)]. Naringin also significantly reduced tumor burden [269 mm3 (control group) and 77.1 mm3 (naringin group)]. Conclusion: naringin and naringenin may be able to inhibit the development of cancer.

PROTECTIONS AGAINST TOXINS IN CHEMOTHERAPY DRUGS AND THE ENVIRONMENT

55 different flavonoids were tested for their effect on oka-
daic acid-inhibited autophagy, measured as the sequestra-
tion of electroinjected [3H] raffinose (Gordon et al. 1995).
Naringin (naringenin 7-hesperidoside) and several other fla-
ovonoids and flavone glycosides (pirunin, neoerioctrin, neo-
hesperidin, apin, rhoifolin, kaempferol 3-rutinoside) of-
ered virtually complete protection against the autophagy-
inhibitory effect of okadaic acid. Conclusion: Naringin and other okadaic acid-antagonistic flavonoids could have poten-
tial therapeutic value as protectants against pathological hyperphosphorylations, environmental toxins, or side ef-
effects of chemotherapeutic drugs.

Supportive effects of naringin on lipopolysaccharide-
induced tumor necrosis factor (TNF) release followed by liver injury were investigated (Kawaguchi et al. 1999). Treatment with naringin 3 h prior to lipopolysaccharide challenge resulted in complete protection from lipopolysac-
charide lethality in b-galactosamine-sensitized mice. Conclu-
sion: Action of naringin is mediated through suppression of lipopolysaccharide-induced TNF production.

Strong protein-placing activity of marine algal toxins, okadaic acid and microcystin-LR, induced phosphorylation of keratin and disruption of the keratin cytoskeleton in freshly isolated rat hepatocytes. In hepatocyte cultures, the toxins elicited DNA fragmentation and apoptotic cell death within 24 h (Blankson et al. 2000). All these toxin effects could be prevented by the grapefruit flavonoid, naringin. The cyto-
protective effect of naringin was apparently limited to nor-
mal hepatocytes, since the toxin-induced apoptosis of hepa-
toma cells, rat or human, was not prevented by the flavo-
noid. Conclusion: Prevention of toxin-induced cytосkeletal disruption and apoptotic liver cell death by the grapefruit flavonoid, naringin.

Authors investigated the effects of five citrus phytochemicals on the in vitro metabolism of the tobacco-specific nitrosamine NNK and on the dealkylation of methoxyresorufin (MROD) and pentoxysresorufin (PORD) in liver and lung microsomes of the Syrian golden hamster (Bear and Teel 2000b). MelQX induced mutagenesis and PhIP induced mutagenesis in S. typhimurium were significantly inhibited by all four flavonoids. Glu-P-1 induced mutagenesis was inhibited by rutin and naringenin. IQ induced mutagenesis was significantly inhibited by each flavonoid except diosmin. Conclusion: Diosmin, naringenin and rutin are chemoprotective towards CYP1A2 mediated mutagenesis of heterocyclic amines (HCAs).

The effect of various doses of naringin was studied on the alteration in the radiation-induced micronucleated polychromatic (MPCE) and normochromatic (MNCE) erythrocytes in mouse bone marrow exposed to 2 Gy of 60Co γ-radiation (Jagetta and Reddy 2002). Naringin is able to protect mouse bone marrow cells against the radiation-induced DNA damage and decline in the cell proliferation as observed by a reduction in the micronucleus frequency and an increase in PCE/NCE ratio, respectively, in the naringin-pretreated irradiated group. Conclusion: Naringin protects against the radiation-induced genomic instability in the mice bone marrow.

The effect of naringin supplements on the alcohol, lipid, and antioxidant metabolism in ethanol-treated rats was investigated (Seo et al. 2003). Naringin would appear to contribute to alleviating the adverse effect of ethanol ingestion by enhancing the ethanol and lipid metabolism as well as the hepatic antioxidant defense system. Conclusion: Naringin supplement regulate lipid and ethanol metabolism.

