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GUGULIPID: A Natural Cholesterol-Lowering Agent

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■ **Abstract** The resin of the *Commiphora mukul* tree has been used in Ayurvedic medicine for more than 2000 years to treat a variety of ailments. Studies in both animal models and humans have shown that this resin, termed gum guggul, can decrease elevated lipid levels. The stereoisomers E- and Z-guggulsterone have been identified as the active agents in this resin. Recent studies have shown that these compounds are antagonist ligands for the bile acid receptor farnesoid X receptor (FXR), which is an important regulator of cholesterol homeostasis. It is likely that this effect accounts for the hypolipidemic activity of these phytosteroids.

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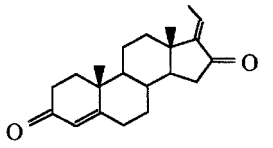
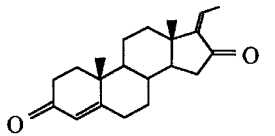
INTRODUCTION

Overview

In Ayurveda, the Indian traditional system of medicine, the gum resin from the tree *Commiphora mukul* has been used for thousands of years in the treatment of arthritis, inflammation, obesity, and disorders of lipid metabolism (27). Gugulipid



E-Guggulsterone



Z-Guggulsterone

Figure 1 Structures of E- and Z-guggulsterone [*cis*- and *trans*-4,17(20)-pregnadiene-3,16-dione].

is an ethyl acetate extract of this resin and has been marketed in India since 1988 as a hypolipidemic agent (28). In animal models and in humans, administration of gugulipid is reported to significantly lower both serum low-density lipoprotein (LDL) cholesterol and triglyceride levels. The active compounds in this extract are the isomers E- and Z-guggulsterone [4,17(20)-pregnadiene-3,16-dione] (Figure 1), which have been shown to lower lipid levels in several animal models. Recently, insight into the mechanism of action for the hypolipidemic activity of guggulsterone was provided by the demonstration that guggulsterone is an effective antagonist of the bile acid receptor farnesoid X receptor (FXR) (40, 42).

History

The use of plants in the treatment of disease occupies an important place in Ayurveda, the traditional medicine of India. The *Sushruta Samhita* (600 B.C.), a well-known Ayurvedic medical text, describes the usefulness of the gum resin from the tree *Commiphora mukul* in the treatment of a number of ailments, including obesity and disorders of lipid metabolism (27). Studies on the lipid-lowering activity of the gum resin, commonly known as gum guggul, began in 1964. Inspired by a strong correlation between the modern concepts of atherosclerosis and obesity and descriptions in the *Sushruta Samhita*, G.V. Satyavati studied the effect of gum guggul on the lipid levels of hyperlipidemic rabbits. In her 1966 thesis entitled "Effect of an indigenous drug on disorders of lipid metabolism with special reference to atherosclerosis and obesity," she demonstrated that administration of gum guggul significantly lowered the serum cholesterol levels of hyperlipidemic rabbits, prevented cholesterol induced arteriosclerosis, and decreased the body weight of the animals (26). A number of animal and clinical studies soon followed, confirming the hypolipidemic activity of gum guggul.

Commiphora Mukul

Known as the guggul tree, *Commiphora mukul* is a member of the *Burseraceae* family and is found in arid areas of India, Bangladesh, and Pakistan (27). A small, bushy tree with thorny branches, it produces a yellowish gum resin in small ducts located throughout its bark. Each collecting season a guggul tree yields between 250–500 grams of dry resin, which is extracted from the bark through a process called tapping. In this process, an incision is made on the bark of the tree. The resin, which then seeps out, is allowed to harden before it is collected. The tree is tapped in the months of November to January and the resin is collected through May or June (30a).

Gugulipid and Guggulsterone

Chemical analysis revealed that the compounds responsible for the hypolipidemic activity of gum guggul are the isomers E- and Z-guggulsterone (27). Using petroleum-ether, alcohol, and ethyl acetate, chemists separated gum guggul into various soluble and insoluble extracts. While the insoluble extract was determined to be toxic to animals and devoid of any activity, the soluble ethyl acetate extract was reported to retain the hypolipidemic and anti-inflammatory activities of gum guggul. Today the ethyl acetate extract, referred to as gugulipid, is prescribed in India for the treatment of hyperlipidemia.

