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Therapeutic Effects of Guggul and Its Constituent Guggulsterone: Cardiovascular Benefits

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ABSTRACT

Oleogum resin (known as guggul) from the guggul tree, *Commiphora mukul,* found in India, Bangladesh, and Pakistan, has been used to treat various diseases including hypercholesterolemia, atherosclerosis, rheumatism, and obesity over several thousands of years. Guggulsterone isolated from guggul has been identified as the bioactive constituent responsible for guggul's therapeutic effects. Since the first study demonstrating the therapeutic effects of guggul in an animal model in 1966, numerous preclinical and clinical trails have been carried out. Although differences in study design, methodological quality, statistical analysis, sample size, and subject population result in certain inconsistencies in the response to therapy, the cumulative data from *in vitro*, preclinical, and clinical studies largely support the therapeutic claims for guggul described in the ancient Ayurvedic text. However, future clinical studies with much larger size and longer term are required to confirm these claims. The cardiovascular benefits of the therapy are derived from the multiple pharmacological activities associated with guggul or guggulsterone, notably its hypolipidemic, antioxidant, and antiinflammatory activities. It has been established that guggulsterone is an antagonist at farnesoid x receptor (FXR), a key transcriptional regulator for the maintenance of cholesterol and bile acid homeostasis. The FXR antagonism by guggulsterone has been proposed as a mechanism for its hypolipidemic effect. A recent study demonstrates that guggulsterone upregulates the bile salt export pump (BSEP), an efflux transporter responsible for

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removal of cholesterol metabolites, bile acids from the liver. Such upregulation of BSEP expression by guggulsterone favors cholesterol metabolism into bile acids, and thus represents another possible mechanism for its hypolipidemic activity. Guggulsterone has been found to potently inhibit the activation of nuclear factor-κB (NF-κB), a critical regulator of inflammatory responses. Such repression of NF-κB activation by guggulsterone has been proposed as a mechanism of the antiinflammatory effect of guggulsterone.

INTRODUCTION

Oleogum resin, known as guggul or gum guggul, is obtained from *Commiphora mukul* (known as guggul tree) found in India, Bangladesh, and Pakistan. The use of guggul for a wide variety of disease conditions, including atherosclerosis, hypercholesterolemia, rheumatism, and obesity is described in the Ayurveda, the ancient Indian medical system. In fact, the herb is mentioned as early as from 3000 to 10,000 years ago in the Vedas, the holy scriptures of India for treating human illnesses.

Guggul was first introduced to the scientific world in 1966 by an Indian medical researcher, G. V. Satyavati (Satyavati 1966). Her studies on the effects of guggul on rabbits were directly inspired by the centuries-old Ayurvedic text, in which guggul was recommended for the treatment of a condition called "coating and obstruction of channel," resembling the description of atherosclerosis. In 1986, with proven efficacy and safety, guggul was approved for marketing in India as a hypolipidemic drug (Arya 1988; Satyavati 1988).

In the middle 1990s, guggul was introduced into the Western medical literature (Singh et al. 1994) and, soon thereafter, the interests in using guggul as a remedy for treating or preventing hypercholesterolemia and related cardiovascular diseases were widely spread in the Western world. Currently, as an over-the-counter dietary supplement, guggul is available in the United States and other Western countries. However, in contrast to the numerous animal and human clinical trials conducted in India, limited studies involving Western populations have been carried out to evaluate the variety of therapeutic effects of guggul. One such clinical trial was conducted in the United States in 2003. However, in contrast to the previous preclinical and clinical data, the study found that gugulipid, the guggul extract, did not appear to have significant hypocholesterolemic effect in the Western subjects, whereas its antiinflammatory effect was detected (Szapary et al. 2003). The study questioned the hypocholesterolemic efficacy of guggul, especially in Western populations (Szapary et al. 2003; Ulbricht et al. 2005).

Starting in the later 1990s, efforts have been turned to the development of novel drugs from herbs to treat or manage various cardiovascular diseases. Guggul became one of those herbs holding huge promises for the development of hypolipidemic and antiatherogenic drugs. Substantial progress has since been made in recent years leading to understanding the molecular mechanisms responsible for the diverse pharmacological effects of guggul, especially its hypolipidemic activity. Guggulsterone, the bioactive constituent of guggul, has been identified as an antagonist at the nuclear receptor farnesoid x receptor (FXR) (Urizar et al. 2002; Wu et al. 2002), a key transcriptional regulator for the maintenance of