The effect of naringin on H2O2-induced cytotoxicity and apoptosis in mouse leukemia P388 cells were investigated (Kanno et al. 2003). H2O2-induced cytotoxicity was significantly attenuated by naringin or the reduced form of glutathione, a typical intracellular antioxidant. Naringin suppressed chromatin condensation and DNA damage induced by H2O2. Conclusion: Naringin from natural products is a useful drug having antioxidant and anti-apoptotic properties.

The radioprotective action of 2 mg/kg naringin in the bone marrow of mice exposed to different doses of 100Co γ-radiation was studied by scoring the frequency of asymmetrical chromatid aberrations that may increase in exposure to 0.5, 1, 2, 3, and 4 Gy γ-radiation (Yeh et al. 2005). The alteration in the antioxidant status and lipid peroxidation was investigated in Swiss albino mice treated with 2 mg/kg b.wt. naringin, a citrus flavoglycoside, before exposure to 0.5, 1, 2, 3, and 4 Gy γ-radiation. Conclusion: There is a protective effect of naringin against radiation-induced damage by elevating the antioxidant status and reducing the lipid peroxidation. The effect of naringin on the cytotoxicity and apoptosis in mouse leukemia P388 cells treated with Ara-C. Ara-C causes cytotoxicity, chromosomal damage, and apoptosis in a concentration- and time-dependent manner in the cells was examined (Kanno et al. 2004a). Naringin remarkably attenuated the Ara-C-induced apoptosis and completely blocked the DNA damage caused by Ara-C treatment at 6 h using the Comet assay. Conclusion: Naringin blocked apoptosis caused by Ara-C-induced oxidative stress, resulting in the inhibition of the cytotoxicity of Ara-C.

The effect of naringin, a bioflavonoid with anti-oxidant potential, was studied on Fe-NTA-induced nephrotoxicity in rats (Singh et al. 2004a). Pretreatment of animals with naringin, 60 min before Fe-NTA administration, markedly attenuated renal dysfunction, morphological alterations, reduced elevated TBARS, and restored the depleted renal anti-oxidant enzymes. Conclusion: There is a protective effect of naringin on Fe-NTA-induced nephrotoxicity in rats.

Whether naringin treatment may help to overcome the iron-induced toxic effects in vitro was studied (Jagetta et al. 2004). Pretreatment of HepG2 cells with naringin resulted in an elevation in all the antioxidant enzymes. Conclusion: Enhanced antioxidant status by naringin could compensate the oxidative stress and may facilitate an early recovery from iron-induced genomic insult in vitro.

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The interaction of β-carotene with three flavonoids-naringin, rutin and quercetin-on DNA damage induced by ultraviolet A (UVA) in C3H10T1/2 cells was studied (Yeh et al. 2005). All three flavonoids had some absorption at the UVA range, but the effects were opposite to those on DNA damage and β-carotene oxidation. Conclusion: A combination of β-carotene with naringin, rutin or quercetin may increase the effectiveness of β-carotene antioxidant. Naringin suppressed chromatin condensation and DNA damage induced by H2O2. Conclusion: Naringin from natural products is a useful drug having antioxidant and anti-apoptotic properties.

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died on bleomycin-induced genomic damage and alteration in the survival of cultured V79 cells (Jagetta et al. 2005). Treatment of cells with naringin before exposure to different concentrations of bleomycin arrested the bleomycin-induced decline in the cell survival accompanied by a significant reduction in the frequency of micronuclei when compared with bleomycin treatment alone. Conclusion: Naringin reduced the genotoxic effects of bleomycin and consequently increased the cell survival. The flavonoid therefore may act as a chemoprotective agent in clinical situations.

A diversity of antioxidants and plant ingredients were examined for their protective effect in cultured Balb/c 3T3 cells against ultraviolet A (UVA)-induced cytotoxicity of extracted air pollutants and benz[a]pyrene (B[a]P) (Hori et al. 2007). The B[a]P phototoxicity was not eliminated by well-known antioxidants but was markedly diminished by diversity of plant ingredients. Conclusion: Among the plant ingredients tested in the current study, morin, naringin, and quercetin were found to be desirable protectors against B[a]P phototoxicity.

