The Effect of Curcumin on some of Traditional and Non-traditional Cardiovascular Risk Factors: A Pilot Randomized, Double-blind, Placebo-controlled Trial

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Abstract

Numerous interventional studies in clinical and preclinical setting stated that intake of curcumin may provide protection against cardiovascular disease. The aim of this trial was investigation of curcumin efficiency on some cardiovascular risk factors in patients with coronary artery disease (CAD). A total of 33 patients with CAD who fulfilled inclusion and exclusion criteria were entered the study. Patients were randomly assigned to receive curcumin or placebo, 500 mg capsules, four times daily for 8 weeks. Lipid profile, blood glucose and high sensitive C-reactive protein (hs-CRP) levels were analyzed at baseline and two months after treatment. Serum levels of triglycerides (P=0.01), LDL-cholesterol (P=0.03) and VLDL-cholesterol (P=0.04) significantly decreased in the curcumin group compared to baseline, without significant changes in total cholesterol, HDL-cholesterol, blood glucose and hs-CRP levels. In all mentioned laboratory parameters, significant difference was not detected between curcumin and placebo. Although curcumin improved some of lipid profile components, it did not show appreciable effect on inflammatory markers in patients with CAD. Therefore, more detailed assessment of metabolic effects or anti-inflammatory activities of curcumin need to perform by extensive human study.

Keywords: Curcumin; Coronary artery disease; Lipid profile; hs-CRP; Blood glucose.

Introduction

Cardiovascular diseases (CVDs) and their complications are considered as a leading cause of death throughout the world. They can also decrease quality of life. Traditional risk factors of cardiovascular diseases include age, gender, hypertension, dyslipidemia, smoking and diabetes mellitus (1). Among these, dyslipidemia is the atheromatous lesion’s foundation, which accompanied with arterial stenosis. Although these risk factors have a strong association with cardiovascular events; they are insufficient to fully elucidate absolute risk. Therefore the probability of interference of other factors in the pathogenesis of atherosclerosis is considerable (2). Numerous studies have pointed to crucial position of inflammation throughout atherosclerosis stages (3, 4). Studies stated
findings for viral infection or requiring treatment with antibiotics); 4) immunosuppressive, anti-inflammatory and or antibiotic drug use; 5) curcumin sensitivity 6) pregnancy or breastfeeding. Eligible patients signed written informed consent before enrollment. Demographic data, drug history, past medical history, family history, cardiovascular risk factors and laboratory data for each patient collected by a questionnaire. Other initial assessments, including physical examination, vital signs, 12-lead electrocardiogram, measurements of height and body weight, calculation of BMI and smoking status have been done at enrollment. Laboratory evaluations including fasting plasma glucose, lipid profile [total cholesterol (TC), Low-density lipoprotein-cholesterol (LDL-C), High-density lipoprotein-cholesterol (HDL-C), and triglyceride (TG)], liver and kidney function were recorded at baseline and two months after treatment.

Materials
Curcumin and curcumin placebo were provided as capsules by Sami Labs Limited Corporation (Bangalore, India). Curcumin C3 complex capsules contain a minimum 95% curcuminoids.

Study design
The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (TUMS), as a randomized double blind placebo controlled trial. Patients were randomly entered into one of the groups (curcumin or placebo) and were treated with curcumin (1 capsule of 500 mg/QID) or placebo in addition to conventional therapies for two months. Initially, patients were provided with 30-day supply of medication (curcumin or placebo). After one month, second supply of capsules was provided. Blood samples from all patients were obtained at the baseline and two months after either curcumin or placebo administration. Blood samples were centrifuged at 4000 rpm for 5 minutes and serum samples separated from fresh blood were stored at -20 °C until analysis time. The serum concentration of hs-C-reactive protein was measured at baseline and two months after treatment by using immunoturbidimetry assays.
(COBAS Integra 400, Roche Diagnostics). Biochemical tests consisting of blood glucose, TC, LDL-C, HDL-C and TG were measured enzymatically (COBAS Integra 400, Roche Diagnostics) after a 12-hour overnight fast. In addition, kidney and liver function tests were also assessed by enzymatic methods according to the manufacturer’s protocol (COBAS Integra 400, Roche Diagnostics).