cholesterol and bile acid homeostasis (Ory 2004; Kalaany and Mangelsdorf 2006; Cai and Boyer 2006). Subsequent studies also found that guggulsterone is a potent antagonist at the mineralocorticoid receptor (MR), glucocorticoid receptor (GR), and androgen receptor (AR), and an agonist at pregnane x receptor (PXR), progesterone receptor (PR), and estrogen receptor (ERα) (Wu et al. 2002; Owsley and Chiang 2003; Brobst et al. 2004; Burris et al. 2005). A recent study demonstrated that guggulsterone upregulates the expression of the bile salt export pump (BSEP), a rate-limiting efflux transporter for eliminating cholesterol metabolites bile acids from the liver. Such upregulation is possibly mediated through the activating protein 1 (AP-1) signaling pathway (Deng et al. 2007). The FXR antagonism and enhanced BSEP expression have been proposed as possible mechanisms for the hypolipidemic effect of guggulsterone (Urizar et al. 2002; Deng et al. 2007). In addition, guggulsterone has been found to be a potent inhibitor of the nuclear factor-κB (NF-κB) (Shishodia and Aggarwal 2004; Ichikawa and Aggarwal 2006; Cheon et al. 2006), a key regulator for inflammatory responses. Such repression of NF-κB activation may represent a mechanism for the antiinflammatory effect of guggelsterone.

CHEMISTRY

The guggul tree (*Commiphora mukul*) is native to India, Bangladesh, and Pakistan. The oleogum resin is a yellowish substance with a balsamic odor. The resin is tapped during the winter and each guggul tree yields about 700–900 g of resin (Satyavati 1988; Schauss and Munson 1999). To identify the bioactive components in guggul, the resin is first extracted with ethyl acetate, a common, moderately nonpolar organic solvent. The extraction yields two fractions: a 45% soluble and a 55% insoluble fraction. The soluble fraction, known as gugulipid, has been shown to contain the bioactive components, whereas the insoluble fraction contains the carbohydrate residues without any therapeutic effects detected. Further fractioning of the soluble gugulipid with pH gradients results in two small acid- and basic-fractions (4% and 1%, respectively), and a major neutral fraction (95%), which contains the bioactive components. Additional fractioning of the neutral fraction leads to isolation of a major nonketonic (88%) and a small ketonic fraction (12%). The hypolipidemic activity was found to be associated with the ketonic preparation, which contains a number of steroids including the two isomers E- and Z-guggulsterone (*cis*- and *trans*-4,17(20)-pregnadiene-3,16-dione). Pharmacological studies revealed that the pure guggulsterone isomers had pronounced hypolipidemic activity (Dev 1987; Bajaj and Dev 1982). Therefore, it is generally accepted that guggulsterone is the bioactive constituent in guggul and gugulipid responsible for the therapeutic effects. With the identification of guggulsterone as the bioactive constituent, the content of guggulsterone in gugulipid is used as a standard for quality control (Satyavati 1988). The oleogum resin and gugulipid contain about 2% and 4–5% guggulsterone, respectively. Currently, 2.5% guggulsterone content becomes the minimum standard for quality gugulipid preparations.

Several metabolites of guggulsterone with bioactivity have been identified in fungi, such as *Aspergillus niger* and *Cephalosporium aphidicola*, commonly used microorganisms for fermentation production of chemical compounds (Atta-ur-Rahman et al. 1998; Choudhary et al. 2005). The hydroxylated metabolites, *cis*- and *trans*-7β-hydroxyl-4,17(20)-pregnadiene-3,16-dione and 6β,11α-dihydroxyl-4,17(20)-pregnadiene-3,16-dione, have

antibacterial activity, whereas 11α-hydroxylated metabolite has free radical scavenging activity (Atta-ur-Rahman et al. 1998; Choudhary et al. 2005). No data are available regarding guggulsterone metabolites in animals and human. Also, it remains to be determined whether any metabolites of guggulsterone are bioactive and play a role in various therapeutic effects of guggulsterone.

PRECLINICAL STUDIES

Hypolipidemic Activity

The hypolipidemic effect of gugulipid and guggulsterone has been consistently demonstrated in various animal species, including rat, mouse, rabbit (Satyavati 1966; Satyavati et al. 1969), chicken (Baldwa et al. 1981), domestic pig (Khanna et al. 1969), dog and monkey (Dixit et al. 1980). The first animal study was conducted in rabbits over a period of 2 years (Satyavati 1966). Rabbits were fed with hydrogenated vegetable oil to raise their cholesterol levels. One group of rabbits was given guggul, whereas the other group served as a control. At the end of the study, rabbits receiving guggul had normal serum cholesterol and lipid levels, whereas in the control rabbits serum cholesterol and lipids were elevated. More importantly, rabbits treated with guggul showed no fatty streaks or plaque deposits in their arteries, whereas such pathology was observed in the control group. These data provided the first experimental evidence to support the claims in the Ayurvedic text that guggul may be effective in the treatment of hypercholesterolemia and atherosclerosis. The encouraging findings in this study caught the attention of the Indian research community and led to more animal experiments, and eventually to human clinical trials.