ANTIOXIDANT EFFECTS

Depletion of hepatic glutathione in phenobarbital-induced rats by phorone (disisopropylidene acetone) led to an enhancement of spontaneous lipid peroxidation in vitro. Addition of exogenous glutathione, dithiocarb or one of the flavonoids (+)-catechin, (-)-epicatechin, 3-O-methylcatechin, quercetin, taxifolin, rutin, naringin or naringenin led in every case to a dose-dependent inhibition of this peroxidative activity (Younes and Siegers 1981). The concentration values yielding 50% inhibition (IC50) varied from 1.0 × 10-6 M for glutathione to 1.9 × 10-5 M for naringenin. Conclusion: Some flavonoids have inhibitory activity on enhanced spontaneous lipid peroxidation following glutathione depletion.

The antioxidant properties of freeze-dried citrus fruit peels (orange, lemon, grapefruit) and methanolic extracts from the peel were studied (Kroyer 1986). Freeze-dried orange peel showed the highest, lemon peel somewhat less and grapefruit peel the lowest but still remarkable antioxidant activity. Conclusion: Citrus fruit peels have antioxidant activity.

Cumene hydroperoxide induces in vitro the peroxidation of erythrocyte membrane. The protective effect of various flavonoids was compared to that of butylated hydroxytoluene (BHT). Protective effect was evaluated by the inhibition of peroxidation product formation (Affany et al. 1987). Quercetin and catechin showed a protective effect against lipid peroxidation as high as that of BHT. Rutin, rutin, trihydroxyethylrutin, and naringin were active but to a lesser degree. Conclusion: Flavonoids have protective effect against lipid peroxidation of erythrocyte membranes.

The in vitro effects of several flavonoids on nonenzymatic lipid peroxidation in the rat brain mitochondria was studied. The lipid peroxidation was indexed by using the 2-thiobarbituric acid test (Ratty and Das 1988). The flavonoids, apigenin, flavone, flavanone, hesperidin, naringin, and rutin promoted the ascorbic acid-induced lipid peroxidation. Conclusion: Polyhydroxylated substitutions on rings A and B, a 2,3-double bond, a free 3-hydroxyl substitution and a 4-keto moiety confer antiperoxidative properties.

The superoxide anions scavenging activity and antioxi- dation of seven flavonoids were studied. The superoxide anions were generated in a phenazin methosulphate-NADH system and were assayed by reduction of nitroblue tetrazo- lium (Chen et al. 1990). The scavenging activity ranked: rutin was the strongest, and quercetin and naringin the second, while morin and hispidulin were very weak. Conclusion: Flavonoids are superoxide scavengers and antioxidants.

A variety of flavonoids, lignans, an alkaloid, a bisbenzyl, coumarins and terpenes isolated from Chinese herbs was tested for antioxidant activity as reflected in the ability to inhibit lipid peroxidation in rat brain and kidney homoge-

nates and rat erythrocyte hemolysis. The pro-oxidant activities of the aforementioned compounds were assessed by their effects on bleomycin-induced DNA damage (Ng et al. 2000). The flavonoid rutin and the terpene tanshinone I manifested potent antioxidative activity in the lipid peroxida- tion assay but no inhibitory activity in the hemolysis assay. The lignan deoxypodophyllotoxin, the flavonoid naringin and the coumarins columbianetin, bergapten and angelicin slightly inhibited lipid peroxidation in brain and kidney homogenates. Conclusion: Aromatic hydroxyl group is very important for antioxidative effects of the compounds. None of the compounds tested exerted an obvious pro-oxidant effect. To determine the antioxidative effects of the citrus bioflavonoids, naringin, a potent cholesterol-lowering agent, compared to the cholesterol-lowering drug, lovastatin, in rabbits fed a high cholesterol diet (Jeon et al. 2001). Naringin regulate antioxidative capacities by increasing the SOD and catalase activities, up-regulating the gene expressions of SOD, catalase, and GSH-Px, and protecting the plasma vitamin E. Lovastatin exhibited an inhibitory effect on the plasma and hepatic lipid peroxidation and increased the he- patic catalase activity. Conclusion: Antioxidative activity of naringin and lovastatin in high cholesterol-fed rabbits.

