Guggulipid for the Treatment of Hypercholesterolemia
A Randomized Controlled Trial

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Context  Herbal extracts from Commiphora mukul (guggul) have been widely used in Asia as cholesterol-lowering agents, and their popularity is increasing in the United States. Recently, guggulsterones, the purported bioactive compounds of guggul, have been shown to be potent antagonists of 2 nuclear hormone receptors involved in cholesterol metabolism, establishing a plausible mechanism of action for the hypolipidemic effects of these extracts. However, there are currently no published safety or efficacy data on the use of guggul extracts in Western populations.

Objective  To study the short-term safety and efficacy of 2 doses of a standardized guggul extract (guggulipid, containing 2.5% guggulsterones) in healthy adults with hyperlipidemia eating a typical Western diet.


Participants and Setting  A total of 103 ambulatory, community-dwelling, healthy adults with hypercholesterolemia in the Philadelphia, Pa, metropolitan area.

Intervention  Oral, 3 times daily doses of standard-dose guggulipid (1000 mg), high-dose guggulipid (2000 mg), or matching placebo.

Main Outcome Measures  Percentage change in levels of directly measured low-density lipoprotein cholesterol (LDL-C) after 8 weeks of therapy. Secondary outcome measures included levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, and directly measured very low-density lipoprotein cholesterol (VLDL-C), as well as adverse events reports and laboratory safety measures including electrolyte levels and hepatic and renal function.

Results  Compared with participants randomized to placebo (n = 36), in whom levels of LDL-C decreased by 5%, both standard-dose guggulipid (n = 33) and high-dose guggulipid (n = 34) raised levels of LDL-C by 4% (P = .01 vs placebo) and 5% (P = .006 vs placebo), respectively, at 8 weeks, for a net positive change of 9% to 10%. There were no significant changes in levels of total cholesterol, HDL-C, triglycerides, or VLDL-C in response to treatment with guggulipid in the intention-to-treat analysis. While guggulipid was generally well tolerated, 6 participants treated with guggulipid developed a hypersensitivity rash compared with none in the placebo group.

Conclusions  Despite plausible mechanisms of action, guggulipid did not appear to improve levels of serum cholesterol over the short term in this population of adults with hypercholesterolemia, and might in fact raise levels of LDL-C. Guggulipid also appeared to cause a dermatologic hypersensitivity reaction in some patients.

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(Reprinted) JAMA, August 13, 2003—Vol 290, No. 6 765
States as a dietary supplement. Guggulipid is marketed in the United States to maintain normal levels of serum cholesterol, and as part of multitherbal supplements for “heart health,” weight loss, and arthritis. Annual retail sales of guggulipid in the United States increased by 72% in 2002 and accounted for approximately $1.3 million in sales that year (C. Gardner, SPINS/AC Nielsen, written communication, May 2003). There are currently no published safety or efficacy data on guggul extracts in Western populations.

We conducted a randomized, placebo-controlled clinical trial to evaluate whether a commonly used dose or a high dose of guggulipid could safely reduce levels of LDL-C in healthy adults with hyperlipidemia eating a typical Western diet.

**METHODS**

**Participants**

Ambulatory, community-dwelling US men and women volunteers older than 18 years with primary hypercholesterolemia were recruited from the Philadelphia, Pa, metropolitan area via mailings and advertisements from March 2000 through August 2001. Participants were required to have a level of LDL-C of 130 to 200 mg/dL (3.37-5.19 mmol/L), with fasting levels of triglycerides less than 400 mg/dL (4.52 mmol/L). Exclusion criteria included any history of clinical cardiovascular disease (myocardial infarction, angina, stroke, heart failure), diabetes, untreated thyroid disorder (thyroid stimulating hormone [TSH] levels of <0.4 or >10.0 µg/dL), liver function test abnormalities (aspartate aminotransferase or alanine aminotransferase levels >2 times upper limit of normal), renal insufficiency (creatinine levels ≥2.5 mg/dL [221 µmol/L]), women who were pregnant or lactating, and use of any lipid-lowering medications or dietary supplements within 30 days prior to screening. Participants with a diagnosis of hypothyroidism could be included only if their level of TSH was within the normal range while they were receiving at least 3 months of a stable dose of thyroid replacement. The protocol was approved by both the General Clinical Research Center and the institutional review board at the University of Pennsylvania. Written informed consent was obtained from each participant.