Most of the subsequent animal studies were conducted in rats. Consistent results were obtained with guggelsterone at doses ranging from 5 to 100 mg/kg of body weight. In one study guggulsterone, 25 mg/kg p.o., lowered serum cholesterol and triglycerides by 27% and 30%, respectively, after a treatment period as short as 10 days (Singh et al. 1990). In parallel with the decrease in cholesterol and triglycerides, low-density lipoprotein (LDL) binding to hepatic cell membranes was significantly increased (Singh et al. 1990). The lipid lowering action of guggulsterone was also investigated in rats with hyperlipidemia induced by triton or cholesterol-feeding (Chander et al. 1996). In triton-fed rats guggulsterone, at a dose of 50 mg/kg p.o., significantly decreased serum lipids. In cholesterol-fed rats guggulsterone, at a dose of 5 mg/kg p.o. for 30 days, decreased lipids, LDL, and very low-density lipoprotein (VLDL) levels. In addition, it was found that guggulsterone treatment increased lipolytic enzyme activity as well as receptor-mediated catabolism of LDL (Chander et al. 1996). In another study, Fisher rats were fed a diet containing 1–5.6% gugulipid for 10 days. Gugulipid dose-dependently decreased serum triglycerides by 22–70%, whereas total serum cholesterol was increased by 8–23%. Further analysis of the serum lipoproteins indicated that the increase in total cholesterol was due to increase in high-density lipoprotein (HDL), whereas LDL and VLDL were actually decreased (Cui et al. 2003).

With proven hypolipidemic efficacy in rats, guggulsterone was used as a positive control to assess the hypolipidemic activity of other chemical compounds (Patra et al. 2003; Kumari and Augusti 2007). In one study, hyperlipidemia was induced by feeding rats with triton WR-1339 at a dose of 200 mg/kg body weight. One group of rats received guggulsterone, 100 mg/kg p.o. At the end of the experiment, guggulsterone reduced total

serum cholesterol by 42%, triglycerides by 24%, and phospholipids by 34% (Patra et al. 2003). In another study, rats received gugulipid at 50 mg/kg p.o. for 45 days (Kumari and Augusti 2007). Guggulsterone significantly reduced serum cholesterol, triglycerides, phospholipids, and atherogenic index. In addition, free fatty acids in serum, liver, and heart were also significantly decreased, whereas lipolytic activity was increased in liver and heart. The study also found that fecal excretion of bile acids and sterols was significantly increased by 57% and 75%, respectively (Kumari and Augusti 2007).

Hypolipidemic effect of guggulsterone was also demonstrated in a mouse model. In one study, mice were fed a high fat diet containing 2% cholesterol to raise their cholesterol levels. One group of mice received guggulsterone at a dose of 100 mg/kg p.o. for 7 days, whereas the other group was treated with vehicle. Mice receiving guggulsterone showed significantly decreased hepatic cholesterol levels in comparison with the control mice that received the cholesterol-containing diet only (Urizar et al. 2002).

Antioxidant and Antiinflammatory Effects

It has been well established that LDL is atherogenic and accumulates in atherosclaotic lesions. Although it is not clear how LDL is oxidized *in vivo*, accumulating evidence indicates that LDL oxidation is essential for atherogenesis (Steinberg 1997; Chisolm and Steinberg 2000). Antioxidants that prevent this oxidation may either delay or prevent atherogenesis. The antioxidant activity of guggulsterone was first reported in the 1990s (Singh et al. 1994; Singh et al. 1997). In those studies, the ability of guggulsterone to prevent oxidation of LDL was demonstrated *in vitro*. LDL isolated from human blood was mixed with a free radical promoting agent alone or in combination with guggulsterone. Samples were then analyzed for the presence of LDL oxidation byproducts. The results showed that guggulsterone strongly protected LDL from being oxidized (Singh et al. 1994; Singh 1997). In a more recent study, using several model oxidation systems, Wang et al. (2004) have demonstrated that both gugulipid and guggulsterone significantly inhibit LDL oxidation. Furthermore, gugulipid dose-dependently decreased accumulation of LDL-derived cholesterol esters in mouse macrophages (Wang et al. 2004). Those findings shed light on how guggul or guggulsterone works against "coating and obstruction of channels" described in the ancient Ayurvedic text.

It is generally accepted that overproduction of nitric oxide is associated with oxidative stress, which is involved in the pathogenesis of cardiovascular diseases, diabetes, rheumatoid arthritis, neurodegenerative diseases, or chronic inflammation (Moncada et al. 1991). In one study, guggulsterone isomers (Z- and E-forms) exhibited potent inhibitory activity against the production of nitric oxide induced by bacterial lipopolysaccharides (LPSs) in macrophages with IC_{50} values of 1.1 and 3.3 μM, respectively (Meselhy 2003). This finding indicated that guggulsterone may be of therapeutic benefit in diseases associated with oxidative stress, such as myocardial ischemia and neurodegenerative diseases.