To further study the ethyl acetate extract of gum guggul, it was separated into basic, acidic, and neutral fractions (27). In these studies the acidic fraction retained an anti-inflammatory activity, while the neutral fraction retained hypolipidemic activity. Additional studies on the neutral fraction revealed that it could be further separated into ketonic and nonketonic fractions (4a). In the ketonic fraction, a number of steroids were identified, including the isomers E- and Z-guggulsterone, which were found to be responsible for the hypolipidemic activity of the gum guggul. These compounds, which constitute approximately 2% of gum guggul and 5% of gugulipid, by weight, are pregnane derivatives [*cis*- and *trans*-4,17(20)-pregnadiene-3,16-dione]. They are reportedly devoid of any estrogenic, antiestrogenic, or progestational activity and recent studies confirm that they do not activate the conventional steroid receptors (40).

METABOLIC EFFECTS: HYPOLIPIDEMIC ACTIVITY

Animal Studies

The hypolipidemic activity of gum guggul has been studied in several animal models. Initial studies reported that administration of gum guggul lowers serum cholesterol levels in hypercholesterolemic rabbits (29). Hypercholesterolemia was induced in male albino rabbits by the administration of cholesterol (500 mg/kg body weight). The experimental group received gum guggul at a dose of 2 g/kg body weight daily for six weeks. In both the control and experimental cholesterol treated

groups, an increase in serum and tissue cholesterol levels was observed; however, the gum guggul group exhibited significantly lower serum and liver cholesterol levels. In this study, a significant decrease in the body weight of the animals fed gum guggul was observed. The effect of gum guggul on triglyceride levels was not reported.

In another study, 30 white leghorn chicks were fed a high-fat diet for one month to induce hyperlipidemia, followed by either a normal diet or a normal diet plus gum guggul at a dose of 3 g/kg body weight (5). As expected, serum cholesterol and triglyceride levels fell when the high-fat diet was replaced with a normal diet; however, in the group treated with gum guggul, lipid levels decreased at a significantly faster rate. Additionally, administration of gum guggul partially reversed the atherosclerosis in the aorta that was induced by the high-fat diet. The hypolipidemic activity of gum guggul has been confirmed in other animal species including the domestic pig (18), Presbytis monkey (8), and albino rat (ethyl acetate extract) (20).

The hypolipidemic activity of the isomers E- and Z-guggulsterone has been studied in animal models as well. Rats treated with guggulsterone at a dose of 25 mg/kg body weight for ten days exhibited a 27% decrease in serum cholesterol levels and a 30% decrease in serum triglyceride levels (35). In the same study, the effect of guggulsterone on LDL receptor activity was examined in membranes prepared from the livers of normal or guggulsterone-treated rats. In the guggulsterone-treated livers, LDL binding increased in the sixth and tenth day by 87% and 64%, respectively (35). Further studies are needed to define the role of the LDL receptor in the hypolipidemic activity of gum guggul.

In another study, administration of guggulsterone significantly lowered serum lipid levels of rats with either triton (WR-1339) or cholesterol-induced hyperlipidemia (6). An increase in liver cholesterol levels was observed in the rats fed the cholesterol diet, and administration of guggulsterone in conjunction with cholesterol suppressed this increase. Administration of Z-guggulsterone at a dose of 100 mg/kg body weight has also been shown to decrease liver cholesterol levels in mice fed a high-cholesterol diet for seven days (40).

Clinical Studies

The lipid-lowering effect of gum guggul and its ether and ethyl acetate fractions has been examined in several clinical studies in India. These studies have generally reported a 10 to 20% decrease in triglyceride levels and a 20 to 30% decrease in cholesterol levels. While administration of gum guggul or of one of its fractions significantly decreased lipid levels in each study, this effect was not observed in all individuals. The basis for the lack of an effect in these patients remains unexplained.

In a study of the crude gum guggul, 40 patients with hyperlipidemia (cholesterol levels >275 mg/dl and/or triglyceride levels >200 mg/dl) were administered a dose of 4.5 grams daily for 16 weeks. Serum cholesterol and triglyceride levels were lowered by 22% and 27%, respectively. Additionally, a 36% increase in HDL-cholesterol levels was observed (41). While the hypolipidemic activity of

gum guggul has been confirmed in several other trials, the effect of gum guggul on HDL cholesterol is not consistent.

In a test of the lipid-lowering activity of the ether extract (fraction A) of gum guggul, 20 patients with elevated lipid levels were given a dose of 0.5 gram daily for 12 weeks. Serum cholesterol, triglyceride, and phospholipid levels were lowered by 27%, 29%, and 18%, respectively (22). In a long-term clinical study in 51 patients with hyperlipoproteinaemia, the hypolipidemic activities of fraction A and clofibrate were comparable (23). Fraction A decreased total cholesterol levels by 37%, while clofibrate decreased total cholesterol levels by 43%. This study also reported that fraction A did not affect body weight. Gum guggul and fraction A have also been tested in patients suffering either from hypercholesterolemia, hyperlipidemia, or obesity. Treatment with gum guggul at a dose of 3 grams three times daily for 21 days and fraction A at a dose of 0.5 grams daily significantly decreased the serum lipid levels in the hypercholesterolemic and hyperlipidemic patients but not in obese hyperlipidemic patients (19).