Follow up

Patients were followed for 2 months after hospital discharge by telephone contact and monthly clinic visits. Investigator evaluated medication compliance by counting the number of capsules returned at study visits. Moreover, safety and tolerability were assessed by patient interview. It should be noted that adverse events including; liver, kidney, gastrointestinal as well as hypersensitivity reaction were recorded specifically during the study.

Statistical evaluation

Statistical analyses were performed using SPSS16 (SPSS Inc., Chicago, IL, USA). Statistical data are presented as mean ± Standard Deviation (SD) or as median with Interquartile range (IQR), as appropriate. For determining statistical significance of quantitative variables, comparisons were performed by using t-tests for normal distribution data and Mann-Whitney test for non-parametric data. For paired data, quantitative variables with normal distribution were analyzed by paired-sample t-test and non-parametric data were assessed by Wilcoxon test. For comparing qualitative variables, Chi square test or Fisher’s exact test was utilized when appropriate. A p-values < 0.05 were considered statistically significant in all statistical evaluations.

Results

Patient characteristics

Forty patients with CAD were enrolled in the trial. Among these, Thirty-three patients completed the study, 17 treated with curcumin (n=17) and 16 with placebo (n=16). The two groups were similar in the demographic, clinical, and baseline characteristics (Table 1). Seven patients did not complete the study for reasons such as unplanned revascularization, loss to follow-up or non-compliance.

The effect of curcumin on cardiovascular risk factors

The results revealed that changes of lipid profile due to the curcumin intervention in comparison with placebo were not statistically significant (Table 3). As illustrated in Table 2, TC slightly decreased in the curcumin group (19.18%, p=0.30) and the placebo group (8.56%, p=0.17); LDL levels after intervention significantly decreased in the curcumin group (28.87%, p=0.03), and to some extent decreased in the placebo group (14.54%, p=0.15). Comparing baseline with two month samples, VLDL values significantly decreased (p=0.04) in the curcumin group, although there was not a significant change in the placebo (p=0.30). HDL levels were trending upward in the curcumin group (5.3%, p=0.20), but the downward trend was observed in the placebo group (2%, p=0.77). Serum triglycerides significantly decreased in the curcumin group (2.7%, p=0.01), while nonsignificantly decreased in the placebo group (2.35%, p=0.61).

Although FBG decreased in the curcumin group (13.16%, p=0.09) and increased in the placebo group (10.51%, p=0.17), no statistically significant differences were observed between the groups (Tables 2, 3).

As indicated in Table 2, there is no statistically significant difference of serum hs-CRP levels between pre- and post-treatment for patients in the curcumin group (p=0.35). There was no significant between-group difference in hs-CRP measurements (p=0.91).

Adverse drug reactions

During the trial, any side effect was evaluated in the study population. Two gastrointestinal (GI) adverse symptoms were reported during the course of study; one patient developed diarrhea (for 2 days from the beginning of therapy) that had no will to continue the treatment. Diarrhea improved after self-cessation of treatment. One patient complained about GI disturbances which resolved by curcumin administration after meal. No statistically significant changes in urea
Table 1. Baseline demographic and clinical characteristics of population study.