Indeed, several studies have reported the cardiac and neuronal protective activity of guggulsterone in animal models. In one study, rats were treated with isoproterenol to induce cardiac damage. Such damage was accompanied by marked increase in creatine phosphokinase, phospholipase, and xanthine oxidase activities, enhanced levels of lipid peroxides, and lowering of superoxide dismutase, indicative of oxidative stress. Guggulsterone reversed

the myocardial damage and the induced metabolic changes (Kaul and Kapoor 1989). In more recent studies, the cardioprotective activity of guggulsterone was compared with that of a hypolipidemic drug, gemfibrozil. Both isomers of guggulsterone, at 50 mg/kg p.o., exhibited significant cardioprotective effect against isoproterenol-induced cardiac damage. In addition, guggulsterone at concentrations of 5–20 μM effectively inhibited LDL peroxidation and generation of free oxygen radicals (Chander et al. 2002, 2003). It should be mentioned that although both isomers exhibited cardiac protective and antioxidant effects, the Z-isomer was more potent than the E-isomer in mediating these effects. In another study, gugulipid was used as a positive control agent to evaluate the antioxidant, cardioprotective, and hypolipidemic activities of a series of synthetic compounds. Rats received gugulipid orally at a dose of 50 mg/kg for 30 days; gugulipid significantly decreased serum total cholesterol (35%) and lipid peroxide levels (57%). Hepatic microsomal lipid peroxidation was also significantly reduced by gugulipid. In addition, gugulipid significantly reversed the cardiac damage and biochemical changes induced by isoproterenol (Batra et al. 2000). The neuroprotective activity of guggulsterone was demonstrated in a recent study in a mouse model. Mice were treated with streptozotocin (STZ) to induce neuronal damage and memory deficits. Gugulipid at 12.5–50 mg/kg p.o. dose-dependently reversed STZ-induced neuronal damage and memory deficits. Paralleled with such reversal, the levels of glutathione (GSH) in the brains of gugulipid-treated mice were significantly increased, suggesting inhibition of oxidative stress in the brain by gugulipid (Saxena et al. 2007). Taken together, these studies consistently demonstrated the antioxidant activity of guggul or guggulsterone under various experimental conditions.

Activation of inflammatory signal pathways and release of inflammatory mediators can cause diverse diseases. The microenvironment present within the atherosclerotic lesion is proinflammatory. In addition to being a disorder of lipid metabolism, atherosclerosis is now recognized as a chronic inflammatory disease (Lusis 2000; Glass and Witztum 2001). Accumulating evidence demonstrates that excessive inflammation within the arterial wall is a risk factor for cardiovascular diseases and can promote atherogenesis. Agents with antiinflammatory activity may, therefore, prove to be beneficial in delaying or preventing atherogenesis. The antiinflammatory activity of guggul was first documented in 1960 (Gujral et al. 1960), and subsequently in 1977 by Sharma and Sharma (1977). In this study, an arthritic condition was induced in the right hock joint of albino rabbits by intraarticular injection of mycobacterial adjuvant. Fraction "A" of guggul extract at 500 mg/kg p.o. decreased the joint swelling during the course of 5 months of treatment. In this study higher than regular doses of guggul extract were used to demonstrate the hypolipidemic activity. Whether the activity could be detectable at the regular doses remains to be determined. In another study, the antiinflammatory activity of several agents including gugulipid was evaluated in rats. Gugulipid significantly inhibited both the maximal and the total carrageenan-induced rat paw edema (Duwiejua et al. 1993). In a recent study involving evaluation of the antiinflammatory activity of guggulsterone in the treatment of inflammatory bowel disease, colitis was induced in mice with dextran sulfate sodium (DSS) in the presence or absence of guggulsterone. Mice receiving guggulsterone exhibited significantly reduced severity of DSS-induced murine colitis as assessed by clinical disease activity score, colon length, and histology, indicating the antiinflammatory activity and possible usefulness of guggulsterone in the treatment of inflammatory bowel disease (Cheon et al. 2006).

CLINICAL STUDIES

Hypolipidemic Effect

A number of clinical trials have been conducted to evaluate the hypolipidemic effect of gugulipid. Most of these studies were carried out in India and one in the United States. Consistent with the preclinical data, most of these studies demonstrated hypolipidemic activity of guggul or gugulipid with an average of 10–30% and 10–20% decrease in total cholesterol and triglyceride, respectively. However, individual variations in responding to guggul treatment have been noted with approximately 70–80% responders and 20–30% nonresponders. In contrast to the findings from most of those studies, the US trial failed to detect the hypolipidemic effect of the therapy. Most of those clinical trials were reviewed in the past few years (Urizar and Moore 2003; Thompson Coon and Ernst 2003; Ulbricht et al. 2005). The studies with excellent or good quality based on Jadad score (Thompson Coon and Ernst 2003; Ulbricht et al. 2005) are highlighted in this communication.