**Study Protocol**

After an initial screening visit, participants were randomized in a 1:1:1 fashion to 1 of 3 treatment groups: placebo, standard-dose guggulipid (SDG) (1000 mg), and high-dose guggulipid (HDG) (2000 mg), each 3 times daily with meals. Randomization was performed by an unblinded investigational pharmacist using a random-number generator (Rando, Hawkeye Softworks, Iowa City, Iowa). To evaluate the possibility of a differential effect of guggulipid on patients with more severe hypercholesterolemia, randomization was stratified by baseline levels of LDL-C (≥160 mg/dL [4.14 mmol/L] vs <160 mg/dL). To minimize possible group imbalances, randomization was also blocked using equal blocks of 6.

All study personnel were blinded to treatment assignment and block size. All participants were told to maintain their usual dietary habits. Diet stability was verified using the Block food frequency questionnaire version 98 (Block Dietary Systems, Berkeley, Calif) administered at baseline and at the last visit. Study assessments took place at baseline and at 4 and 8 weeks after the initiation of treatment. At each study visit, participants were weighed on a standardized scale, had full vital signs measured, were asked about adverse events, and had blood samples obtained for lipid and chemistry analyses. At each visit participants were queried about changes in medications and adverse events.

**Guggul Extract**

An investigational new drug application for the use of guggulipid in treatment of hypercholesterolemia was approved by the US Food and Drug Administration prior to the initiation of this trial. Per the manufacturer, each guggulipid tablet was standardized to contain 2.5% of the E- and Z-guggulsterone isomers. As part of quality control by the manufacturer, high-pressure liquid chromatography (HPLC) was performed on the test product, verifying that each 1000-mg tablet contained at least 25 mg of the E- and Z-guggulsterones. Using a previously reported HPLC method, we performed additional independent testing on 20 randomly selected guggulipid tablets taken from the single batch used in this study. In brief, the guggulsterones from these ground tablets were extracted and separated on a C18 reversed-phase column, with a mobile phase of acetonitrile-water and detected at 242 nm. The amount of guggulsterones was quantified using calibration curves obtained from a 99% pure synthetic guggulsterone standard (Steraloids Inc, Wilton, NH). The results, which were averages of 2 separate analyses (coefficient of variance, 1.2%), indicated that each capsule contained on average 21 mg of the E- and Z-guggulsterone isomers. Thus the product used in this trial was adequate, containing at least 85% of the predicted amount of the bioactive constituents. Randomly selected placebo tablets also were tested at the start of the study and were found not to contain any guggulsterones. Guggulipid and placebo caplets were identical in shape, color, texture, and taste. Masking was assessed by questionnaire at the conclusion of the study. Adherence to study medication was assessed by pill count at each postrandomization study visit.

**Lipoprotein Analyses**

Lipid parameters were analyzed from EDTA plasma collected after a 12-hour fast in a US Centers for Disease Control and Prevention–standardized lipid laboratory. Plasma levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were measured enzymatically on a Cobas Fara II autoanalyzer (Roche Diagnostic Systems Inc, Indianapolis, Ind) using Sigma reagents (Sigma Chemical Co, St Louis, Mo). Levels of LDL-C
and very low-density lipoprotein cholesterol (VLDL-C) were determined after ultracentrifugation at a density of 1.006 g/mL. Levels of lipoprotein(a) [Lp (a)] were measured using DiaSorin reagents (DiaSorin Inc, Stillwater, Minn). Additionally, samples were assayed for high-sensitivity C-reactive protein (hs-CRP) with an ultra-high-sensitivity latex turbidimetric immunoassay (Wako Pure Chemical Industries Ltd, Osaka, Japan) on a Cobas Fara II analyzer (intra-assay coefficient of variation, 9%). All safety laboratory tests were performed using standard methods at the Hospital of the University of Pennsylvania clinical laboratory.

Assessment of Adverse Events

Adverse events were assessed at both 4 and 8 weeks after initiation of the study drug. At both visits, nursing research staff asked participants about changes in their general health since their last visit. These questions were followed by specific questions from a checklist about common previously reported events. For each reported adverse event, study investigators judged and recorded the severity, relationship to study agent, and action taken. Adverse events also included clinically significant changes in laboratory values at both 4 and 8 weeks compared with baseline. All recorded adverse events, despite severity or relationship to study agent, were reported to the University of Pennsylvania institutional review board.

