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Full Communication

The Safety of Flavocoxid, a Medical Food, in the Dietary Management of Knee Osteoarthritis

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ABSTRACT This study was designed to determine the safety of a medical food, flavocoxid, a proprietary blend of free-B ring flavonoids and flavans from the root of *Scutellaria baicalensis* (Chinese skullcap) and the bark of *Acacia catechu* in the dietary management of knee osteoarthritis. The 12-week, randomized, double-blind, placebo-controlled trial in an academic medical center enrolled 59 patients with moderate osteoarthritis of at least one knee who were recruited who were classified as having ''below average'' to ''a moderately above average cardiovascular risk'' with a Framingham-based scoring tool. Subjects were randomized to flavocoxid 250 mg twice a day versus identical placebo. Safety measures, including recording of adverse events, incidence of serious adverse events, and results of routine laboratory values, were compared between the two groups. There were no major differences in the baseline demographic characteristics of the placebo and flavocoxid groups. With one exception no significant differences were found between the two groups with respect to adverse events by body system, blood pressure, or laboratory values. There was a significantly higher incidence of upper respiratory adverse events in the placebo group (35.4% vs. 5.8%, $P = .0003$). There were no intra- or inter-group differences in any of the laboratory parameters from study baseline to completion. Thus, flavocoxid is safe when used in a population with ''below average'' to ''moderately above average cardiovascular risk'' compared to placebo.

KEY WORDS: • ***flavocoxid*** • ***knee*** • ***medical food*** • ***osteoarthritis***

INTRODUCTION

MEDICAL FOODS ARE CLASSIFIED by the Food and Drug Administration as ''foods providing nutritional support specifically modified for the management of the unique nutrient needs that result from a specific disease or condition as determined by medical evaluation.''[1,2] Medical foods are produced under rigid good manufacturing practices and have high standards of labeling to ensure safety for the patient. They are specially formulated to contain dietary ingredients that are generally recognized as safe and approved food additives. There is a requirement for the phrase ''to be used under medical supervision'' to be in the label.

Flavocoxid (Limbrel®, Primus Pharmaceuticals Inc., Scottsdale, AZ, USA) is a patent-pending medical food that inhibits the activities of cyclooxygenase (COX)-1, COX-2, and 5-lipoxygenase.[3,4] Flavocoxid contains a proprietary blend of free-B ring flavonoids and flavans from the root of *Scutellaria baicalensis* (Chinese skullcap) and the bark of *Acacia catechu.* The primary components of flavocoxid are baicalin and catechin, concentrated and standardized to greater than 90% purity. Historically, the plants and extracts of the *Acacia* bark have been utilized as astringents to treat gastrointestinal disorders, diarrhea, and indigestion and to stop bleeding.[5–7] Extracts from *Scutellaria* root have been reported to have antispasmogenic, vasoconstrictor, antihypertensive, antiplatelet aggregation, and anti-inflammatory activities.[8–21] Extracts of different *Scutellaria* species have also been shown to inhibit COX activity *in vitro*, suggesting an anti-inflammatory activity.[22,23] Flavocoxid is currently used as a prescription medical food for the management of the metabolic processes involved in the pathogenesis of osteoarthritis (OA).[24]

The safety of *S. baicalensis* and *A. catechu* has been established.[25–27] The mechanisms of action and safety of flavocoxid extracts similar to but less pure than flavocoxid have been extensively studied both *in vitro* and in laboratory animals. Bacterial reverse mutation screening and the Ames test showed no mutagenic activity with and without metabolic activation.[28] Acute (14-day), subchronic (28-day), and chronic (90-day) safety experiments have been performed in ICR mice (Harlan Laboratories, Indianapolis, IN, USA), in which either *A. catechu*, *S. baicalensis*, or a blend of *A. catechu* and *S. baicalensis* was administered as a gavage

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dose in olive oil.[28] There were no significant differences in weight gain between treated and placebo groups. Histopathological analysis of tissues (liver, kidney, duodenum, and stomach) and blood chemistry tests confirmed that the mice were not different compared to placebo-treated controls. A recent 1-month pilot clinical trial evaluated the safety and efficacy of flavocoxid compared to naproxen in knee OA.[3] There was no difference in types or numbers of adverse events between the flavocoxid and naproxen groups.

The present study was designed to test the hypothesis that flavocoxid is safe when compared to placebo when used for the treatment of knee OA.