A randomized controlled double-blind trail was conducted in 1978 by Kuppurajan et al. A total of 120 patients with hyperlipidemia were enrolled in the study. Gum guggul at 2 g twice daily or fraction "A" extract at 500 mg three times daily for 21 days significantly reduced the serum lipid levels in hyperlipidemic non-obese patients. These beneficial effects were not observed in hyperlipidemic obese subjects, indicating that the pathological conditions, such as obesity, are factors contributing to the variations in the response to the therapy. Similar results were obtained in a previous study with obese patients. No significant changes in cholesterol levels were observed after 21 days of treatment with either guggul or extract fraction "A" (Kuppurajan et al. 1973; Ulbricht et al. 2005). The reasons for such discrepancy in responding to guggul treatment between nonobese and obese patients are not clear. Considering that in 10 healthy volunteers guggulsterone at 25 mg twice daily for 8 weeks significantly decreased serum total cholesterol levels (Ghorai et al. 2000), negative findings with guggul in obese patients may represent an obesity-specific phenomenon.

Three clinical trials with a before-and-after comparison were conducted prior to the 1990s. The first study with 48 patients was conducted in 1979 by Kotiyal et al. Fraction "A" of guggul extracts at a dose of 500 mg three times a day for 4 weeks significantly reduced both total cholesterol and triglycerides levels. Another study enrolled 85 patients with hyperlipidemia. Fraction "A" at a dose of 500 mg three times daily for 12 weeks significantly decreased total cholesterol levels in comparison with baseline levels. In the third study with 40 patients, gum guggul at 4.5 g daily for 16 weeks significantly decreased total cholesterol and triglyceride levels when compared with the baseline levels (Verma and Bordia 1988). However, lesser reductions were noted in comparison between guggul-treated and placebo groups in the last two studies. It is conceivable that other factors, such as diet and lifestyle changes, may also contribute to the efficacy of the therapy.

The largest clinical trial with 205 hypercholesterolemic or hypertriglyceridemic patients was conducted in 1989 (Nityanand et al. 1989). When these patients were treated with 500 mg gugulipid daily for 12 weeks, total serum cholesterol and triglycerides decreased by 24% and 23%, respectively. It should be mentioned that such hypolipidemic effects were observed in 70–80% patients with no effect in the remaining subjects. No detailed description for those nonresponders was given, for example, whether or not they were obese. A crossover follow-up study to this preliminary investigation was conducted to compare gugulipid with an antihyperlipidemic drug clofibrate in a total of 233 patients (Nityanand et al. 1989). One

hundred and twenty five patients were treated with gugulipid at 500 mg daily for 12 weeks, whereas 108 patients were treated with clofibrate at the same dose. At the end of the study, gugulipid significantly decreased total serum cholesterol by 11% and triglycerides by 17%. These effects were comparable to those of clofibrate (10% and 22% reduction in cholesterol and triglyceride levels, respectively). The beneficial effects of gugulipid became evident within the first 3–4 weeks of the study. In addition, HDL level was increased in 60% of the responders to gugulipid therapy, whereas clofibrate had no effect on HDL levels. More detailed analysis of the results indicated that hypercholesterolemic patients responded better to the gugulipid therapy than did hypertriglyceridemic patients, and vice versa for clofibrate. The study clearly demonstrated the benefits of guggul therapy in reducing cholesterol and lipid levels in hypercholesterolemic and hypertriglyceridemic patients.

Consistent with the results from previous studies is the finding from a clinical trial that was first published in Western literature in 1994 (Singh et al. 1994**)**. In this study, sixty one patients with hypercholesterolemia were randomly divided into two groups (31 treatment vs. 30 placebo). All patients were instructed to eat a low-fat diet with fruit- and vegetable-enrichment for 12 weeks prior to the treatment. After the 12-week diet stabilization, patients received gugulipid 50 mg twice daily for 24 weeks, followed by a 12-week washout period. The diet stabilization for 12 weeks produced significant reduction in total cholesterol and triglycerides levels, indicating the importance of dietary restraining on improving lipid profile. Gugulipid further reduced total cholesterol levels by 11.7%, LDL by 12.5%, and triglycerides by 12%, whereas a 3.5% reduction in total cholesterol, 3% increase in LDL, and 3.7% increase in triglyceride were observed in the placebo group. HDL was also increased in both groups, but the increase was not statistically significant. After a 12-week washout period, subjects treated with gugulipid exhibited substantial increases in total cholesterol by 6.5%, LDL by 6.6%, and triglycerides by 7.7%, whereas such increase was not observed in the placebo group. The results indicate that long-term therapy (24 weeks) with gugulipid in conjunction with dietary modification significantly reduces cholesterol and lipid levels in patients with hypercholesterolemia.