Twenty male rabbits were served a high-cholesterol diet or high-cholesterol diet supplemented with naringin or probucol for 8 weeks to compare the antioxidative effects of the naringin and antioxidative cholesterol-lowering drug (probucol) (Jeon et al. 2002). The probucol supplement was very potent in the antioxidative defense system, whereas naringin exhibited a comparable antioxidant capacity based on increasing the gene expressions in the antioxidative enzymes, increasing the hepatic SOD and CAT activities, sparring plasma vitamin E, and decreasing the hepatic mito-ochondrial H2O2 content. Conclusion: Antioxidant effects of naringin and probucol in cholesterol-fed rabbits.

A variety of in vitro models such as β-carotene-linoleic acid, 1,1-diphenyl-2-picryl hydrazyl (DPPH), superoxide, and hamster low-density lipoprotein (LDL) were used to measure the antioxidative activity of 11 citrus bioactive compounds (Yu et al. 2005). Flavonoids, which contain a chro- manol ring system, had stronger antioxidant activity as compared to limonoids and bergapten, which lack the hydroxy groups. Conclusion: Several structural features were linked to the strong antioxidant activity of flavonoids.

The influence of naringin versus red grapefruit juice on plasma lipid levels and plasma antioxidant activity in rats fed cholesterol-containing and cholesterol-free diets was compared (Gorinstein et al. 2005). After 30 days of different feeding, it was found that diets supplemented with red grapefruit juice improved arterial function and the plasma lipid levels mainly in rats fed cholesterol and increased the plasma antioxidant activity. Conclusion: Naringin is a powerful plasma lipid lowering and antioxidant activity increasing flavonone. However, fresh red grapefruit is preferable than naringin.

The relationship between the influence of flavonoids on cell population growth and their antioxidant activity was studied (Hsu and Yen 2006). The relationship between the influence of flavonoids on cell population growth and their antioxidant activity was studied (Hsu and Yen 2006). The relationship between the influence of flavonoids on cell population growth and their antioxidant activity was studied (Hsu and Yen 2006). The relationship between the influence of flavonoids on cell population growth and their antioxidant activity was studied (Hsu and Yen 2006). The relationship between the influence of flavonoids on cell population growth and their antioxidant activity was studied (Hsu and Yen 2006). The relationship between the influence of flavonoids on cell population growth and their antioxidant activity was studied (Hsu and Yen 2006).
ANTIMICROBIAL EFFECTS

Coumarins, flavonoids and polysaccharopeptide were tested for antibacterial activity. The bacteria used for this study included clinical isolates of Staphylococcus aureus, Shigella flexneri, Salmonella typhi, Escherichia coli and Pseudomonas aeruginosa (Ng et al. 1996). When tested at the dose of 128 mg/l, the flavonoids (rutin, naringin and baicalin) inhibited 25% or less of P. aeruginosa and only baicalin was active against S. aureus. Conclusion: Naringin inhibited P. aeruginosa.

The effect of hesperetin, naringenin and its glycoside form on the Sindbis neurovirulent strain (NSV) replication in vitro was studied. All flavonanes tested were not cytotoxic on Baby Hamster cells 21 clone 15 (BHK-21) (Paredes et al. 2003). Hesperetin and naringenin had inhibitory activity on NSV infection. However their glycosides, hesperidin and naringin did not have inhibitory activity. Implying that the presence of rutinose moiety of flavonanes blocks the antiviral effect. Conclusion: Anti-Sindbis activity of flavonanes hesperetin and naringenin.

Antibacterial and antifungal activity of ethanolic extract of grapefruit (Citrus paradisi Macf., Rutaceae) seed and pulp was examined against 20 bacterial and 10 yeast strains (Coombs and Knezevic 1999). Ethanolic extract exhibited the strongest antimicrobial effect against Salmo nella enteritidis (MIC 2.06%, m/V). Other tested bacteria exhibited the strongest antimicrobial effect against Citrus paradisi. For comparison, the effects of hesperetin, naringenin and its glycoside were studied to evaluate the drug interaction in humans (Bailey et al. 1999). Naringenin present in grapefruit juice inhibits in vitro the metabolism of simvastatin, a HMG-CoA reductase inhibitor. Conclusion: In vitro inhibition of simvastatin metabolism in rat and human liver by naringenin.