RESEARCH DESIGN AND METHODS

Study design

Human use approval was obtained from the Institutional Review Board at the University of Alabama at Birmingham. The protocol was a 12-week, double-blind, placebo-controlled trial of flavocoxid 250 mg twice a day versus an identically appearing placebo twice a day.

Subjects were recruited by newspaper ads and flyers and were sent an informed consent document. After meeting the initial screening criteria and signing the informed consent document, the subject was asked to discontinue using nonsteroidal anti-inflammatory drugs for 1 week followed by a visit to the University of Alabama at Birmingham General Clinical Research Center and Arthritis Clinical Investigational Program unit for screening visit. After documentation that the subjects met all inclusion and exclusion criteria they were randomized to receive either flavocoxid or an identical placebo twice a day on an empty stomach.

Inclusion criteria included: (1) women and men 40–75 years old, (2) able and willing to give informed consent, (3) Kellgren-Lawrence grade 2–3 OA of the knee meeting the American College of Rheumatology clinical classification,[29] (4) able and willing to discontinue nonsteroidal anti-inflammatory drugs, natural therapies, and other pain medications for OA for 1 week prior to the first study visit and for the duration of the 12-week trial, (5) knee pain rated >4 cm on a 10-cm visual analog scale, and (6) otherwise in good medical and psychological health as judged by the investigator.

Exclusion criteria included: (1) serious or unstable concomitant medical or psychological illnesses that would impair the patient's ability to complete the study, (2) significant cardiac disease and/or history of myocardial infarction in the last 12 months and/or uncontrolled hypertension, (3) significant bleeding disorders, other than those related to gastrointestinal disease and hemorrhoids, in which there has been a bleeding episode in the last 12 months and are uncontrolled, (4) history of gastrointestinal disease that is uncontrolled or resulted in bleeding in the past 60 days (subjects with uncomplicated ulcers that were controlled were not excluded), (5) alcohol, intravenous, or prescription drug abuse, (6) pregnancy or breastfeeding or inability to practice contraception in individuals of childbearing age, (7) inflammatory arthritis, gout, pseudogout, Paget's disease, or any chronic pain syndrome, (8) severe anserine bursitis, acute joint trauma, or complete loss of articular cartilage in the index knee, (9) taking an investigational drug within 30 days of screening, (10) planning to move or not able to complete a 12-week protocol, (11) use of anticoagulants such as warfarin, (12) inflammatory arthritis necessitating utilization of biologic immunomodulators, (13) subjects who had received intravenous, intramuscular, or intra-articular steroids to the index knee joint within 60 days of screening or oral corticosteroids or other immunosuppressants within 6 months of screening, (14) hypersensitivity to analgesics, COX inhibitors, lipoxygenase inhibitors, or flavonoid ingredients, (15) liver enzyme (serum glutamic oxaloacetic transaminase, serum glutamic pyruvate transaminase, and alkaline phosphatase) levels greater than or equal to twice the upper limit of normal, impaired renal function (creatinine >1.5 mg/dL), leukocyte counts $<3.5\times10^9$/L, platelet counts $<150\times10^9$/L, or laboratory values outside the normal range determined by the investigator to be of clinical significance that would have the potential to confound or interfere with the efficacy or safety evaluation or pose risk to the patient, (16) subjects with "high" 10-year absolute cardiovascular risk score calculated using the Framingham-based Cardiac Global Risk assessment equation,[30] or (17) Kellgren-Lawrence grading of 0, 1, or 4 on x-ray of target joint taken within 12 months of the screening visit.

Study assessments with the primary outcome measurement of toxicity

Subjects were seen at 2, 4, 8, and 12 weeks after enrollment. Subjects were also contacted by telephone every 2 weeks between study visits to assess clinical adverse effects and use of concomitant medications. The primary outcome was a difference in the frequency and severity of adverse effects of flavocoxid compared to placebo. Central nervous system effects were assessed using the Hamilton Anxiety Scale[31] and Beck Depression Inventory.[32–36] Other safety measures were evaluated by laboratory tests, including serum chemistries (sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, and albumin and total protein), liver function tests (alanine aminotransferase and aspartate aminotransferase activities), a complete blood count with differential, a lipid profile, erythrocyte sedimentation rate, and prothrombin and partial thromboplastin times (PT and PTT, respectively).

Statistical methods

The closed envelope randomization method (using a randomly permuted blocked randomization scheme) was utilized to assign patients to either the placebo or flavocoxid group. With the exception of the biostatistician and study pharmacist, the randomization was blinded to all investigators until the end of the trial.

