

STANDARDIZATION OF COMMIPHORA MUKUL EXTRACT In Dislipidemia and Cardiovascular Disease

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INTRODUCTION

Atherosclerosis and its consequence, cardiovascular disease were recognized in principle and documented at least 3000 years ago. The Ayurvedic medical treatises from as early as 1000 B.C. already referred to the detrimental outcome to overall health with unbalanced nutrition and a sedentary life style. These two factors were reported to contribute to 'coating and obstruction of channels', which translates to atheromatous changes in the blood vessels. To counteract this development, Ayurveda practitioners prescribed an amber-like resin, commonly known as gum guggul, sapped from incisions made in the bark of the *Commiphora mukul* or *Balsamodendron mukul* (Hook.) and *Commiphora wightii* (Arpott) (N.O. Burseraceae) tree (1,2).

The pharmacology of gum guggul began to be studied in India in the 1960's, first at the Banaras Hindu University, Varanasi and later at the Central Drug Research Institute (CDRI), Lucknow, where the gum was evaluated for its potential in the treatment of elevated blood cholesterol. For these studies, a standardized gum guggul extract was prepared (Fig 1).

PRE-CLINICAL STUDIES

Analysis of the activity of the extracts (1) determined that the ethyl acetate-soluble, i.e. ketonic and neutral portion of the gum, had most of the hypolipidemic properties. The neutral fraction was

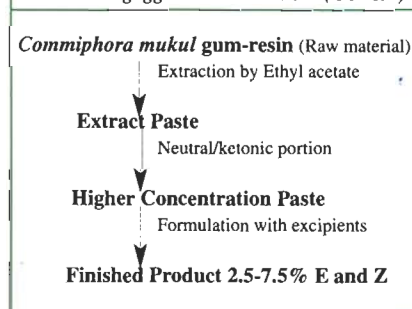
found to be a source of sterol compounds identified as E- and Z-guggulsterone (cis- and trans-4,17(20)-pregnandiene-3,16-dione, respectively). E- and Z-guggulsterone will henceforth be called GSE&Z.

The acute toxicity of GSE&Z standardized gum guggul extract was established based on the LD₅₀ in mice (1600 mg/kg i.p.) and LD₅₀ (1600 mg/kg, p.o.) in mice and rats. Sub-chronic and chronic toxicity studies of gum guggul preparations, performed in rats, beagle dogs and rhesus monkeys, showed that a dose range of 125 to 500 mg/kg body weight, administered orally for 90 and 180 days, did not produce adverse effects and did not alter clinical biochemical or patho-

Key Words

Commiphora mukul
Balsamodendron mukul
Commiphora wightii
Gugulipid
Extract
standardization
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Cardiovascular disease

Figure 1 Conventional solvent extraction process of gum guggul providing standardized levels of guggulsterones E and Z (GSE&Z)



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logical parameters of the tested animals (3).

Mutagenic and teratogenic studies performed on rats (125 mg/kg, p.o.) and rabbits (100 to 200 mg/kg, p.o.) for 180 days showed no mutagenic effects as indicated by micronucleus and dominant lethality tests respectively. There were insignificant skeletal changes in the teratogenic studies detected in rabbits at a higher oral dose of preparation at 200 mg/kg. Moreover the GSE&Z gum guggul preparation was devoid of estrogenic, anti-estrogenic, progestational and antiprogestational activities in immature rodents (50-100 mg/kg, p.o.) and rabbits (100 mg/kg, s.c.) (3).

In experimentally induced hyperlipidemia in rats treated with triton or fed a high fat diet, the GSE&Z gum guggul preparation in an oral dose of 200 mg/kg, for 14-30 days, caused a statistically significant decrease (30-60%) in serum cholesterol and in serum triglyceride levels (30%) (3). In the same experiments the hypolipidemic activity of GSE&Z was found comparable to that of clofibrate and nicotinic acid. Oral administration of GSE&Z gum guggul preparation at 50 to 120 mg/kg to hyperlipidemic rabbits or rhesus monkeys for 8-12 weeks resulted in a significant lowering of serum cholesterol (30-40%) and triglycerides (30%).