Several clinical studies have demonstrated that administration of gugulipid, the ethyl acetate extract of gum guggul, significantly lowers LDL cholesterol and triglyceride levels in patients with hyperlipidemia. In 15 out of the 19 patients with primary hyperlipidemia (cholesterol levels >250 mg/dl and triglyceride levels >200 mg/dl), administration of gugulipid lowered serum cholesterol and triglyceride levels by 17% and 30%, respectively (1). Similarly, in 13 out of 22 patients with hyperlipidemia (cholesterol levels >240 mg/dl and/or triglyceride levels >200 mg/dl), administration of gugulipid at a dose of 500 mg three times daily for six weeks also lowered the serum cholesterol levels by 25% and serum triglyceride levels by 27% (13).

In the largest reported study of 205 patients with cholesterol levels greater than 220 mg/dl and/or triglyceride levels greater than 150 mg/dl, gugulipid administered at a dose of 500 mg daily for 12 weeks significantly decreased serum cholesterol (24%) and triglyceride (23%) levels (24). However, these decreases were observed in 70 to 80% of the patients, with little or no effect in the remaining subjects. The reason for the lack of effect in some patients remains unclear.

The hypolipidemic activities of gugulipid and clofibrate were compared in a double-blind crossover study in 105 patients with hyperlipidemia. Administration of 500 mg gugulipid daily for 12 weeks decreased serum cholesterol and triglyceride levels by 13% and 16%, respectively, and clofibrate at the same dose decreased serum cholesterol and triglyceride levels by 15% and 23% (24). Nonresponders were also observed in this study, but the percent change in serum lipid levels was calculated using the results from both the responder and nonresponder patients.

In the first study published in Western medical literature, the effect of gugulipid or placebo on serum lipid levels when administered in conjunction with a fruit- and vegetable-enriched prudent diet was compared in 61 patients with hypercholesterolemia (cholesterol levels >200 mg/dl). The study consisted of a 12-week diet stabilization period, followed by a 24-week treatment period. Each patient received either gugulipid or placebo at a dose of 50 mg twice daily for

24 weeks (34). On average, administration of gugulipid decreased LDL cholesterol by 13% and triglyceride levels by 12%. HDL levels remained unchanged in this study.

The hypolipidemic activity of gugulipid has also been studied in healthy individuals. In this study the effect on lipid levels by gugulipid, allicin, and of whole germinated seeds from *Cicer arietinum* were compared. In ten healthy individuals, administration of gugulipid significantly decreased serum total cholesterol levels (11).

Other Potential Activities

In addition to the hypolipidemic effect, gum guggul has been reported to have beneficial effects on obesity, inflammation, and acne, and stimulatory effects on the thyroid gland and drug metabolism. Unlike the hypolipidemic activity of gum guggul, which has been extensively studied in animal models as well as in clinical trials, these other activities require further experimental support before strong conclusions can be drawn.

Although a few studies have reported a significant reduction in body weight in animal models and in humans treated with gum guggul (27), other clinical and animal studies have reported no significant reduction in body weight. Thus, support for this reported activity is limited.

In India, gum guggul is also used in the treatment of arthritis and inflammation, and these activities have been studied in several animal models. Gum guggul displayed significant anti-inflammatory activity in normal and adrenalectomized rats with formaldehyde-induced arthritis (15, 16), in rat and rabbits with Freund's adjuvant arthritis (30, 32), and in rats with paw edema induced by carrageenan (30). Additionally, the aqueous extract and the steroid fraction of gum guggul exhibited anti-inflammatory activity in rats with paw edema induced by carrageenan and in rats with Freund's adjuvant arthritis (3, 9). While these studies suggest that gum guggul may have anti-inflammatory activity, additional studies will be required to clarify the nature of these effects and identify the compounds that may be responsible.

Several studies have reported a stimulatory effect by guggulsterone on the thyroid gland, which has been considered a possible mechanism for the lipid-lowering activity of guggulsterone. In rats, administration of guggulsterone at a dose of 10 mg/kg body weight increased thyroid function (38). In this study, both iodine uptake and oxygen consumption by the thyroid were increased. In another study, administration of guggulsterone at a dose of 10 mg/kg body weight restored thyroid activity in hypothyroid rats (39). Moreover, administration of guggulsterone at a dose of 5 mg per day restored thyroid activity in neomercazole-treated white leghorn chicks (37). It is unclear whether guggulsterone also increases thyroid function in humans. Additional studies are needed to clarify the effects of guggulsterone on the thyroid and to determine the role of this potential activity in the hypolipidemic effect.