|                                | Placebo, n=16 | Curcumin, n=17 | P       |
|--------------------------------|--------------|----------------|---------|
| **Age, y, mean ± SD**          | 64.3±8.42    | 61.5±8.7       | 0.33a   |
| **Male, n (%)**                | 14 (87.5)    | 10 (58.8)      | 0.12b   |
| **Weight, Kg**                 | 79.71±1.06   | 73.30±8.36     | 0.10a   |
| **Height, m**                  | 167.3±7.4    | 162.61±9.7     | 0.17a   |
| **BMI, Kg/m², mean ± SD**      | 28.5±3.67    | 27.94±3.62     | 0.20a   |
| **Waist circumference, cm**    | 102.2±6.1    | 106.6±7.2      | 0.63a   |
| **Active smoker, n (%)**       | 3(18.8)      | 6(35.3)        | 1.00b   |
| **Fax history of CHD, n (%)**  | 4(25)        | 7(41.2)        | 0.39a   |
| **Prior history**              |              |                |         |
| **Diabetes, n (%)**            | 5(31.3)      | 9(52.9)        | 0.20b   |
| **Hypertension, n (%)**        | 9(56.3)      | 13(76.5)       | 0.47a   |
| **Dyslipidemia, n (%)**        | 8(50)        | 12(70.6)       | 0.22b   |
| **Drug history**               |              |                |         |
| **ACEIs**                      | 4 (25)       | 7 (41.2)       | 0.32a   |
| **ARBs**                       | 5(31.3)      | 2(11.8)        | 0.23a   |
| **Statins**                    | 11(68.8)     | 13(76.5)       | 0.71a   |
| **β-blockers**                 | 9 (56.3)     | 12 (70.6)      | 0.39a   |
| **Ca-blockers**                | 3(18.8)      | 0(0)           | 0.10a   |
| **Nitrates**                   | 10 (62.5)    | 9 (52.9)       | 0.58a   |
| **Antiplatelet**               | 14 (87.5)    | 14 (82.4)      | 1.00b   |
| **Diuretics**                  | 1 (6.3)      | 3 (17.6)       | 0.60a   |
| **Insulin**                    | 1 (6.3)      | 4 (23.5)       | 0.34a   |
| **Hypoglycaemic agents**       | 4 (25)       | 6(35.3)        | 0.71b   |
| **Clinical parameters**        |              |                |         |
| **Ef %, mean ± SD**            | 50.62±6.80   | 52.18±6.82     | 0.50a   |
| **Heart rate, bpm, mean ± SD** | 71.07±9.33   | 69.47±9.56     | 0.64a   |
| **Systolic BP, mm Hg, mean ± SD** | 138.60±16.95 | 128.82±36.76  | 0.35a   |
| **Diastolic BP, mm Hg, mean ± SD** | 80.13±12.42  | 79.88±13.00    | 0.95a   |
| **Baseline blood tests**       |              |                |         |
| **TC, mg/dl, mean ± SD**       | 165.21±24.36 | 172.53±45.75   | 0.60a   |
| **HDL-C, mg/dl, mean ± SD**    | 43.14±10.82  | 39.06±10.80    | 0.24a   |
| **LDL-C, mg/dl, mean ± SD**    | 95.23±20.72  | 118±44.05      | 0.10b   |
| **VLDL, mg/dl, mean ± SD**     | 17.85±6.91   | 28.53±12.38    | 0.06a   |
| **TG, mg/dl, mean ± SD**       | 108.58±42.27 | 145.92±52.72   | 0.06a   |
| **FBG, mg/dl, mean ± SD**      | 105.38±32.27 | 141.06±55.20   | 0.05a   |
| **Cr, mg/dl, mean ± SD**       | 0.91±0.22    | 0.89±0.22      | 0.83a   |
| **Urea, mg/dl, mean ± SD**     | 37.68±11.35  | 36.79±9.77     | 0.81a   |
| **WBC, /cumm, mean ± SD, median (IQR)** | 8427.50±4505.64 | 8325.29±2051.36 | 0.23a |
| **PLT-Count, mean ± SD**       | 190381.8±34487.15 | 240800±84967.71 | 0.08a   |
| **hs-CRP, mean ± SD, median (IQR)** | 0.54±0.58, 0.33 (0.19-0.75) | 2.14±5.00, 0.36 (0.14-0.85) | 0.79a |

*a* t-tests, *b* Fisher's exact test, *c* Chi square test, *d* Mann-Whitney test.

BMI, body mass index; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers; Ef, ejection fraction; TC, total cholesterol; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; VLDL, very low-density lipoprotein cholesterol; TG, triglycerides; FBG, fasting blood glucose; Cr, creatinine; WBC, white blood cell; CUMM, cubic millimeter; IQR, interquartile range; PLT, platelet.
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(p=0.73) and creatinine (P=0.13) were observed at baseline and 2 months after administration (Table 3).

**Discussion**

In the current study, curcumin significantly reduced serum levels of LDL and triglycerides compared with baseline. But there was no significant difference in comparison to the placebo group. Levels of HDL-C increased and levels of total cholesterol decreased with curcumin but not to a significant degree. Nonsignificant differences between the study groups is probably due to small sample size. The within group statistical analyzes revealed significant differences in some lipid variables before and after curcumin treatment. The results can be due to comparing patients with themselves as a control in order to eliminate confounding factors.