The GSE&Z gum guggul preparation also prevented the formation of atheroma and contributed to regression of atheromatous lesions in hyperlipidemic rabbits and rhesus monkeys treated orally with 200 mg/kg for 90 days (3). It was observed that there was 50% reduction of atheroma in treated animals as compared to a 60%

increase of atheromatous changes in untreated animals. In addition blood coagulation parameters (prothrombin time and euglobin lysis time) in treated vs. untreated rabbits returned to normal levels.

Administration of GSE&Z gum guggul in rats, rabbits and monkeys (50-100 mg/kg, p.o.) produced a statistically significant two-fold increase in cholic and deoxycholic acids excreted in feces probably from the conversion of cholesterol.

Studies *in vitro* and *in vivo* showed that GSE&Z gum guggul inhibits cholesterol biosynthesis (at comparable levels to clofibrate), prevents adrenaline-induced free fatty acids release from fat cells (antilipolytic activity), and inhibits adrenaline-induced platelet aggregation (3).

CLINICAL STUDIES

There are nine published human clinical trials performed in India evaluating the biological and hypolipidemic effects of gum guggul extracts (4-12):

- of these, five studies used GSE&Z standardized for daily delivery of approximately 75 mg of E- and Z-guggulsterones (4-8)
- two of these trials were randomized (6,7)
- one was placebo-controlled (10).

In the two randomized studies, GSE&Z reduced significantly total cholesterol by 11%, low density lipoprotein cholesterol (LDL-C) by 12% and triglycerides (TGs) by 15%. This effect was independent of age, sex or body weight, and the treatment was found especially useful in cases with total cholesterol levels of 220 mg/dl or higher and triglycerides of 170 mg/dl or higher. The other referenced clinical studies confirmed results reported in the two randomized studies.

The traditional experience of crude gum guggul described in Pharmacographia Indica, and some clinical trials done with standardized gum guggul extracts, reported transient side effects such as skin rashes, diarrhea and irregular menstruations (1).

Based on pre-clinical and clinical studies conducted mostly by the CDRI, the GSE&Z standardized preparation was approved by India's Drug Regulatory Agency in the late 1980s for inclusion in the Indian Pharmacopoeia (13), for the treatment of dislipidemia type IIb and IV.

US Clinical studies

IND (Initial New Drug Application) study

In January 2000, the Sabinsa Corporation in cooperation with the Department of Medicine and Center for Clinical Epidemiology & Biostatistics, University of Pennsylvania (Philadelphia, PA, USA) submitted documentation to the US FDA for an IND clinical study of Gugulipid® (3). This was a pioneering effort, since until then there was no safety or efficacy data on gum guggul preparations in Western populations. To the best of the authors' knowledge this was the first IND approved study on a botanical ingredient for its potential in the management of dislipidemias.

Protocol

The main objective of the randomized, placebo-controlled study was to evaluate whether a commonly used dose of 75 mg/day (SDG) of Gugulipid® or higher dose, 150 mg/day (HDG), could safely and effectively be used in hyperlipidemic adults eating a typical North American diet. Ambulatory, community-dwelling. US men and women (103 volunteers) over age 18 with primary hypercholesterolemia were recruited from the greater Philadelphia metropolitan area via mailings and advertisements between March, 2000 through August, 2001. Subjects were required to have a level of LDL-C of 130-200 mg/dl, with fasting TGs levels <400 mg/dl. They were distributed in three groups by randomization and treated with placebo (36 subjects), and 75 (33 subjects) and 150 mg/kg/day (34 subjects) of Gugulipid® for 8 weeks.

The primary endpoints were percent changes in LDL-C, HDL-C, TGs, VLDL, Lp(a) lipoprotein, high sensitivity C-reactive protein and safety, measured at 0, 4 and 8 weeks of treatment.