Data on adverse signs and symptoms were collected in a standard fashion across the two treatment arms. The frequencies of adverse events by body system were tabulated across the two treatment arms. The number of adverse events

Table 1. Study Subject Demographics

Parameter	Number (%)		P value[a]
	Flavocoxid	*Placebo*	
Gender			
Female	24 (80%)	24 (82.8%)	.79
Male	6 (20%)	5 (17.2%)	
Age (years)			
Mean	57.86	61.17	.16
Median	58	63	
Race			
African-American	7 (23.3%)	6 (20.7%)	.56
Caucasian	22 (73.3%)	23 (79.3%)	
Other	1 (3.3%)	0	
BMI (kg/m^2)			
Mean (SEM)	34.46 (1.59)	29.90 (0.94)	.04
Median	32.73	30.36	
Study completers			
No	6 (20%)	7 (24.1%)	.75
Yes	23 (76.7%)	22 (75.9%)	

BMI, body mass index.

[a]*P* values for continuous variables were generated by analysis of variance with treatment as a factor, whereas *P* values for categorical variables were derived by the χ^2 test.

by body system, the proportion of patients experiencing an adverse event, and the proportion discontinuing the study agents were compared across the two treatment groups by Fisher' exact test. In addition, the total number of events (more than one event possible per person) was compared across the two treatment groups in a similar fashion. The data from the Hamilton Anxiety Score[31] and Beck Depression Inventory[32–36] were tabulated as the difference between baseline and the 12-week follow-up between the flavocoxid and the placebo groups and compared by *t* tests. Differences in continuous laboratory values from the baseline to the 12-week follow-up were also compared across groups by *t* tests.

RESULTS

Fifty-nine patients were randomized to the trial. Table 1 displays the baseline study demographics. There were no differences except for the body mass index, which was significantly higher in the flavocoxid group compared to the placebo group (34.5 vs. 29.9, $P = .04$).

With one exception, described below, there was no difference in adverse events by body system, between the flavocoxid and the placebo groups (Table 2). There were two episodes of blood in the stool in the flavocoxid group and no episodes of blood in the stool in the placebo group ($P = .5$). When additional analysis was conducted omitting subjects who took additional naproxen or ibuprofen during the treatment period ($n = 56$), there were no significant differences in cardiovascular, constitutional, gastrointestinal, genitourinary, musculoskeletal, neurological, pulmonary, or skin events. However, there were significantly fewer sinus headaches in the flavocoxid versus placebo group ($P = .02$). There was no difference in the change in body weight from baseline to week 12 between the two treatment groups ($P = .75$).

The single significant difference in adverse events was that the flavocoxid group experienced a significantly lower incidence of ear, nose, and throat events ($P = .003$), and this difference was more prominent when pulmonary events (mostly cough and bronchitis) were combined with ear, nose, and throat events (35.4% vs. 5.8%, $P = .0003$).

There were no overall differences in the complete blood count with differential, chemistries, lipid profile, alanine aminotransferase, aspartate aminotransferase, PT, PTT, or erythrocyte sedimentation rate at baseline or 12 weeks between the study groups. The changes in the means were also not significant across the groups (data not shown).

Thirteen patients were discontinued from the study: six in the flavocoxid group and seven in the placebo group. In the flavocoxid group one subject was lost to follow-up, one withdrew because of lack of commitment to participate, one individual had hives, one individual had a rash, and one individual had abdominal gas discomfort and blood in the stool. In the placebo group one individual had an intra-articular steroid injection, one individual did not want to take ''so many'' pills, one individual took naproxen for increasing knee pain, and three individuals were discontinued because they could not tolerate increasing knee pain. There were

Table 2. Number (%) of Adverse Events by Body System

Body system	*Flavocoxid* (n = *52 events*)	*Placebo* (n = *48 events*)	*Fisher's exact test (two-tail)* P *value*
Cardiovascular	0 (0.0%)	1 (2.1%)	.48
Constitutional	5 (9.6%)	1 (2.1%)	.21
Skin	3 (5.8%)	0 (0.0%)	.24
Ear, nose and throat	2 (3.8%)	12 (25.0%)	.003
Pulmonary	1 (1.9%)	5 (10.4%)	.10
Ear, nose, and throat and pulmonary	3 (5.8%)	17 (35.4%)	.0003
Gastrointestinal	13 (25.0%)	12 (25.0%)	1.0000
Genitourinary	1 (1.9%)	2 (4.2%)	.61
Musculoskeletal	19 (36.5%)	12 (25.0%)	.28
Neurological	7 (13.5%)	2 (4.2%)	.16
No adverse events[a]	9 (30%)	9 (31%)	1.0000

[a]The denominator for the percentage of no adverse events is the number of subjects.