In vitro and in vivo effects of naringin on microsomal monoxygenase were studied to evaluate the drug interaction of this flavonoid (Ueng et al. 1999). Naringenin is a potent inhibitor of benzo(a)pyrene hydroxylase activity in vitro and naringin reduces the P450 1A2 protein level in vivo. Conclusion: These effects may indicate a chemopreventive role of naringin against protocanics activated by P450 1A2.

To see whether grapefruit juice flavonoids alter the permeation of vincristine across the blood-brain barrier, we conducted experiments with cultured mouse brain capillary endothelial cells (MBEC4 cells) in vitro and ddY mice in vivo (Mitsunaga et al. 2000). The in vivo brain-to-plasma concentration ratio of [3H]vincristine in ddY mice was decreased by coadministration of 0.1 mg/kg quercetin, but increased by 1.0 mg/kg quercetin. Kaempferol had a similar biphasic effect. Chrysirin, flavon, hesperetin, naringenin increased [3H]vincristine uptake in the 10-50 μM range, and glycosides (hesperidin, naringin, rutin) were without effect. Conclusion: Patients taking drugs which are P-glycoprotein substrates may need to restrict their intake of bioflavonoid-containing foods and beverages, such as grapefruit juice.

The pharmacokinetics of nisoldipine coat-core tablet were studied in a Latin square-designed trial in which 12 healthy men were administered the drug with water, grapefruit juice, or encapsulated naringin powder at the same amount as that assayed in the juice (Bailey et al. 1993b). The bioavailability of some dihydropridine calcium antagonists can be markedly augmented by grapefruit juice. The naringin capsule did not change nisoldipine pharmacokinetics, indicating that the bioavailability of some dihydropridine calcium antagonists can be augmented by grapefruit juice but does not involve naringin.

To investigate whether the presence of naringin is demanded for the inhibition of the coumarin 7-hydroxylase in man or other compounds are responsible for it (Runkel et al. 1997). While increasing amounts of grapefruit juice delay the excretion of 7-hydroxycoumarin by 2 h, increasing doses of naringin in water up to twofold do not cause any alteration in the time course of excretion. Conclusion: As naringin alone is ineffective, the inhibitory effect of grapefruit juice on the metabolism of coumarin is caused by at least one compound other than naringin.

A randomized crossover interaction study on the effects of grapefruit juice on the pharmacokinetics of nimodipine and its metabolites (Fuhr et al. 1998). Grapefruit juice increased by 1.0 mg/kg quercetin. Kaempferol had a similar concentration ratio of [3H]vincristine in ddY mice was decreased by coadministration of 0.1 mg/kg quercetin, but increased by 1.0 mg/kg quercetin. Kaempferol had a similar biphasic effect. Chrysirin, flavon, hesperetin, naringenin increased [3H]vincristine uptake in the 10-50 μM range, and glycosides (hesperidin, naringin, rutin) were without effect. Conclusion: Patients taking drugs which are P-glycoprotein substrates may need to restrict their intake of bioflavonoid-containing foods and beverages, such as grapefruit juice.

The effects of naringin on the growth of periodontal pathogens such as A. actinomycetemcomitans and P. gingivalis were studied in vitro. For comparison, the effects of naringin on several oral microbes were also studied (Tsui et al. 2008). Naringin also had an inhibitory effect against all bacteria and yeasts tested. Conclusion: Naringin possesses significant antimicrobial properties on periodontal pathogens in vitro. It also has an inhibitory effect on some common oral microorganisms in low concentrations.

Drug Interactions

The effects of grapefruit juice and naringenin on the activity of the human cytochrome P450 isoform CYP1A2 were evaluated using caffeine as a probe substrate (Fuhr et al. 1993). In vitro naringin was a potent competitive inhibitor of caffeine 3-demethylation by human liver microsomes (Ki = 7-29 μM). In vivo grapefruit juice decreased the oral clearance of caffeine and prolonged its half-life. Conclusion: Grapefruit juice and naringenin inhibit CYP1A2 activity in man.