Outcomes and Sample-Size Calculations

The primary end point of the study was percentage change from baseline in directly measured levels of LDL-C at 8 weeks. This was calculated as [(week 8 LDL-C level – baseline LDL-C level)/baseline LDL-C level] × 100 for each participant. Secondary end points included percentage changes in levels of all other major lipoproteins (total cholesterol, HDL-C, VLDL-C, triglycerides) at 4 and 8 weeks, as well as safety laboratory tests (electrolyte levels, renal function, hepatic function). Based on the published literature, we anticipated reductions of 0%, 10%, and 15% of baseline LDL-C values for the placebo, SDG, and HDG groups, respectively. Accounting for dropouts, we estimated that a sample size of 34 per group would provide at least 90% power to detect differences among the 3 groups, using a 2-tailed α of .05 and an estimated within-group SD of 10%.

Statistical Analysis

The primary analysis was by intent-to-treat, using the last observation carried forward for all missing lipid parameters. The secondary analysis was a per-protocol analysis only using values for those participants who had completed all study visits. For continuous variables, differences between treatment groups were evaluated using analysis of variance or the Wilcoxon rank-sum test using generalized linear modeling procedures in SAS version 8.2 (SAS Institute Inc, Cary, NC). For discrete variables, StatXact software (Cytel, Cambridge, Mass) was used for analysis of counts or percentages and to produce exact tests of significance. All primary lipid analyses were performed applying an analysis of variance appropriate for a 2-factor design (treatment assignment, and LDL-C level ≥ or <160 mg/dL [4.14 mmol/L]) using percentage change from baseline for each participant as the response variable of interest. The 2 nonnormally distributed lipid values (triglycerides and VLDL-C) were log transformed before analysis by generalized linear modeling as described above. For ease of interpretation, percentage changes on raw data are presented for these log-transformed variables. Levels of Hs-CRP and Lp(a) were also skewed rightward, and here intra-group differences were analyzed by the Wilcoxon signed rank test, while between-group differences were analyzed using the Kruskal-Wallis tests of significance. All P values are 2-tailed.

RESULTS

Patient Characteristics

Over an 18-month period, 163 healthy individuals were screened for the study, and 103 were deemed eligible based on entry criteria. Eighty-five of the 103 participants completed all study-related visits (17% drop-out rate). Eighty-three percent of participants assigned to receive placebo completed the study, compared with 88% of participants assigned to receive SDG and 76% of those assigned to receive HDG (P = .46). Participants who dropped out did not differ significantly from the rest of the participants in terms of demographics, medical history, and baseline characteristics. The flow of study participants is illustrated in FIGURE 1.

Demographic characteristics of the enrolled participants are presented in TABLE 1. Of those enrolled, 51% were men, and 80% were white, 14% African American, 4% Asian, and 2% other. The mean (SD) age was 51.5 (12.8) years and the mean (SD) body mass index was 26.0 (4.3). There were no statistically significant differences in any of the baseline lipid parameters (TABLE 2) or in major dietary variables among the 3 treatment groups (TABLE 3). There also were no significant differences across the 3 treatment groups in any baseline characteristics except for body mass index (P = .03). However, weight was not significantly different between the 3 groups (Table 3).

Effects on LDL-C Levels

There were no statistically significant changes in weight, dietary fat, dietary cholesterol, and dietary fiber between baseline and week 8 for each of the treatment groups as assessed by the food frequency questionnaire, suggesting that diet remained stable during the 8-week treatment period among each of the 3 treatment groups (Table 3).

Directly measured levels of LDL-C decreased by 5% in the placebo group, while they increased by 4% in the SDG group (P = .01 vs placebo) and by 5% in the HDG group (P = .006 vs placebo) after 8 weeks of therapy (Table 2; FIGURE 2A). Thus, levels of LDL-C were 9% to 10% higher in the groups treated with guggulipid. No differences in percentage change in levels of
LDL-C between the SDG and HDG groups were found. In the stratified analysis, there was no apparent differential effect of guggulipid in patients with higher (≥160 mg/dL) vs lower (<160 mg/dL [4.14 mmol/L]) levels of LDL-C. In the per-protocol analysis, levels of LDL-C decreased by 5% in the placebo group while they increased by 5% in the SDG group (P = .009 vs placebo) and by 7% in the HDG group (P = .002 vs placebo) (Figure 2B). The increases in levels of LDL-C began as early as 4 weeks in both groups treated with guggulipid, but were only statistically different from placebo in the HDG group.