Administration of gugulipid has been reported to be effective in the treatment of nodulocystic acne. A study in 21 patients found that gugulipid was as effective

as tetracycline in the treatment of this condition (36). Interestingly, the patients with oily faces responded better to the gugulipid treatment.

Finally, it appears that gugulipid can affect the bioavailability of other drugs. Administration of gugulipid at a single dose of one gram to 17 healthy volunteers significantly reduced peak plasma concentration of diltiazem and propranolol, which are used for the treatment of cardiovascular disease (7). It is likely that this decrease is due to an increase in their metabolic rate, as it has been shown in rats that administration of guggulsterone significantly increases the expression of cytochrome P450 genes, which are responsible for metabolizing most of the drugs taken today (17). As described below, guggulsterone activates the pregnane X receptor (PXR). Because this nuclear hormone receptor regulates the expression of several cytochrome P450 genes and other aspects of drug metabolism, it is likely that this activation accounts for the observed effects.

MECHANISM OF ACTION

Farnesoid X Receptor

Recent studies have shown that the isomers E- and Z-guggulsterone are effective antagonists of the bile acid receptor farnesoid X receptor (FXR), a ligand-dependent transcription factor that regulates the expression of genes involved in maintaining cholesterol/bile acid homeostasis (42, 40). Importantly, expression of FXR is required for the lipid-lowering activity of guggulsterone in mice, which suggests that guggulsterone may lower lipid levels by inhibiting the transcriptional activity of FXR (40).

FXR is a member of the nuclear hormone receptor superfamily and is primarily expressed in the liver, kidney, and small intestine (31). The physiological ligands of FXR are the bile acids, which also function to facilitate the absorption of dietary lipids and fat-soluble vitamins. Upon activation by bile acids, FXR regulates the expression of genes involved in cholesterol/bile acid homeostasis, including the ileal-bile acid binding protein (I-BABP), which mediates bile acid uptake in the ileum (14); the bile salt export pump (BSEP), critical for ATP-dependent transport of bile acids across the hepatocyte canalicular membrane (2); and the orphan receptor SHP, known to repress expression of the cholesterol 7α-hydroxylase (CYP7A), the rate-limiting enzyme in bile acid biosynthesis (21, 12). FXR regulation of these genes suggests that it plays a key role in maintaining steroid homeostasis. This role was recently confirmed by the generation of FXR null mice, which exhibit higher serum and hepatic lipid levels and die when challenged with a bile acid diet (33).

E- and Z-guggulsterone inhibit the activation of FXR target genes in response to bile acids or the synthetic agonist GW4064 (40, 42), and block coactivator recruitment to the ligand-binding domain of FXR (40, 42). In addition, administration of Z-guggulsterone at a dose of 100 mg/kg body weight decreases hepatic cholesterol levels in wild-type mice fed a 2% cholesterol diet but not in FXR null mice fed the same diet. Thus, FXR expression is required for the lipid-lowering activity of guggulsterone.

These studies also showed that guggulsterone weakly activates the nuclear receptor PXR, which regulates the metabolism of potentially toxic foreign compounds (xenobiotics) (40, 42). Because studies have shown that PXR activation does not result in changes in lipid levels in humans (4, 10, 25), this weak activation is not likely responsible for the lipid-lowering activity of guggulsterone. In addition, studies have shown that PXR agonists do not lower lipid levels in mice fed a high-cholesterol diet (40). As noted above, however, it is likely that PXR activation accounts for the reported effects of gugulipid on drug metabolism.

TOXICITY AND SIDE EFFECTS

In clinical studies, gum guggul and its ether and ethyl acetate fractions did show some side effects, including headaches, diarrhea, and skin rashes (13, 23, 24, 34). Purification of gum guggul decreased the incidence of these symptoms. Gugulipid, the ethyl acetate extract of gum guggul, is reported to be devoid of any adverse side effects on liver function, kidney function, or in hematological parameters when administered at a dose of 400 mg per day for four weeks (1).

From a medical perspective, guggulsterone is likely to interact with the many drugs whose metabolism is increased in response to PXR activation. Therefore, gugulipid should be used only with caution in combination with other drugs.

SUMMARY

More than 40 years ago, Dr. G.V. Satyavati was prompted by an ancient Ayurvedic text to test the effects of the resin of the *Commiphora mukul* tree on lipid levels. Following her studies, a wide range of efforts have confirmed the hypolipidemic effects of gum guggul and identified guggulsterones as the active agents. It is likely that the function of these compounds as antagonists for the bile acid receptor FXR is the molecular basis for these hypolipidemic effects.

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