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Meta-analyses

A systematic review and meta-analysis of randomized controlled trials investigating the effects of curcumin on blood lipid levels

Amirhossein Sahebkar [a,b,*]

[a] Biotechnology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran
[b] Department of Modern Sciences and Technologies, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

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SUMMARY

Background & aims: Curcumin is a polyphenolic natural compound with diverse and attractive biological activities. There has been *in-vitro*, preclinical and clinical evidence on the cardioprotective and lipid-lowering effects of curcumin. The present review aimed to systematically review and meta-analyze current clinical evidence on the effects of curcumin supplementation on blood lipids.

Methods: A comprehensive literature search in Medline, Scopus, AMED, Cochrane and clinical trial registry databases was performed to identify randomized controlled trials investigating the effect of curcumin on any component of serum lipid profile including total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides. Meta-analysis of eligible studies was conducted using a random-effects approach.

Results: Five studies comprising 10 treatment arms ($n = 133$ in the curcumin and 90 in the control group) fulfilled the inclusion criteria. Meta-analysis of findings did not indicate a significant effect of curcumin on any of the lipid parameters. The estimated pooled mean changes (95% confidence interval) following curcumin supplementation were 8.97 (95% CI: −4.56 to 22.51) mg/dL (for total cholesterol; $p = 0.19$); 16.15 (−4.43 to 36.74) mg/dL (for LDL-C; $p = 0.12$); −0.59 (−1.66 to 0.49) mg/dL (for HDL-C; $p = 0.28$) and −1.29 (−9.05 to 6.48) mg/dL (for triglycerides; $p = 0.75$). In the same manner, subgroup analysis of studies on patients at cardiovascular risk did not indicate any significant effect of curcumin on circulating lipid levels. There was a significant heterogeneity for the impact of curcumin on total cholesterol, LDL-C and triglycerides but not HDL-C.

Conclusions: In light of the present meta-analysis, curcumin supplementation has apparently no effect on serum total cholesterol, LDL-C, triglycerides and HDL-C levels when considering heterogeneous populations. However, further randomized controlled trials with longer supplementation duration, and bioavailability-improved formulations of curcumin are warranted to be conducted in dyslipidemic subjects for a more robust assessment of the lipid-modulating properties of this phytochemical.

1. Introduction

Cardiovascular disease (CVD) is the dominant cause of mortality in the western world and accounts for >2200 deaths per day (equivalent to 1 out of every 3 deaths) in US based on 2008 statistics.[1] Given the increasing trend in its prevalence, worldwide CVD mortality is predicted to reach 25 million per year by 2020.[2,3] Most cases of CVD often stem from an advanced state of atherosclerosis. Therefore, the primary mission for CVD prevention would be blunting atherogenesis via controlling the causative risk factors. Several epidemiologic findings have consistently shown an association between elevated circulating concentrations of low-density lipoprotein cholesterol (LDL-C) and triglycerides with increased risk of CVD.[4,5] On the other hand, elevated plasma high-density lipoprotein cholesterol (HDL-C) levels are associated with a reduced risk of CVD.[4,5] Thus far, several classes of lipid-modulating agents have been introduced, each targeting a specific lipid class or affecting all lipid parameters. Among the lipid-lowering drugs, inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A, or statins, have been the most effective and the most widely prescribed drug category. Although statins confer considerable benefit for both primary and secondary prevention of CVD, there are a number of drawbacks that need to be addressed. Briefly, these drawbacks include significant residual cardiovascular risk remaining after statin monotherapy and limited effectiveness on some components

* Biotechnology Research Center, Mashhad University of Medical Sciences, Mashhad 91775-1365, Iran. Tel.: +98 5118823255 66; fax: +98 5118823251.
E-mail address: sahebkarah811@mums.ac.ir.

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of lipid profile such as HDL-C and triglycerides.[6] Moreover, statins are known to give rise to some serious adverse effects such as myopathies and hepatotoxicity.[7,8] These latter side effects are also observed with another popular class of lipid-lowering agents namely fibric acid derivatives. Due to these concerns, there has been an increasing attempt to use functional natural products as alternatives to the conventional lipid-modulating treatments.