In contrast to the results from most of the previous clinical trials conducted in India, the first clinical trial conducted in the U.S. population reached a different conclusion. Gugulipid did not appear to improve levels of serum cholesterol and might in fact raise levels of LDL (Szapary et al. 2003). In this randomized controlled trial, 103 patients with moderate hypercholesterolemia were enrolled and assigned to three groups: the placebo and two treatment groups (low and high doses). Treatment of gugulipid at doses of 1000 or 2000 mg three times daily for 8 weeks resulted in an increase in LDL levels by 4% and 5%, respectively, whereas patients who received placebo exhibited a 5% decrease in LDL level. There were also no significant changes in levels of total serum cholesterol, HDL, VLDL, and triglyceride following the treatment. Further analysis within the groups revealed that 18% of patients in treatment groups responded favorably to gugulipid treatment, with a more than 5% decrease in LDL. However, such response rate (18%) is much smaller than the 70–80% response rate observed in most of the previous studies. For the subjects (45 participants) with high baseline levels of LDL (160 mg/dL or greater), gugulipid treatment significantly reduced serum triglyceride (14% and 10% decreases for the high- and low-dose groups, respectively), whereas triglyceride levels increased by 10% in subjects receiving placebo. The results from this study indeed raised a question regarding the hypocholesterolemic effect of the therapy (Szapary et al. 2003; Ulbricht et al. 2005). Several possible explanations were discussed for the discrepancy from prior

trials. Differences in ethnic and genetic backgrounds, dietary restraints, and lifestyle all may potentially contribute to the observed discrepancy in response to the therapy. In addition, lack of data on bioavailability, pharmacokinetics, and metabolism of gugulipid and guggulsterone in the subjects among all the trials makes it difficult to precisely explain the discrepancy, since these parameters could determine the efficacy of a therapy.

Antioxidant and Antiinflammatory Effects

Limited clinical trials have been conducted to evaluate the antioxidant and antiinflammatory effects of guggul. In one study, the cardioprotective activity of gum guggul in combination with *Inula racemosa*, another Ayurvedic botanical, was examined in 200 patients suffering from ischemic heart disease with abnormal electrocardiogram (ECG) and chest pain (Singh et al. 1993; Miller 1998). After treatment with guggul for 6 months, the levels of total cholesterol, triglyceride, and total blood lipids were decreased by 39%, 51%, and 32%, respectively, consistent with the hypolipidemic activity of guggul and *Inula*. More importantly, at the end of the study, in 26% of the patients the normal ECG was restored with another 59% of subjects showing improvement in the ECG. In addition, after treatment with guggul 25% of the patients experienced no more chest pain with the rest having less pain. The results suggest cardioprotective benefits of guggul in ischemic patients, presumably through its antioxidant activity.

High-sensitivity C-reactive protein (hs-CRP), an acute-phase reactant mainly synthesized in the liver in response to the cytokine stimulation, is an index of inflammation that is now believed to directly promote all stages of atherosclerosis, including plaque rupture (Jialal et al. 2004). In the human clinical trial conducted in the United States, it was found that the median serum hs-CRP level was decreased by 29% in the group receiving gugulipid at a dose of 2000 mg daily, while the hs-CRP level was increased by 25% in the group receiving placebo during the trial period (Szapary et al. 2003), indicating the antiinflammatory activity of gugulipid.

In another study, the antiinflammatory activity of guggul was evaluated in 30 patients with arthritis in at least one knee (Singh et al. 2003). Gum guggul at 500 mg three times daily for one month significantly improved the WOMAC (Western Ontario and McMaster Osteoarthritis Index) total score and continued to improve it at the 2-month marker and follow-up. With the secondary measures of pain in the visual analog scales, patients exhibited significant improvement after 2 months of treatment. Thus, the results demonstrate the beneficial effect of the therapy in arthritic patients. Although the study was focused on arthritis, the finding suggests the antiinflammatory effect of guggul therapy.

MECHANISMS OF ACTIONS

Hypolipidemic Activity

Several possible mechanisms have been proposed for hypolipidemic activity of guggulsterone. Conversion of cholesterol to bile acids and subsequent excretion through the enterohepatic circulation represent a major pathway to remove excessive cholesterol from the body (Russell 2003). The cholesterol 7α-hydroxylase (CYP7A1) is the rate-limiting

enzyme in the classic pathway of bile acid synthesis from cholesterol in the liver (Russell 2003; Fuchs 2003). The expression of CYP7A1 is negatively regulated by bile acids through a negative feedback circuit involving several nuclear receptors including bile acid sensor FXR, liver receptor homolog 1 (LRH-1), and small heterodimer partner (SHP) (Lu et al. 2000; Goodwin et al. 2000; Davis et al. 2002). As FXR agonists, bile acids activate FXR and upregulate a myriad of FXR target genes, including SHP. SHP, a transcriptional repressor, in turn strongly represses CYP7A1 expression through heterodimerization with LRH-1, which is required for maximal expression of CYP7A1. Recent studies have established that guggulsterone is an FXR antagonist and downregulates FXR target genes (Urizar et al. 2002; Wu et al. 2002). Such FXR antagonism has been suggested as a mechanism for the cholesterol-lowering effect of guggulsterone (Urizar et al. 2002). In support of such a mechanism, guggulsterone downregulates SHP expression *in vitro* and *in vivo* (Urizar et al. 2002), which presumably leads to increase in CYP7A1 expression and bile acid synthesis. The study also showed that in contrast to the results obtained with wild type mice, guggulsterone failed to exert its hypolipidemic effect in FXR knockout mice, indicating the involvement of FXR in guggulsterone-mediated hypolipidemic action (Urizar et al. 2002). However, inconsistent with this proposed mechanism is the finding that hypolipidemic effects are observed in rats treated with a selective synthetic FXR agonist (Willson et al. 2001). Therefore, it remains unclear whether an FXR agonist or antagonist is beneficial in the treatment of hypercholesterolemia.