Curcumin was reported to have health benefits and potential cardioprotective effect (7, 11, 12). Cardioprotection can be attributed partly to lipid lowering and anti-inflammatory abilities. Taking into consideration the above results and reported effects in the literature curcumin can have a favorable effect on traditional and nontraditional cardiovascular risk factors. Quiles et al. reported cardioprotective effect of curcumin in atherosclerotic rabbits. They stated curcumin prevents lipoperoxidation of subcellular...

| Placebo Pre-treatment | Post-treatment | Curcumin Pre-treatment | Post-treatment |
|-----------------------|----------------|------------------------|----------------|
| TC                    | 165.21 ± 24.36 | 151.07 ± 50.31         | 172.53 ± 45.75, 154.13 ± 40.10, 0.30p |
| LDL-C                 | 95.23 ± 20.72  | 81.38 ± 43.41          | 118 ± 44.05, 111 (80-147), 0.03p |
| HDL-C                 | 43.14 ± 10.82  | 42.28 ± 6.54           | 39.06 ± 10.80, 41.13 ± 9.20, 0.20p |
| VLDL                  | 17.85 ± 6.91   | 17.25 ± 7.31           | 28.53 ± 12.38, 22.68 ± 8.10, 0.04p |
| TG                    | 108.58 ± 42.27 | 108.75 ± 53.32         | 145.92 ± 52.72, 120.15 ± 10.47, 0.01p |
| FBG                   | 105.38 ± 32.27 | 116.46 ± 24.96         | 141.06 ± 55.20, 122.50 ± 35.68, 0.09p |
| hs-CRP                | 0.54 ± 0.58, 0.33 (0.19-0.75) | 0.23 ± 0.18, 0.19 (0.11-0.30) | 2.14 ± 5.00, 0.59 ± 0.76, 0.35p |

| Placebo Pre-treatment | Post-treatment | Curcumin Pre-treatment | Post-treatment | p |
|-----------------------|----------------|------------------------|----------------|---|
| ΔTC ± SD              | 26 ± 19.85     | 18.40 ± 51.17          | 0.63p          | -39.90-24.70 |
| ΔLDL-C ± SD           | 21.25 ± 19.88  | 34.15 ± 45.01          | 0.36p          | -16.11-41.92 |
| ΔHDL-C ± SD           | 0.85 ± 11.14   | -2.06 ± 5.98           | 0.38p          | -2.92-3.29 |
| ΔVLDL ± SD            | 1.62 ± 8.51    | 5.84 ± 7.16            | 0.27p          | -3.64-12.08 |
| ΔTG ± SD              | 3.57 ± 44.04   | 25.76 ± 31.30          | 0.14p          | -8.31-52.70 |
| ΔFBG ± SD, median (IQR) | -11.07 ± 27.66, -5.00 (-25.50-7.50) | 18.56 ± 41.05, 3.50 (-12.50-40.50) | 0.16p | - |
| Δhs-CRP ± SD, median (IQR) | 0.30 ± 0.64, 0.05 (-0.07-0.63) | 1.54 ± 4.89, 0.06 (-0.16-0.50) | 0.91p | - |
| ΔUrea ± SD            | 2.95 ± 9.73    | 1.03 ± 11.76           | 0.64p          | -10.37-6.53 |
| ΔCr ±SD               | 0.02 ± 0.08    | -0.06 ± 0.16           | 0.08p          | -0.18-0.01 |

Values are mean ± SD or median (IQR). *Two Independent- Samples t-tests, bMann-Whitney test.

TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein; VLDL, very low-density lipoprotein cholesterol; TG, triglycerides; FBG, fasting blood glucose; hs-CRP, high-sensitive C-reactive protein.
Controversial observations from studies conducted in different population and used different doses have been reported. The studies reporting hypolipidemic effects were not RCT and were done in healthy subjects. In addition, they were short trials using different doses of curcumin and not concurrently evaluating all components of the lipid profile. These differences between previous studies and this trial may explain the discrepancies in the reported results.

Curcumin is found to be associated with hypoglycemia in streptozotocin induced diabetic rats (22). Curcumin activated PPAR-γ and lowered blood glucose levels in diabetic mice (23, 24). It also enhanced insulin release by induction of β-cell electrical activity (25). Other investigators demonstrated that the dietary curcumin supplement improved insulin resistance and hyperglycemia in diabetic mice with a simultaneous increase in plasma leptin and insulin levels (26). In the present study blood glucose was decreased in the curcumin group and increased in the placebo group, although not statistically significant.