The pharmacokinetics of felodipine and its single primary oxidative metabolite, dehydrofelodipine, were studied after drug administration with 200 ml water, grapefruit juice, or naringin in water at the same concentration as the juice in a randomized crossover trial of nine healthy men (Bailey et al. 1993a). Grapefruit juice produces a marked and variable increase in felodipine bioavailability. Naringin solution produced much less of an interaction, showing that other factors were important. Conclusion: Grapefruit juice produces a marked and variable increase in felodipine bioavailability.
To evaluate the inhibition of CYP3A4 activity in human liver microsomes by flavonoids, furanocoumarins and related compounds and investigate possibly more important and potential inhibitors of CYP3A4 in grapefruit juice (Ho et al. 2001). Bergapten (5-methoxyxosoralen) with the lowest IC50 value (19-36 microM) was the most potent CYP3A4 inhibitor. Conclusion: Bergapten appears to be a potent inhibitor of CYP3A4, and may therefore be primarily responsible for the effect of grapefruit juice on CYP3A4.

The effect of naringin on the bioavailability and pharmacokinetics of paclitaxel after oral administration of paclitaxel or its prodrug coadministered with naringin to rats was studied (Choi and Shin 2005). The bioavailability of paclitaxel coadministered as a prodrug with or without naringin was remarkably higher than the control. Conclusion: Enhanced paclitaxel bioavailability after oral coadministration of the paclitaxel prodrug with naringin to rats.

The pharmacokinetics of verapamil and one of its metabolites, norverapamil, were investigated after oral administration of verapamil at a dose of 9 mg/kg without or with oral naringin at a dose of 7.5 mg/kg in rabbits (Kim and Choi 2005). With naringin, the total area under the plasma concentration-time curve (AUC) of verapamil was significantly greater, the AUC(verapamil)/AUC(norverapamil) ratio was conversely greater. Conclusively, the formation of verapamil and the formation of norverapamil were inhibited by naringin possibly by inhibition of CYP3A in rabbits.

Pharmacokinetic parameters of diltiazem and desacetyl-diltiazem were determined in rats following an oral administration of diltiazem to rats in the presence and absence of naringin (Choi and Han 2005). Absolute and relative bioavailability values of diltiazem in the presence of naringin were significantly higher than those from the control group. Conclusion: The concomitant use of naringin significantly enhanced the oral exposure of diltiazem in rats.

The effect of naringin on the pharmacokinetics of verapamil and its major metabolite, norverapamil in rabbits were studied (Yeum and Choi 2006). Pretreatment of naringin enhanced the oral bioavailability of verapamil. Conclusion: Verapamil dosage should be adjusted when given with naringin or a naringin-containing dietary supplement.

The effects of oral naringin on the pharmacokinetics of intravenous paclitaxel in rats were studied (Lim and Choi 2006). After intravenous administration of paclitaxel, the AUC was significantly greater, and Cl was significantly slower than controls. Conclusion: The inhibition of hepatic P-gp by oral naringin could also contribute to the significantly greater AUC of intravenous paclitaxel by oral naringin.

Inhibition of OATP1A2 transport by flavonoids in grapefruit (naringin) and orange (hesperidin) was conducted in vitro. Two randomized, crossover, pharmacokinetic studies were performed clinically (Bailey et al. 2007). Naringin most probably directly inhibited enteric OATP1A2 to decrease oral fexofenadine bioavailability. Inactivation of enteric CYP3A4 was probably not involved. Conclusion: Naringin is a major and selective clinical inhibitor of organic anion transporting polypeptide 1A2 (OATP1A2) in grapefruit juice.

The esterase-inhibitory potential of 10 constitutive flavonoids and furanocoumarins toward P-nitrophenylacetate (PNPA) hydrolysis was investigated (Li et al. 2007). In Caco-2 cells, demonstrated to contain minimal CYP3A activity, the permeability coefficient of the prodrugs lovastatin and enalapril was increased in the presence of the active flavonoids kaempferol and naringenin, consistent with inhibition of esterase activity. Conclusion: Kaempferol and naringenin are shown to mediate pharmacokinetic drug interaction with the prodrugs lovastatin and enalapril due to their capability of esterase inhibition.