Written informed consent was obtained from each participant. Exclusion criteria included: any history of clinical cardiovascular disease (myocardial infarction, angina, stroke, heart failure), diabetes, liver function test abnormalities, renal insufficiency, females who were pregnant or lactating, and use of any lipid lowering medications or dietary supplements within 30 days prior to screening. The protocol was approved by both the General Clinical Research Center and the Institutional Review Board (IRB) at the University of Pennsylvania.

Results

The results of the short-term (8 weeks) safety and

efficacy of 2 doses of the standardized guggul extract in healthy North American adults with hyperlipidemia eating a typical Western diet, showed the complex nature of treatment with Gugulipid® (14).

Compared with placebo, 75 and 150 mg/kg/day of Gugulipid® raised levels of LDL-C by 4% and 5% respectively, at 8 weeks.

The increases in LDL-C began as early as 4 weeks in both treated groups, but were only statistically different from placebo in the HDG group. There were no significant changes in levels of total cholesterol, HDL-C, TGs, or VLDL-C in response to treatment in the SDG and HDG groups in the intention-to-treat analysis. However, secondary analyses did find modest but statistically significant ($p = 0.049$) reductions in fasting TGs in patients with elevated baseline LDL-C. Accordingly, in those subjects who had baseline LDL > 160 mg/dl ($n = 45/85$), both SDG and HDG reduced TGs by 14% ($p = 0.018$) and 10% ($p = 0.028$) respectively compared to placebo treated subjects, in whom TGs increased by 10%. This finding is supported in human literature where a standardized gum guggul preparation reduced triglycerides by 12-24% in patients with primary hypercholesterolemia and accompanying mild hypertriglyceridemia (6,7).

Interestingly, the study showed that Gugulipid® did appear to have other potentially important systemic effects. HDG reduced fasting glucose by 6 mg/dl ($p = 0.04$) and insulin by 1.9 mIU/ml ($p = 0.03$) and increased the quantitative insulin sensitivity check index (QUICKI) by 4.2% ($p = 0.04$).

Gugulipid® in 150 mg/day lowered high-sensitivity C-reactive protein (hs-CRP) by 31% ($p = 0.02$) and oxidized low density lipoprotein (oxLDL) by 12% ($p = 0.05$) after

tion by chenodeoxycholic acid, the most potent of the bile acids activating FXR (15). These results may imply that guggulsterones enhance conversion of cholesterol into bile acids which could be excreted in the feces lowering the liver and body cholesterol levels.

Guggulsterones have also been found to significantly inhibit activated pregnane X nuclear receptor (PXR) which participates in the production of bile acids in a similar way to that of FXR (15).

Another type of nuclear receptor that may participate in the mechanism of action of GSE&Z is peroxisome proliferator-activated receptors (PPARs). These receptors, like FXR, modulate gene expression in response to a broad spectrum of compounds and may activate several enzymes metabolizing lipids and lipoproteins. PPARs are recognized nuclear receptors for polyunsaturated fatty acids, some eicosanoids, guggulsterones and antidiabetic drugs.

A potential mechanism for the previously mentioned triglyceride reduction in North American subjects could be that guggulsterones themselves are modest peroxisome proliferator-activated receptor alpha (PPAR- α) agonists *in vitro* (15).

Both omega-3 fatty acids and fibrate drugs are also PPAR- α agonists, and both clinically reduce serum triglycerides while sometimes raising LDL-C (18,19).

Based on systematic study of gum guggul, it has been found that the ethyl acetate fraction of gum guggul shows significant anti-inflammatory and antioxidant effects *in vitro* (20). These biological properties have been attributed to a novel ferulate compound derived from gum guggul (21).

The antioxidant properties of the ferulate compound were evaluated *in vitro* in a DPPH free-radical scavenging assay (20). In the DPPH method, the ability of an antioxidant to bind the 1,1 diphenyl-2-picrylhydrazyl-radical (a very stable free radical species) is measured, using various concentrations of the selected antioxidant.