One of diverse mechanism by which curcumin mediates protection against CVDs is anti-inflammatory activities. Experimental study results of cardiopulmonary bypass and cardiac ischemia and reperfusion (I/R) suggested that curcumin considerably decreased proinflammatory cytokines and subsequent cardiomyocytic injury (27). CRP, as a nontraditional cardiovascular risk factor, is a well known predictor of CVDs. Nuclear factor-κB pathway Regulates CRP (28). Curcumin is a potent modulator of transcription factors such as NF-κB that exhibit critical role in signal transduction pathways in inflammatory illnesses. So curcumin has a favorable effect on chronic inflammatory disease; inflammatory bowel disease, rheumatoid arthritis and Alzheimer (8, 29). A pilot study reported curcumin clinically improved patients with inflammatory bowel disease in addition to decrease of sedimentation rate and CRP level (30). This clinical trial was not a double-blind placebo-controlled study. In a double-blind RCT, curcumin’s antirheumatic activity was compared to phenylbutazone. Curcumin with daily doses of 1200 mg for 2

detected changes of lipid profile (e.g. LDL & TG) the current study are compatible with what Ramirez-Tortosa et al. and Pungcharoenkul and Thongnopnua reported. According to researches, suggested mechanisms of cholesterol reduction by curcumin include; inhibition of intestinal absorption, up-regulation of the LDL receptor and cholesterol 7α-hydroxylase, conversion of cholesterol into bile acids and fecal excretion of bile acids and cholesterol (21, 22).
weeks improved clinical symptoms in patients with rheumatoid arthritis (31). Another clinical trial evaluated the effect of curcumin as a maintenance therapy in 82 patients with quiescent ulcerative colitis. Subjects received daily doses of 2 g curcumin for six months and experienced improvement. Response was subjectively indicated by clinical activity index and objectively reported by the endoscopic index (32). Other clinical studies (33-35) reported curcumin efficacy in clinical inflammatory processes but they did not measure inflammatory biomarkers. Results of current study verify these findings as curcumin therapy was associated with improvement in hs-CRP values. However, significant difference was not detected compared to baseline or the placebo group. Clinical studies, that addressed the curcumin’s anti-inflammatory properties taking into consideration of curcumin poor bioavailability (36), used daily doses of 1200 mg-2 g. Patients did not report any serious side effects. According to the results of previous studies, curcumin with doses up to 12 g is well tolerated (10).

Regarding observed outcomes, we concluded that small sample size was a major limitation of this research, although it should be noted that this study was a pilot study. However, studies with larger number of patients may lead to decisive results.

Conclusions

According to the results, curcumin seems to be a potential candidate for decreasing cholesterol and triglyceride levels. Nonetheless, it has no appreciable effect on inflammatory biomarkers in patients with CAD. Further and larger human studies need to be done in order to establish a detailed assessment of metabolic effects and or anti-inflammatory actions of curcumin.