To evaluate whether there were subgroups of participants who had favorable responses to guggulipid, we performed secondary analyses of the 85 participants who took guggulipid for the full 8 weeks of the study. We defined a positive response as a 5% or greater reduction in levels of LDL-C and a negative response as a 5% or greater increase in levels of LDL-C, with the rest categorized as nonresponders. Only 10 of 55 participants (18%) treated with guggulipid had a positive response, while 28 (51%) had a negative response, and 17 (31%) had no response (P = .03). The 10 positive guggulipid responders did not differ from the group in sex, race, age, adherence, or any other baseline characteristics.

Effects on Other Lipoprotein Levels
There was a borderline significant trend toward reduced levels of HDL-C in both the SDG and HDG groups (P = .06 vs placebo) at 8 weeks (Table 2; Figure 2A). This was statistically significant only in the per-protocol analysis for the SDG group (Figure 2B). There were no significant changes in the overall group in levels of either triglycerides or directly measured VLDL-C (Table 2; Figure 2). However, in the per-protocol analysis, there was a significant treatment by LDL-C interaction for triglycerides (P = .049). Thus, in those participants who had baseline LDL-C levels of 160 mg/dL (4.14 mmol/L) or greater (45/85 [53%]), both SDG and HDG reduced levels of triglycerides by 14% (P = .02 vs placebo) and 10% (P = .03 vs placebo), respectively, compared with participants receiving placebo, in whom levels of triglycerides increased by 10%. Finally, we found no significant effect of guggulipid on total cholesterol/HDL-C and LDL-C/HDL-C ratios, as well as on levels of non-HDL cholesterol. In an exploratory analysis of a subset of 42 participants with elevated baseline levels of Lp(a), defined as Lp(a) greater than 20...
Triglycerides

High-Dose Guggulipid (n = 23)

Baseline, Mean (SD) | Change, % | P Value vs Baseline |
-------------------|-----------|-------------------|
Total cholesterol  | 247 (24)  | −2.45 (11)        | .17 |
LDL-C              | 160 (26)  | −4.93 (16)        | .06 |
HDL-C              | 50 (15)   | +1.43 (9)         | .33 |
VLDL-C             | 36 (22)   | +36.40 (121)      | .13 |

Standard-Dose Guggulipid (n = 34)

Baseline, Mean (SD) | Change, % | P Value vs Baseline |
-------------------|-----------|-------------------|
Total cholesterol  | 247 (24)  | −2.45 (11)        | .17 |
LDL-C              | 160 (26)  | −4.93 (16)        | .06 |
HDL-C              | 50 (15)   | +1.43 (9)         | .33 |
VLDL-C             | 36 (22)   | +36.40 (121)      | .13 |

High-Dose Guggulipid (n = 34)

Baseline, Mean (SD) | Change, % | P Value vs Baseline |
-------------------|-----------|-------------------|
Total cholesterol  | 248 (29)  | +1.67 (9)         | .28 |
LDL-C              | 156 (21)  | +3.86 (13)        | .16 |
HDL-C              | 52 (15)   | −2.72 (10)        | .12 |
VLDL-C             | 35 (21)   | +6.38 (120)       | .88 |

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol.

*All percentage changes reported as least-squares means from 2-factor analysis of variance.

Table 2. Results of Intention-to-Treat Analysis (N = 103) for Lipoprotein Parameters at Week 8

Table 3. Changes in Selected Dietary Variables Between 3 Groups at Baseline and at 8 Weeks

Nonlipid Effects

There was no significant effect of guggulipid on weight or on levels of TSH. A secondary analysis of hs-CRP on all 83 participants who completed the study found that HDG reduced median levels of hs-CRP by 29% compared with a 25% increase in the group receiving placebo, while there was no change in levels of hs-CRP in the SDG group (P = .10). Treatment with HDG reduced median levels of hs-CRP by 0.2 mg/L (P = .11 vs baseline), while receiving placebo increased levels of hs-CRP by 0.1 mg/L (P = .57 vs baseline).

Safety and Tolerability

There were no significant changes in renal function or in levels of liver-associated enzymes or electrolytes among any of the treatment groups. Overall, there was a total of 75 reported adverse events by 42 participants; 2 events (1 in the placebo group and 1 in the SDG group) were classified as serious adverse events. Of the 42 participants who reported adverse events, 13 were assigned to the placebo group, 14 to the SDG group, and

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15 to the HDG group (P = .77). Guggulipid was generally well tolerated without statistically significant differences in rates of any adverse events among the treatment groups. For the expected adverse events of loose stools or diarrhea, there were 8 reports in the HDG group, 3 in the SDG group, and 4 in the placebo group (P = .19).