The IC₅₀ of the ferulate fraction was determined to be 16.0 mcg/ml (28 mM). By comparison, known antioxidants like gallic acid (present in myrobalan fruits *Terminalia chebula*) and catechins (present in tea) have IC₅₀ values of 10.6 mM and 18.6 mM, respectively. The results of the *in vitro* study indicate that the ferulate compound may play an important role in hypolipidemic and metabolic effects of the GSE&Z standardized gum guggul preparations.

The cumulative data from *in vitro*, pre-clinical and clinical studies indicates that GSE&Z gum guggul preparations may exert biological effects by inhibiting cholesterol biosynthesis, modifying cholesterol metabolism, inhibiting platelet aggregation, normalizing fibrinolytic activity, anti-inflammatory and antioxidant properties and by lowering serum C-reactive protein levels. Furthermore, identification and characterization of the ferulate compound indicates that guggulsterones may not be the only active components of gum guggul responsible for its cardiovascular properties.

PERSPECTIVES ON EXTRACT STANDARDIZATION AND SAFETY

Gum resin from *Commiphora mukul* comes with a rather long history of use, and its standardized extract has been used in several clinical trials with adverse effects less serious than those induced by the current generation of hypolipidemic treatments, such as statins, cholestyramine and clofibrate.

In clinical studies, the administration of standardized gum guggul GSE&Z caused relatively mild side effects such as skin rash, diarrhea and irregular menstruation. The skin rash side effect was more pronounced when a crude extract was administered to the patients.

Standardization of gum guggul extract is a key to the safety and efficacy of the preparation. The analysis of standardization of gum guggul extracts include ultraviolet (UV) spectrophotometry and high pressure liquid chromatography (HPLC) which respectively yield the total amount of sterone, sterol and steroidal components present in the gum guggul extract, and a

adjustment. In an analysis of 42 subjects with elevated baseline Lp(a), defined as Lp(a) >20 mg/dl, the study found that both SDG and HDG doses reduced mean Lp(a) by 7% and 5% respectively, but this was not significantly different from placebo (+1%) ($p=0.436$).

An additional positive finding was a statistically significant 0.8 mg/dl reduction in serum uric acid in the HDG group ($p=0.005$ vs. placebo). Thus, a high dose of Gugulipid® may improve insulin sensitivity in non-diabetic adults, lower a validated serum marker of inflammation, and exert antioxidant activity *in vivo*.

While Gugulipid® was generally well tolerated, 6 participants treated developed a hypersensitivity rash compared with none in the placebo group. The breakdown of this rash by treatment group was as follows: 5 subjects (5/34, 15%) in the HDG, 1 subject in the SDG (1/33, 3%) and none in the placebo group. In all 6 subjects the rash occurred within 48 hours of starting the study protocol and all symptoms resolved within 1 week of discontinuation of the treatment.

Follow-up study

Based on the above data the FDA has agreed to extend the IND approval for a follow-up clinical study. This study has been aimed to address potential short-comings of the original trial, e.g. to increase length of treatment from 8 weeks to 12 weeks with a double-blind crossover design, and to further explore potential hypolipidemic and systemic effects of Gugulipid® in healthy North American adults with hyperlipidemia.

The follow-up study will be performed at Our Lady of Mercy Hospital (New York, NY) and use a

randomized, placebo-controlled, crossover design in which 30 volunteers will be treated with Gugulipid® (75mg/day) and placebo, during separate 12-week treatment periods, in three equally divided doses along with their daily meals. Before treatment and at the end of 12 weeks, the following parameters will be evaluated: total cholesterol, LDL-C, HDL-C and TGs, oxidative markers such as serum malondialdehyde and C-reactive protein.