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References

(1) Wang TJ. New cardiovascular risk factors exist, but are they clinically useful? Eur. Heart J. (2008) 29: 441-444.
(2) Saito M, Ishimitsu T, Minami J, Ono H, Ohru M and Matsuoka H. Relations of plasma high-sensitivity C-reactive protein to traditional cardiovascular risk factors. Atherosclerosis (2003) 167: 73-79.
(3) Libby P, Ridker PM and Maseri A. Inflammation and atherosclerosis. Circulation (2002) 105: 1135-1143.
(4) Nasiripour S, Gholami Kh, Mousavi S, Mohagheghi A, Radfar M, Abdollahi M, Khazaeipour Z and Mojtahedzadeh M. Comparison of the effects of enoxaparin and heparin on inflammatory biomarkers in patients with st-segment elevated myocardial infarction: a prospective open label pilot clinical trial. Iran. J. Pharm. Res. (2014) 13: 583-590.
(5) Acharjee S, Qin J, Murphy SA, McCabe C and Cannon CP. Distribution of traditional and novel risk factors and their relation to subsequent cardiovascular events in patients with acute coronary syndromes (from the PROVE IT-TIMI 22 Trial). Am. J. Cardiol. (2010) 105: 619-623.
(6) Kohli K, Ali J, Ansari MJ and Raheman Z. Curcumin: a natural antiinflammatory agent. Indian J. Pharmacol. (2005) 3: 141-147.
(7) Kapakos G, Youreva V and Srivastava A. Cardiovascular protection by curcumin: molecular aspects. Indian J. Biochem. Biophys (2012) 49: 306-315.
(8) Goel A, Kunnumakkara AB and Aggarwal BB. Curcumin as curcumin: from kitchen to clinic. Biochem. Pharmacol. (2008) 75: 787-809.
(9) Hamed OA, Mehdawi N, Taha AA, Hamed EM, Al-Nuri MA and Hussein AS. Synthesis and antibacterial activity of novel curcumin derivatives containing heterocyclic moiety. Iran. J. Pharm. Res. (2013) 12: 47-56.
(10) Lao CD, Ruffin MT, Normolle D, Heath DD, Murray SI, Bailey JM, Boggs ME, James Crowell J, Rock CL and Brenner DE. Dose escalation of a curcuminoid formulation. BMC. Compl. Altern. Med. (2006) 6: 10-13.
(11) Quiles JL, Aguilera C, Mesa MD, Ramirez-Tortosa MC, Baro L and Gil A. An ethanolic-aqueous extract of Curcuma longa decreases the susceptibility of liver microsomes and mitochondria to lipid peroxidation in atherosclerotic rabbits. Biofactors (1998) 8: 51-57.
(12) Wongcharoen W and Phrommintikul A. The protective role of curcumin in cardiovascular diseases Int. J. Cardiol. (2009) 133: 145-151.
(13) Ramirez-TortosaMC, Mesa MD, Aguilera MC, Quiles JL, Baro L, Ramirez-Tortosa CL, Martinez-Victoria E and Gil A. Oral administration of a turmeric extract inhibits LDL oxidation and has hypocholesterolemic effects in rabbits with experimental atherosclerosis. Atherosclerosis (1999) 147: 371-378.
(14) Olszanecki R, Jawien J, Gajda M, Mateuszuk L,
Gebsko A, Korabiowska M, Chlopicki S and Korbut R. Effect of curcumin on atherosclerosis in apoE/LDLR-double knockout mice. J. Physiol. Pharmacol. (2005) 56: 627-635.

(15) Kim M and Kim Y. Hypocholesterolemic effects of curcumin via up-regulation of cholesterol 7a-hydroxylase in rats fed a high fat diet. Nutr. Res. Pract. (2010) 4: 191-195.

(16) Soni KB and Kuttan R. Effect of oral curcumin administration on serum peroxides and cholesterol levels in human volunteers. Indian J. Physiol. Pharmacol. (1992) 36: 273-275.

(17) Ramirez-Bosca A, Soler A, Carrion MA, Mira DP, Zapata JP, Diaz J, Bernd A, Almagro EQ and Miquel J. Anhydroalcoholic extract of curcuma longa lowers the apo B/apo A ratio. Implications for atherogenesis prevention. Mech. Ageing. Dev. (2000) 119: 41-47.

(18) Baum L, Cheung SK, Mok V, Lamb CW, Leung V, Hui E, Ng C, Chow M, Ho PC, Lam S, Woo J, Chiu HF, Goggins W, Zee B, Wong A, Mok H, Cheng KF, Fong C, Lee JS, Chanh MH, Szeto S, Lui V, Tsos J, Kwok T, Chang IH and Lam CW. Curcumin effects on blood lipid profile in a 6-month human study. Pharmacol. Res. (2007) 56: 509-514.

(19) Alwi I, Santoslo T, Susono S, Sutrisno B, Suyatna FD, Kresno SB and Ernie S. The effect of curcumin on lipid level in patients with acute coronary syndrome. Acta. Med. Indones (2008) 40: 201-210.

(20) Pungcharoenkul K and Thongnopnua P. Effect of different curcuminoid supplement dosages on total in-vivo antioxidant capacity and cholesterol levels of healthy human subjects. Phytother. Res. (2011) 25: 1721-1726.

(21) Feng D, Ohlsson L and Duan R. Curcumin inhibits cholesterol uptake in Caco-2 cells by down-regulation of NPC1L1 expression. Lipids Health Dis. (2010) 9: 40.