During the treatment period, we noted the development of a hypersensitivity drug rash judged as at least possibly related to guggulipid in 6 participants. In all 6 participants the rash occurred within 48 hours of starting guggulipid and was associated with itching, and in 5 of the 6 cases, led to dropout from the study. All symptoms resolved within 1 week of discontinuation of therapy, although 1 participant who dropped out required oral steroids. The breakdown of this rash by treatment group was as follows: 5 of 34 participants (15%) in the HDG group, 1 participant in the SDG group (3%), and none in the placebo group (P = .02), for an overall incidence of 9%.

Adherence and Masking

Overall adherence as measured by pill count was 93% (range, 57%-118%). There were no differences in the results of the lipid analyses when non-compliers (ie, participants who took <80% of pills) were excluded from the analysis. At the end of the study, all 85 participants who had completed the study were asked to guess which of the 3 groups they had been assigned to. Forty-two percent guessed their treatment group correctly, while 58% guessed incorrectly (P = .19), suggesting adequate masking of the study agent.

COMMENT

In this first randomized clinical trial of guggulipid done outside of India, neither a commonly used dose nor a high dose of standardized guggulipid improved any of the measured levels of lipoproteins in this large group of patients with moderate hypercholesterolemia and eating a Western diet. Surprisingly, guggulipid increased levels of directly measured LDL-C by clinically significant amounts and tended to depress levels of HDL-C. While the increase in levels of LDL-C appeared to be dose related, this difference was not statistically significant. This paradoxical increase in levels of cholesterol in response to guggulipid was suggested by 2 published case reports.17,18 Despite suggestions in the literature that guggulipid might increase thyroid hormone metabolism and thus up-regulate LDL-C catabolism,19,20 there were no significant changes in thyroid function as assessed by a sensitive third-generation TSH assay. Secondary analyses in patients who completed the protocol did demonstrate modest reductions in fasting levels of triglycerides in patients with elevated baseline levels of LDL-C. This finding is supported in both the animal literature5 and in human literature in which guggulipid reduced levels of triglycerides by 12% to 24% in patients with primary hypercholesterolemia and accompanying hypertriglyceridemia.9,10

The overall favorable response rate (18%) in levels of LDL-C to guggulipid is markedly lower than what has previously been described in Indian populations, in whom the response rate ranges from 60% to 80%.7 All previous clinical trials were conducted in Indian populations with dietary and possibly genetic differences that could affect lipid metabolism. It is clear from 1 previous study that persons in the Indian population studied were thinner and ate less total fat (27% of total energy) and more dietary fiber (24 g/d) than those in our population, suggesting that the diets were in fact different.10 Also, many of the previous trials were not randomized, and some studies only reported data in the subgroup of responders in whom levels of total cholesterol dropped by 5% to 10%.8,9 Additionally, none of the previous studies used the criterion standard ultracentrifugation technique to directly measure levels of LDL-C. This quality-control step is especially important in patients with hypertriglyceridemia who made up a substantial number of the patients in the largest trial published to date.9

Our results suggest that guggulsterones do not reduce levels of serum cholesterol in humans consuming a Western diet, despite recent evidence identifying potential mechanisms of action. The regulation of bile acid synthesis is important in cholesterol metabolism and is mediated by several enzymes, including the hepatic enzyme 7α-hydroxylase (CYP7A), believed to be the rate-limiting step in the conversion of cholesterol to bile acid.21 Regulation of CYP7A is controlled by several nuclear hormone receptors, especially FXR.22 Two studies have found that, in vitro, E- and Z-guggulsterones were potent and specific antagonists of FXR.5 This antagonism would be expected to up-regulate CYP7A and thus facilitate cholesterol catabolism.4,23 This was corroborated by animal experiments in which FXR-null mice fed a high-cholesterol diet had significantly reduced levels of hepatic cholesterol in response to high doses of Z-guggulsterone (100 mg/kg).4 However, the effect of guggulsterones on serum cholesterol concentrations in these knockout mice is not known. Finally, a third study found that both Z-guggulsterone and a synthetic guggulsterone analog antagonized the BAR, another nuclear hormone receptor.6 Antagonism of the BAR would be expected to reduce the absorption of cholesterol in the gut via its effect on the intestinal bile acid transporter.6,22 Thus while guggulsterones act as FXR and BAR antagonists in vitro and in some animal models, our study demonstrates that in humans even high doses of guggulipid, delivering up to 150 mg of E- and Z-guggulsterone, do not reduce plasma levels of LDL-C. However, it may be that guggulsterones have both antagonist and agonist activity on FXR,5 and that like phytoestrogens, guggulsterones may have different lipid effects in different populations, partially explaining our lipid findings.