In the liver, the conversion of cholesterol to bile acids is initiated by the rate-limiting enzyme CYP7A1, whereas removal of bile acids from the liver is mediated by the rate-limiting bile acid transporter BSEP (Fuchs 2003; Kullak-Ublick et al. 2004). The expression of BSEP is positively regulated by cholesterol metabolites bile acids and oxysterol through FXR activation pathway (Ananthanarayanan et al. 2001; Plass et al. 2002; Deng et al. 2006). Therefore, the expressions of CYP7A1 and BSEP are coordinately regulated by the bile acids/FXR pathway through the negative feedback and positive feed-forward mechanism, respectively. Such coordinated regulation represents an elegant protective mechanism against hepatic injury by excessive accumulation of bile acids. However, this regulatory mechanism is not effective in removing excessive cholesterol from the body by either FXR agonist or antagonist. FXR agonist upregulates BSEP expression but suppresses CYP7A1 transcription, which decrease the conversion of cholesterol into bile acids. On the other hand, FXR antagonist enhances CYP7A1 but suppresses BSEP expression, which results in accumulation of bile acids in hepatocytes and in turn suppresses CYP7A1. A recent study demonstrated that guggulsterone strongly transactivated BSEP by itself and synergistically upregulated BSEP expression with bile acids (Deng et al. 2007), which is clearly in contrast to the expected inhibitory effect of guggulsterone on BSEP as an FXR antagonist. Further analysis revealed that guggulsterone transactivated BSEP possibly through the AP-1 activation pathway and such transactivation is dominant over its FXR-antagonism (Deng et al. 2007). The unique properties associated with guggulsterone as FXR antagonist as well as BSEP activator separated itself from the classes of sole FXR agonists or antagonists. The upregulation of BSEP expression by guggulsterone without activating FXR to suppress CYP7A1 favors cholesterol metabolism into bile acids by removing the trigger, bile acids, for the negative feedback suppression on CYP7A1. With the new findings from the study, it was proposed that enhanced BSEP expression by guggulsterone represented a possible mechanism by which guggulsterone exerts its hypolipidemic effect (Deng et al. 2007). Consistent with such mechanism is the finding that guggul treatment

resulted in significant increase (57%) in fecal excretion of bile acids (Kumari and Augusti 2007).

Studies also demonstrated that guggulsterone is a ligand for multiple other nuclear receptors (Wu et al. 2002; Owsley and Chiang 2003; Brobst et al. 2004; Burris et al. 2005). In an *in vitro* agonist testing mode, guggulsterone strongly activated PXR (Wu et al. 2002), indicating that guggulsterone is an agonist for PXR. Such finding is confirmed by subsequent studies (Owsley and Chiang 2003; Brobst et al. 2004). Although it has been speculated that inhibition of CYP7A1 through guggulsterone-mediated activation of PXR is a possible mechanism for the hypolipidemic effect of guggulsterone (Owsley and Chiang 2003), the PXR agonistic activity of guggulsterone is more likely to have implications in drug metabolism and interaction as PXR is the master transcriptional regulator for drug metabolizing enzymes. Studies also found that guggulsterone is an agonist for PR and ERα (Brobst et al. 2004; Burris et al. 2005), and a much more potent antagonist for nuclear receptors MR, GR, and AR than for FXR. Considering the fact that guggulsterone-mediated antagonism is 20–125-fold more pronounced for MR, GR, and AR than for FXR, it was suggested that such strong antagonism to these nuclear receptors may be involved in guggulsterone-mediated therapeutic effects including its hypolipidemic activity (Burris et al. 2005). However, further studies are required to substantiate this hypothesis.

Antioxidant and Antiinflammatory Effects

Although the antioxidant effect of guggul and guggulsterone has been demonstrated *in vitro* and *in vivo*, the underlying mechanism remains largely to be determined. Guggulsterone was found to reverse both isoproterenol-induced production of xanthine oxidase and isoproterenol-mediated decrease of superoxide dismutase (SOD) (Kaul and Kapoor 1989). Xanthine oxidase is an enzyme that promotes the production of reactive oxygen species, whereas SOD is an important antioxidant enzyme catalyzing the conversion of superoxide anion to oxygen and hydrogen peroxide. Based on this preliminary result, it appears that guggulsterone inhibits the production of toxic oxygen free radicals. Further studies are, however, required to dissect the molecular insights into the antioxidant activity of guggulsterone.