Curcumin is a polyphenolic compound which is mainly present in the dried rhizomes of *Curcuma longa L.* (commonly known as turmeric). This phytochemical is responsible for the yellowish color as well as most of the medicinal properties of turmeric. Curcumin is undoubtedly one of the most bioactive molecules ever discovered from nature.[54–58] Heretofore, numerous *in-vitro*, animal and clinical studies have suggested the therapeutic efficacy of curcumin against a wide and diverse range of chronic diseases comprising colon, lung, liver, prostate, breast and skin cancers,[9–15] Alzheimer's disease,[16] Parkinson's disease,[17] inflammatory bowel syndrome,[18] rheumatoid arthritis[19] and diabetic complications.[20] Another interesting activity of curcumin is its beneficial effects on the cardiovascular system. Cardioprotective effects of curcumin include, but are not limited to, prevention of myocardial infarction,[21,22] attenuation of adriamycin-induced cardiotoxicity,[23] ischemia-reperfusion injury[24] and cardiac hypertrophy and remodeling[25,26] while improving endothelial function[27,28] and exerting membrane stabilizing effects in cardiomyocytes.[23] Most of these cardioprotective effects are due to the well-known modulatory effects of curcumin on inflammation an oxidative stress[1] as underlying causes of atherosclerosis and CVD. There have been also a number of reports indicating hypolipidemic activity of curcumin. Another interesting cardioprotective effect of curcumin pertains to its hypolipidemic effects.[29–34] Several pharmacological studies have reported that curcumin can reduce plasma and hepatic levels of lipids, thereby protecting against hypercholesterolemia and subsequent atherosclerosis.[29–34] However, the findings of clinical studies have been equivocal.[35–41] While some studies have reported promising effects from curcumin or *Curcuma* extract,[35–38] others have failed to find any significant effect.[39–41] Regarding these inconsistencies in clinical findings, a meta-analysis of published clinical trials can provide a more accurate and precise estimate of the overall effect of curcumin on circulating lipid levels.

2. Methods

2.1. Search strategy

A comprehensive and systematic literature search for English-language articles was performed in the following databases from inception through September 2012: PubMed-Medline (http://www.ncbi.nlm.nih.gov/pubmed), SCOPUS (http://www.scopus.com), Ovid-AMED (http://www.ovid.com/site/products/ovidguide/ameddb.htm), clinical trial registry (http://clinicaltrials.gov/) and Cochrane databases for intervention studies and the Cochrane Database of Systematic Review (http://www.cochrane.org). Relevant studies were identified using the combination of the following search terms: (curcumin OR curcuminoid) AND (hyperlipidemia OR hyperlipidemic OR hypolipidemic OR dyslipidemia OR dyslipidemic OR hypercholesterolemia OR hypercholesterolemic OR hypocholesterolemic OR "low-density lipoprotein" OR "high-density lipoprotein" OR cholesterol OR triglycerides OR hypertriglyceridemia OR hypotriglyceridemic). The wild-card term "*" was used to increase the sensitivity of the search strategy. The bibliographies of all included trials were hand-searched for additional relevant studies.

2.2. Study selection

Studies were included if they fulfilled all of the following criteria: (1) intervention study, (2) controlled design: drug- or placebo-controlled parallel or cross-over randomized trial, (3) study design consisted of random allocation of study participants to curcumin or control treatment; (4) reported mean ± SD (or mean ± SE) of at least one serum lipid parameter (total cholesterol, HDL-C, LDL-C, triglycerides) in both intervention and treatment groups at baseline as well as at the end of trial (regardless of the lipid level being in the normal or abnormal range); (5) used purified curcumin or curcuminoids mixture, or standardized *Curcuma* spp. extracts with determined content of curcumin or curcuminoids. The studies which investigated the effects of crude non-standardized *Curcuma* spp. extracts or synthetic curcumin analogs were excluded.

2.3. Data extraction

Data on study design, publication year, type of intervention, administered daily dose of curcumin, study design, duration of treatment period, type of study population, age, gender, number of participants and frequencies of smoking habit, dyslipidemia, diabetes mellitus, hypertension and coronary heart disease were extracted from all retrieved articles. In addition, mean ± SD (or mean ± SEM) of serum/plasma lipid parameters at baseline and at the end of trial (or treatment period in case of cross-over trials) were individually recorded.

2.4. Statistical analysis

Meta-analysis was conducted using the Cochrane Program Review Manager version 5.1. Blood lipid levels were collated in mg/dL. A multiplication by 38.7 or 88.6 was used to convert cholesterol (total cholesterol, HDL-C or LDL-C) and triglyceride levels expressed in mmol/L into mg/dL, respectively. Standard deviations at one time point were calculated with the formula SD = SEM × square root n (SEM: standard error of the mean, n: number of participants). Standard deviations (SDs) of the mean difference were calculated using the formula: square root $[(SD_{pre\text{-}treatment})^2 + (SD_{post\text{-}treatment})^2 - (2R \times SD_{pre\text{-}treatment} \times SD_{post\text{-}treatment})]$, assuming a correlation coefficient (R) = 0.5.[42]

In order to avoid double-counting of subjects and consequent unit-of-analysis error in the trials with more than 1 treatment arm, the control group was evenly (where possible) splitted into 2 (in case of trials #[38,39]) or 3 (in case of trial #[40]) sections.

For parallel and cross-over trials, net changes in measurements were calculated as follows: (measure at end of follow-up in the treatment group − measure at baseline in the treatment group) − (measure at end of follow-up in the control group − measure at baseline in the control group). A random-effects model and the generic inverse variance method were used to accommodate for the heterogeneity of studies in terms of design (parallel or cross-over), duration, nature of included populations (underlying disease, age and gender) and curcumin dosages that were used. In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using the one-study remove approach.[59,60] To examine potential publication bias, a funnel plot was constructed where the sample size of each study was plotted against its corresponding effect size.

2.5. Assessment of risk of bias in included studies

The quality of included studies was methodologically assessed as described in the Cochrane Handbook for Systematic