Table 3. Mean Beck Depression Inventory (BDI) and Hamilton Anxiety Scores at Baseline and After 12 Weeks of Therapy in the Two Study Groups

	Mean ± SD (n)			
Score, interval	*Flavocoxid*	*Placebo*	*Change in score*	P *value*
BDI score				
Baseline	7.25 ± 10.44 (8)	10.00 ± 5.48 (11)		.1186
Week 12	6.38 ± 13.94 (8)	5.73 ± 5.66 (11)		
Change	−0.88 ± 4.76 (8)	−4.27 ± 5.98 (11)	3.4	.2024
Hamilton Anxiety Score				
Baseline	8.68 ± 10.42 (22)	4.46 ± 2.67 (24)		.309
Week 12	5.59 ± 9.19 (22)	3.83 ± 3.82 (24)		
Change	−3.09 ± 5.86 (22)	−0.63 ± 4.38 (24)	−2.47	.216

three serious adverse events over the study period. One subject in the flavocoxid group was hospitalized because of a broken pelvis suffered in a fall. One subject in the placebo group was hospitalized with interstitial pneumonitis after completing the protocol. Another subject in the placebo group was hospitalized with chest pain after completion of the protocol. All of these serious events were deemed as unrelated to the study protocol or to the treatment.

The results from the Beck Depression Inventory[32–36] and the Hamilton Anxiety Score[31] at baseline and after 12 weeks of therapy are given in Table 3. There was no difference in the means at baseline or after 12 weeks of therapy between the flavocoxid and placebo groups. The changes in the means were also not significant.

DISCUSSION

Flavocoxid has an acceptable safety and tolerability profile compared to placebo. These data confirm preliminary safety data found in other studies.[3,28] Flavonoids, in general, have been shown to decrease platelet aggregation and increase bleeding times.[37] Green tea catechins have been shown to affect coagulation parameters *in vitro* but did not affect PT or PTT *in vivo*.[38] Likewise, the flavocoxid preparation used in this study, containing nearly pure forms of baicalin and catechin, did not significantly increase PT or PTT compared to placebo. Of interest is that flavocoxid administration resulted in a significantly lower number of upper respiratory-related adverse events. This could be explained by the fact that flavonoids have been shown to have both antibacterial and antiviral activities.[39] Baicalin, for example, has some clinical efficacy against severe acute respiratory syndrome.[40] Gargling with green tea catechins is reported to inhibit infection by influenza virus.[41] The reduction in upper airway disturbances compared to placebo found in this trial seems to support these previous findings. The serious adverse events were not related to flavocoxid administration.

Recent concerns related to increased cardiovascular disease risk associated with the use of COX-2 inhibitors[42–46] made it important to document the safety of a dual COX and 5-lipoxygenase inhibitor for knee OA. In our screening process, we removed individuals with high cardiovascular risk using the Framingham-based scoring tool.[30] Therefore, our study documents that, at least in this small population sample, in individuals with ''below average'' to ''a moderately above average cardiovascular risk,'' flavocoxid does not increase the risk of adverse events. We conclude that flavocoxid has an acceptable safety profile in knee OA in patients who do not have ''high'' cardiovascular risk.[30]

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AUTHOR DISCLOSURE STATEMENT

No author had a competing financial interest.

REFERENCES

1. U.S. Food and Drug Administration. http:/www.cfsan.fda.gov/-comm/cp21002.html (accessed September 19, 2008).
2. Morgan SL, Baggott JE: Medical foods: products for the management of chronic diseases. *Nutr Rev* 2006;64:495–501.
3. Levy R, Saikovsky R, Shmidt E, Khokhlov A: Safety and efficacy of flavocoxid (Limbrel) compared with naproxen in subjects with osteoarthritis of the knee: a pilot study. *Osteoarthritis Cartilage* 2007;15:B91–B94.
4. Burnett BP, Jia Q, Zhao Y, Levy RM: A medicinal extract of *Scutellaria baicalensis* and *Acacia catechu* acts as a dual inhibitor of cyclooxygenase and 5-lipoxygenase to reduce inflammation *J Med Food* 2007;10:442–451.
5. Bodeker G, Burford G, Chamberlain J, Bhat K: The underexploited medicinal potential of *Azadirachta indica* A Juss (Meliaceae) and *Acacia niolotic* (L.) Willd, Ex Del (Leguminosae) in sub-Saharan Africa: a case for a review of priorities. *Int Forest Rev* 2001;4:285–298.