(22) Mahesh T, Sri Balasubashini MM and Menon VP. Photo-irradiated curcumin supplementation in streptozotocin-induced diabetic rats: effect on lipid peroxidation. Therapie. (2004) 59: 639-644.

(23) Kuroda M, Mimaki Y, Nishiyama T, Mae T, Kishida H, Tsukagawa M, Takahashi K, Kawada T, Nakagawa K and Kitahara M. Hypoglycemic effects of turmeric (Curcuma longa L. rhizomes) on genetically diabetic KK-Ay mice. Biol. Pharm. Bull. (2005) 28: 937-939.

(24) Nishiyama T, Mae T, Kishida H, Tsukagawa M, Mimaki Y, Kuroda M, Sashida Y, Takahashi K, Kawada T, Nakagawa K and Kitahara M. Curcuminooids and sesquiterpenoids in turmeric (Curcuma longa L.) suppress an increase in blood glucose level in type 2 diabetic KK-Ay mice. J. Agric. Food Chem. (2005) 53: 959-963.

(25) Best L, Elliott AC and Brown PD. Curcumin induces electrical activity in rat pancreatic b-cells by activating the volume-regulated anion channel. Biochem. Pharmacol. (2007) 73: 1768-1775.

(26) Seo K, Choi M, Jung U, Kim H, Yeo J, Jeon S and Lee M. Effect of curcumin supplementation on blood glucose, plasma insulin, and glucose homeostasis related enzyme activities in diabetic db/db mice. Mol. Nutr. Food Res. (2008) 52: 1-10.

(27) Yeh CH, Chen TP, Wu YC, Lin YM and Jing Lin P. Inhibition of NF-kappaB activation with curcumin attenuates plasma inflammatory cytokines surge and cardiomyocytic apoptosis following cardiac ischemia/ reperfusion. J. Surg. Res. (2005) 125: 109-116.

(28) Kawanami D, Maemura K, Takeda N, Harada T, Nojiri T, Saito T, Manabe I, Imai Y and Nagai R. C-reactive protein induces VCAM-1 gene expression through NF-kappaB activation in vascular endothelial cells. Atherosclerosis (2006) 185: 39-46.

(29) Biswas S and Rahman I. Modulation of steroid activity in chronic inflammation: A novel anti-inflammatory role for curcumin. Mol. Nutr. Food Res. (2008) 52: 987-994.

(30) Holt PR, Katz S and Kirshoff R. Curcumin therapy in inflammatory bowel disease: a pilot study. Dig. Dis. Sci. (2005) 50: 2191-193.

(31) Deodhar SD, Sethi R and Srimal RC. Preliminary study on antirheumatic activity of curcumin (diferyloloyl methane). Indian J. Med. Res. (1980) 71: 632-634.

(32) Hanai H, Iida T, Takeuchi K, Watanabe F, Maruyama Y, Andoh A, Tsujikawa T, Fujiyama Y, Mitsuyama K, Sata M, Yamada M, Iwaoka Y, Kanke K, Hiraishi H, Hirayama K, Ara H, Yoshii S, Uchijima M, Nagata T and Koide Y. Curcumin maintenance therapy for ulcerative colitis: randomized, multicenter, double-blind, placebo-controlled trial. Clin. Gastroenterol. Hepatol. (2006) 4: 1502-1506.

(33) Bundy R, Walker AF, Middleton RW and Booth J. Turmeric extract may improve irritable bowel syndrome symptomology in otherwise healthy adults: a pilot study. J. Altern. Compl. Med. (2004) 10: 1015-1008.

(34) Satoskar RR, Shah SJ and Shenoy SG. Evaluation of anti-inflammatory property of curcumin (diferuloyl methane) in patients with postoperative inflammation. Int. J. Clin. Pharmacol. Ther. Toxicol. (1986) 24: 651-654.

(35) Lal B, Kapoor AK, Aggrawal PK, Asthana OP and Srimal RC. Role of curcumin in idiopathic inflammatory orbital pseudotumours. Phytother. Res. (2000) 14: 443-447.

(36) Sharma RA, Steward WP and Gescher AJ. Pharmacokinetics and pharmacodynamics of curcumin. Adv. Exp. Med. Biol. (2007) 595: 453-470.

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