Not only was guggulipid ineffective in lowering cholesterol levels in our population, it seemed to cause a hypersensitivity drug reaction in a sub-
set of patients. There also seemed to be a suggestion of a dose effect, as 5 of the 6 cases occurred in the HDG group. While none of the 4 randomized clinical trials that used the same extract reported rash as an adverse effect, several reports from the early literature using crude guggul extracts did report a dose-related incidence of rash. Because of the complex nature of herbal preparations, this rash may have been due to any number of constituents in the guggulipid product used in this trial.54

Our study has several potential limitations. It may be that 8 weeks of treatment is not a long enough time to see a benefit of guggulipid. However, several studies have shown an improvement in levels of total cholesterol and LDL-C by as early as 2 to 4 weeks.8,9,12,13 In fact, our study found that the mean increase in levels of LDL-C began as early as 4 weeks, a trend that persisted until the end of the study. Another potential limitation is that we did not recommend a specific diet in this study. Our goal was to evaluate the real-world effect of guggulipid as it might be used in the general population of patients with hypercholesterolemia who purchase this dietary supplement alone or as part of a multiherbal dietary supplement to lower their cholesterol levels. Thus we asked participants to maintain stable dietary habits, which they did, as measured by a food frequency questionnaire. While some studies showing efficacy placed participants on a low-fat, high-fiber diet prior to administration of guggulipid, several previous trials did not use a dietary run-in period.8,9,14

It also may be that the guggulipid product used in this study did not contain a sufficient amount of guggulsterones to demonstrate a lipid-lowering effect. Each tablet of guggulipid used in this study was standardized to guggulsterone content and contained on average 21 mg of the bioactive E- and Z-guggulsterones. By using both a dose of guggulsterones used in most previous positive studies (75 mg/d) and the highest dose of guggulsterones (150 mg/d) studied to date, we believe we should have observed an effect on LDL-C levels. It also may be that guggulsterones themselves, used to standardize guggulipid preparations, are not as bioactive in humans as previously thought, and that other constituents of guggulipid, which might not have been adequately contained in our preparation, are responsible for its purported lipid-lowering effects. This problem with standardization of botanicals is real and has been suggested as a reason for the failure of some studies of St John’s Wort in the treatment of depression.25

Despite having an unfavorable effect on levels of LDL-C, guggulipid did appear to have other potentially important systemic effects. The small but not statistically significant reduction in levels of other cardiovascular surrogate markers such as Lp(a) and hs-CRP have never been reported and need to be evaluated in adequately powered studies. Since guggulipid has some in vitro and in vivo anti-inflammatory properties, it’s effect on levels of hs-CRP is plausible and warrants further investigation.

Our goal in this study was to assess whether a standardized herbal extract of guggulipid, commonly used by patients with hypercholesterolemia and recently reported to have a biologically plausible mechanism of action, could safely and effectively lower levels of LDL-C. We found that in a typical American population of adults with hypercholesterolemia and eating a typical Western diet, using this standardized guggulipid product did not reduce and actually raised levels of LDL-C compared with placebo, and in a subset of patients caused a hypersensitivity drug reaction. These results do not support the use of dietary supplements containing guggulipid for reduction of LDL-C levels by the general population, and raise 2 important issues. With regards to efficacy, our findings reinforce the importance of performing well-designed, placebo-controlled, randomized trials to scientifically evaluate dietary supplements, even those supplements with supportive evidence from the basic sciences. With regards to safety, this study reminds us that supplements cannot be assumed to be safe and that they require clinical trial evidence of safety before being widely used or recommended.

Future studies using chemically modified isolated guggulsterones in selected groups of patients with hypertriglyceridemia might help resolve whether this interesting class of compounds can safely modify lipids and other cardiovascular risk factors.

The man who never alters his opinion is like standing water, & breeds reptiles of the mind.
—William Blake (1757-1827)