6. Ahmed S, Rahman A, Hasnain A, Lalonde M, Goldberg VM, Haqqi TM: Green tea polyphenol epigallocatechin-3-gallate inhibits the IL-1 beta-induced activity and expression of cyclooxygenase-2 and nitric oxide synthase-2 in human chondrocytes. *Free Radic Biol Med* 2002;33:1097–1105.
7. Lin YL, Lin JK: (−)-Epigallocatechin-3-gallate blocks the induction of nitric oxide synthase by down-regulating lipopolysaccharide-induced activity of transcription factor nuclear factor B. *Mol Pharmacol* 1997;52:465–472.
8. Chen YC, Shen SC, Chen LG, Lee TJ, Yang LL: Wogonin, baicalin, and baicalein inhibition of inducible nitric acid synthase and cyclooxygenase-2 gene expressions induced by nitric oxide synthase inhibitors and lipopolysaccharide. *Biochem Pharmacol* 2001;61:1417–1427.
9. Chung HL, Yue GG, To KF, Su YL, Huang Y, Ko WH: Effect of Scutellariae Radix extract on experimental dextran-sulfate sodium-induced colitis in rats. *World J Gastroenterol* 2007;13:5605–5611.
10. Enomoto R, Sugahara C, Suzuki C, *et al*.: Wogonin prevents glucocorticoid-induced thymocyte apopotosis without diminishing its anti-inflammatory action. *J Pharmacol Sci* 2007;104:355–365.
11. Hsieh CJ, Hall K, Ha T, Li C, Krishnaswamy G, Chi DS: Baicalen inhibits IL-1beta and TNF-alpha-induced inflammatory cytokine production from human mast cells via regulation of the NF-kappa B pathway. *Clin Mol Allergy* 2007;26:5.
12. Huang Y, Tsang SY, Yao X, Chen ZY: Biological properties of baicalein in cardiovascular system. *Curr Drug Targets Cardiovasc Haematol Disord* 2005;5:177–184.
13. Koga T, Meydani M: Effects of plasma metabolites of (+)-catechin and quercetin on monocyte adhesion to human aortic endothelial cells. *Am J Clin Nutr* 2001;73:941–948.
14. Krakauer T, Li BQ, Young HA: The flavonoid baicalin inhibits superantigen-induced inflammatory cytokines and chemokines. *FEBS Lett* 2001;500:52–55.
15. Lai MY, Hsiu SL, Hou YC, Tsai SY, Chao PD: Significant decrease of cyclosporine bioavailability in rats caused by a decoction of the roots of *Scutellaria baicalensis*. *Planta Med* 2004; 70:132–137.
16. Li BQ, Fui T, Gong WH, *et al*.: The flavonoid baicalin exhibits anti-inflammatory activity by binding to chemokines. *Immunopharmacology* 2000;49:295–306.
17. Makino T, Hishida A, Goda Y, Mizukami H: Comparison of the major flavonoid content of *S. baicalensis*, *S. lateriflora*, and their commercial products. *J Nat Med* 2008;62:294–299.
18. Mehendale S, Aung H, Wang CZ, *et al*.: *Scutellaria baicalensis* and a constituent flavonoid, baicalein, attenuate ritonavir-induced gastrointestinal side-effects. *J Pharm Pharmacol* 2007;59:1567–1572.
19. Park HG, Yoon SY, Choi JY, *et al*.: Anticonvulsant effect of wogonin isolate from *Scutellaria baicalensis*. *Eur J Pharmacol* 2007;5742:112–119.
20. Kim YO, Leem K, Park J, *et al*.: Cytoprotective effect of *Scutellaria baicalensis* in CA1 hippocampal neurons of rats after global cerebral ischemia. *J Ethnopharmacol* 2001;77:183–188.
21. Scheck AC, Perry K, Hank NC, Clark WD: Anticancer activity of extracts derived from the mature roots of *Scutellaria baicalensis* on human malignant brain tumor cells. *BMC Complement Altern Med* 2006;16:27.
22. Alcarez MJ, Ferrandiz ML: Modification of arachidonic acid metabolism by flavonoids. *J Ethnopharmacol* 1987;21:209–229.
23. Kimura Y, Kubo M, Tani T, Arichi S, Ohminami H, Okuda H: Studies on Scutellariae radix. III. Effects on lipid metabolism in serum, liver, and fat cells of rats. *Chem Pharm Bull* 1981;29: 2308–2312.
24. Burnett BP, Levy R, Cole BJ: Metabolic mechanisms in the pathogenesis of osteoarthritis. *J Knee Surg* 2006;19:191–197.