Inflammation is believed to be pivotal in all phases of atherosclerosis from the fatty streak lesion to acute coronary syndromes. NF-κB is a transcription factor playing a central role in the regulation of diverse cellular processes including inflammation, immune response, differentiation, proliferation, and apoptosis. Activation of NF-kB can be achieved by induction with proinflammatory molecules, such as tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), and phorbol myristate acetate (PMA). On the other hand, a number of NF-κB target genes have a primarily inflammatory function, such as monocyte chemotactic protein (MCP)-1, regulated upon activation normal T-cell expressed and secreted protein (RANTES), interleukin-1 (IL-8), C-X-C motif ligands (CXCLs), and C-C motif ligand 20 (CCL20). Thus, it becomes obvious that NF-κB is a critical regulator for inflammatory responses. Under the resting condition, NF-κB is associated with an inhibitory subunit of NF-κB (IκB) in cytoplasm. Upon stimulation by various agents, IκB is phosphorylated by IκB kinase (IKK) for ubiquitin-dependent degradation, leading to nuclear translocation of NF-κB and activation of NF-κB target genes. Recent studies have demonstrated that guggulsterone inhibits NF-κB activation induced by a variety of agents in several cell types

(Shishodia and Aggarwal 2004; Ichikawa and Aggarwal 2006). Such repression of NF-κB activation is mediated through a direct inhibition of IKK activation by guggulsterone (Shishodia and Aggarwal 2004). With the new finding from the study, it was proposed that repression of NF-κB activation through inhibition of IKK activity represents a mechanism of the antiinflammatory effect of guggulsterone. This proposed mechanism is supported by the results from another study in which guggulsterone blocked the NF-κB signaling pathway by targeting IKK complex in intestinal epithelial cells and attenuated DSS-induced acute murine colitis (Cheon et al. 2006).

SIDE EFFECTS

Currently, no clinical studies have been conducted to evaluate the safety of long-term use of guggul or guggulsterone. In short-term use (less than 6 months), either guggul or gugulipid are generally safe. No significant side effects have been observed on renal and liver functions, hematological parameters, and electrolytes (Agarwal et al. 1986; Szapary et al. 2003). Such a safety profile is consistent with its long history of use in Ayurvedic medicine and practice. However, some adverse reactions have been noted in clinical trials. Gastrointestinal discomfort is the predominant side effect reported. Other side effects included loose stools, mild nausea, and hiccup (Singh et al. 1994; Nityanand et al. 1989; Szapary et al. 2003). Skin rashes or hypersensitivity reactions have been reported in some clinical studies. In one study, 9% of participants developed moderate to severe adverse cutaneous reactions within 48 hours of the initiation of the therapy (Szapary et al. 2003; Gelfand et al. 2005). In addition, a case of rhabdomyolysis was reported that might have been associated with the use of gum guggul (Bianchi et al. 2004). Furthermore, drug interaction was implicated in a study with healthy subjects. Co-administration of gugulipid with the β-blocker propranolol or calcium channel blocker diltiazem resulted in significant decrease in bioavailability of the two drugs (Dalvi et al. 1994). Such drug interaction is likely to be due to the activation of PXR by guggulsterone (Wu et al. 2002; Owsley and Chiang 2003; Brobst et al. 2004), leading to upregulation of the enzymes responsible for biotransformation of propranolol and diltiazem. Finally, safety in young children, pregnant or nursing women, or those with severe liver or kidney disease has not been established.

CONCLUDING REMARKS

Guggul and gugulipid have a long history in the treatment of cardiovascular diseases including hypercholesterolemia and atherosclerosis. Although differences in study design, methodological quality, statistical analysis, sample size, and subject population in various clinical trails led to inconsistency in the response to the therapy, the cumulative data from *in vitro*, preclinical and clinical studies largely support the therapeutic claims for guggul described in the ancient Ayurveda. Larger clinical studies and longer therapy may confirm such claims. The cardiovascular therapeutic benefits of guggul and guggulsterone appear to be due to the multiple pharmacological activities, notably the hypolipidemic, antioxidant, and antiinflammatory effects. For the hypolipidemic activity, individual variations in responding to guggul treatment are consistently observed in the clinical trials, especially with subjects of different ethnic background, dietary habits, obesity status, and

severity of hyperlipidemia. Additional studies are required to determine the contributing effects of these variables to the efficacy of guggul or guggulsterone in the therapy for hypercholesterolemia.

In contrast to numerous clinical trials in hyperlipidemia, clinical studies of the antioxidant and antiinflammatory activities of guggul or guggulsterone are limited, although such activities have been demonstrated *in vitro* and *in vivo* in preclinical studies. Future studies are required to evaluate those activities and the associated benefits in the prevention or treatment of cardiovascular diseases, especially myocardial ischemia and atherosclerosis in humans. Although recent progress has been made in understanding the underlying mechanisms of guggul or guggulsterone-mediated diverse activities, further studies are required to firmly establish the mechanisms of actions. Finally, no data on bioavailability, metabolism, and pharmacokinetics of guggulsterone in animal models or humans are currently available. The knowledge of these basic parameters is needed for proper evaluation of the clinical findings with guggul or guggulsterone.

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