The potential interaction between selected ingredients of grapefruit juice and, the transport of talinolol, a P-gp substrate, across Caco-2 cells monolayers was determined in the absence and presence of distinct concentrations of grapefruit juice, bergamottin, 6,7-dihydroxybergamottin, 6,7′-epoxybergamottin, naringin, and naringenin (de Castro et al. 2007). The flavonoid aglycone naringenin was around 10-fold more potent than its glycoside naringin with IC50 values of 236 and 2409 μM, respectively. Conclusion: The in vitro data suggest that compounds present in grape-fruit juice are able to inhibit the P-gp activity modifying the disposition of drugs that are P-gp substrates such as talinolol.

The cellular uptake of benzoic acid was examined in the presence of the juice of naringin, naringenin, morin, silybin and quercetin in Caco-2 cells (Shim et al. 2007). All the tested flavonoids except naringin significantly inhibited the cellular uptake of [(14)C]-benzoic acid. Particularly, naringenin and silybin exhibited strong inhibition effects. Conclusion: Some flavonoids appeared to be competitive inhibitors of monocarboxylate transporter 1 (MCT1).

**ANTINFLAMMATORY EFFECTS**

Experiments are carried out on 35 male albino rats. The effect of the flavonoids naringin and rutin on the level of mastoctic and nonmastoctic histamine is studied, as well as on its release induced by compound 48/80 (2 mg/kg i. p.). The histamine content is determined fluorimetrically (Lamb- bev et al. 1980a). Naringin and rutin have no effect on the levels of mastoctic and nonmastoctic histamine. They prevent the release of mastoctic histamine, induced by compound 48/80. Conclusion: Flavonoids with antioxidant action (naringin and rutin) prevent the release of mastoctic and nonmastoctic histamine.

The authors examined antioxidative activity of bioflavonoids naringin and rutin in comparative aspect in two models of acute inflammation. The experiments were carried out on 180 male white rats and 24 guinea pigs (Lamb- bev et al. 1980b). The two flavonoids manifested marked antioxidative effect in rats with experiments peritonitis. Conclusion: Naringin has antiinflammatory effect of in experimental pulmonary edema and peritonitis.

Eleven flavonoids included flavone, quercetin, taxifolin, chalcone, apigenin, fisetin, rutin, phloretin, tangeretin, hes- peretin, and naringin were studied for their effects on human basophil histamine release triggered by six different stimuli (Middleton and Drzewiecki 1984). The flavonoids, quercetin and fisetin, and the flavone, apigenin, exhibited a predilection to inhibit histamine release stimulated by IgE-dependent ligands (antigen, anti-IgE, and con A). The flava- none derivatives, taxifolin and hesperetin, were inactive, as were the glycosides, rutin and naringin. The open chain congeners, chalcone and phloretin, also possessed inhibitory activity. Conclusion: Flavonoid inhibited human basophil histamine release stimulated by various agents.

The passive cutaneous anaphylaxis-inhibitory activity of the flavonones isolated from the pericarp of Citrus un- shiu (Family Rutaceae) and the fruit of Poncirus trifoliata (Family Rutaceae) was studied (Park et al. 2005). Naringenin, hesperetin and ponciretin potentially inhibited IgE-induced β-hexosaminidase release from RBL-2H3 cells and the PCA reaction. Conclusion: Flavonone glycosides can be activated by intestinal bacteria, and may be effective toward IgE-induced atopic allergies.

**OTHER EFFECTS**

Flavonoids containing phenol B rings, e.g. naringenin, naringin, hesperetin and apigenin, were studied if they formed prooxidant metabolites that oxidised NADH upon oxidation by peroxidase/H2O2 (Chan et al. 1999). Prooxidant phenoxy radicals formed by these flavonoids coxoi- dise NADH to form NAD radicals which then activated oxygen. Conclusion: Naringin and naringenin have been identified as prooxidants independent of transition metal catalysed autoxidation reactions.
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