25. Final report of the safety assessment of *Acacia catechu* gum, *Acacia concinna* fruit extract, *Acacia dealbata* leaf extract, *Acacia dealbata* leaf wax, *Acacia decurrens* extract, *Acacia farnesiana* extract, *Acacia farnesiana* flower wax, *Acacia farnesiana* gum, *Acacia senegal* extract, *Acacia senegal* gum, and *Acacia senegal* gum extract. *Int J Toxicol* 2005;24:75–119.
26. Kim HM, Moon EJ, Li E, Kim KM, Nam SY, Chung CK: The nitric oxide-producing activities of *Scutellaria baicalensis*. *Toxicology* 1999;135:109–115.
27. Schmitt D, Tran N, Riefler S, *et al*.: Toxicologic evaluation of modified gum acacia: mutagenicity, acute and subchronic toxicity. *Food Chem Toxicol* 2008;46:1048–1054.
28. Burnett BP, Silva S, Mesches MH, Wilson S, Jia Q: Safety evaluation of a combination, defined extract of *Scutellaria baicalensis* and *Acacia catechu*. *J Food Biochem* 2007;31:797–825.
29. Altman R, Asch E, Bloch D, *et al*.: Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. *Arthritis Rheum* 1986;29:1039–1049.
30. Grundy SM, Pasternak R, Greenland P, Smith S, Fuster V: Assessment of cardiovascular risk by use of multiple-risk factor assessment equations. A statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation* 1999;100:1048–1092.
31. Hamilton M: The assessment of anxiety states by rating. *Br J Med Psychol* 1959;32:50–55.
32. Beck AT, Steer RA, Ball R, Ranieri WF: Comparison of Beck Depression Inventories-IA and-II in psychiatric outpatients. *J Personality Assessment* 1996;67:588–597.
33. Beck AT, Steer RA, Brown GK: *Manual for the Beck Depression Inventory-II*. Psychological Association, San Antonio, TX, 1996.
34. Steer RA, Ball R, Ranieri WF, Beck AT: Dimensions of the Beck Depression Inventory-II in clinically depressed outpatients. *J Clin Psychol* 1999;55:117–128.
35. Steer RA, Clark DA, Beck AT, Ranieri WF: Common and specific dimensions of self-reported anxiety and depression: the BDI-II versus the BDI-IA. *Behav Res Ther* 1999;37:183–190.
36. Beck AT: *Beck Depression Inventory*, 2nd ed. Harcourt Assessment, Inc., Oxford, UK, 1993.
37. Robak J, Gryglewiski RJ: Bioactivity of flavonoids. *Pol J Pharmacol* 1996;48:555–564.
38. Kang WS, Lim IH, Yuk DY, *et al*.: Antithrombotic activities of green tea catechins and (−) epigallocatechin gallate. *Thromb Res* 1999;96:229–237.
39. Cowman MM: Plant products as antimicrobial agents. *Clin Microbiol Rev* 1999;12:564–583.
40. Lau AC, Yam LY, So LK: Management of critically ill patients with severe acute respiratory syndrome (SARS). *Int J Med Sci* 2004;1:1–10.
41. Yamada H, Takuma N, Daimon T, Hara Y: Gargling with tea catechin extracts for the prevention of influenza infection in elderly nursing home residents: a prospective clinical study. *J Altern Complement Med* 2006;12:669–672.
42. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C: Do selective cyclo-oxygenase-2 inhibitors and

traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006;332:1302–1308.

43. Laine L, White WB, Rostom A, Hochberg M: COX-2 selective inhibitors in the treatment of osteoarthritis. *Semin Arthritis Rheum* 2008;38:165–187.
44. Mukherjee D: Risk of cardiovascular events associated with selective COX-2 inhibitors. *JAMA* 2002;286:954–959.
45. Mukherjee D: Selective cyclooxygenase-2 (COX-2) inhibitors and potential risk of cardiovascular events. *Biochem Pharmacol* 2002;63:817–821.
46. Sorensen R, Abildstrom SZ, Torp-Pedersen C, Gislason GH: Use of selective cyclo-oxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs in high doses increases mortality and risk of reinfarction in patients with prior myocardial infarction. *J Cardiovasc Nurs* 2008;23:14–19.