The study groups will exclude: pregnant or lactating women, subjects with a history of myocardial infarction, angina, transient ischemic attack, stroke, or peripheral artery disease, subjects with diabetes mellitus or uncontrolled hypertension (>180 mmHg/>100 mm Hg), subjects with a history of gastrointestinal malabsorption, or recent/active gastrointestinal illness (as these may interfere with the absorption of both the treatment and dietary lipids from the small intestine), subjects with liver test abnormalities (>1.5 x upper limit of normal), renal insufficiency, defined as a creatinine ≥ 1.5 mg/dL, subjects with excessive alcohol intake (>14 drinks/week), subjects who use any prescription or non-prescription medications to lower serum lipid levels or diminish lipid absorption, or who used any nutritional or herbal supplements to lower serum lipids during the 30 days immediately preceding volunteer screening, subjects with a history of a psychological illness or conditions that would interfere with their ability to understand and follow the requirements of the study, and lastly, the inability to participate in a treatment trial that may take about 36 weeks to complete.

MECHANISM OF ACTION

The recently explored *in vitro* (15-17) hypolipidemic mechanism of GSE&Z relates to regulation of cholesterol conversion into bile acids in the liver. This conversion process is regulated by a negative feedback loop that decreases the rate of bile acid production from cholesterol when bile acid levels are high. The feedback mechanism is regulated by the farnesoid X receptor (FXR), a nuclear hormone receptor that affects gene expression and can be activated by a number of compounds not structurally related to bile acids.

While guggulsterones E (GSE) or Z (GSZ) had no effect on FXR activity *per se*, both compounds statistically and dose dependently inhibited FXR activa-

more accurate analysis of the guggulsterones E and Z content, with each component quantified separately, giving accurate total guggulsterones readings (Fig 2).

Further steps are being undertaken to improve the quality of gum guggul extract by removing substances responsible for allergic reactions experienced by some subjects. The standardized ethyl acetate extract of gum guggul was separated into several fractions using column chromatography on silica gel. The first chromatography was done to broadly separate the extract into polar, medium polar and non-polar components. Additional chromatography on silica gel yielded ten fractions which will be the subject of human dermal sensitization studies.

A newly developed extraction procedure now results in a 100% solvent free end product standardized for guggulsterones involving supercritical carbon dioxide solvent-free extraction (SCFE) of the ethyl acetate portion of gum guggul (Fig 3). Since most of the laboratory and clinical studies were done using the

ethyl acetate portion of *Commiphora mukul* extract, this has been a starting material for a solvent free SCFE process. The SCFE is repeated twice, so that the material in the second extraction is solvent free.

Physical properties of the SCFE extract differ from GSE&Z, i.e. the product is lighter (amber vs. dark brown) in color and has a different and distinct aromatic scent in comparison to the original solvent obtained extract. However, the SCFE extract is still standardized for 2.5 to 7.5% of guggulsterones E and Z and the HPLC analysis of the extract is practically identical to the solvent obtained extract (Fig 2).

Figure 3 SCFE of gum guggul extract process (*Gugulipid*[®]) resulting in solvent-free extract

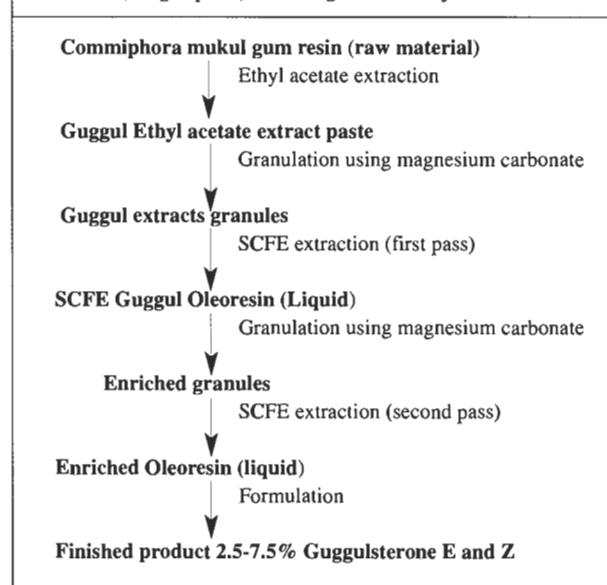
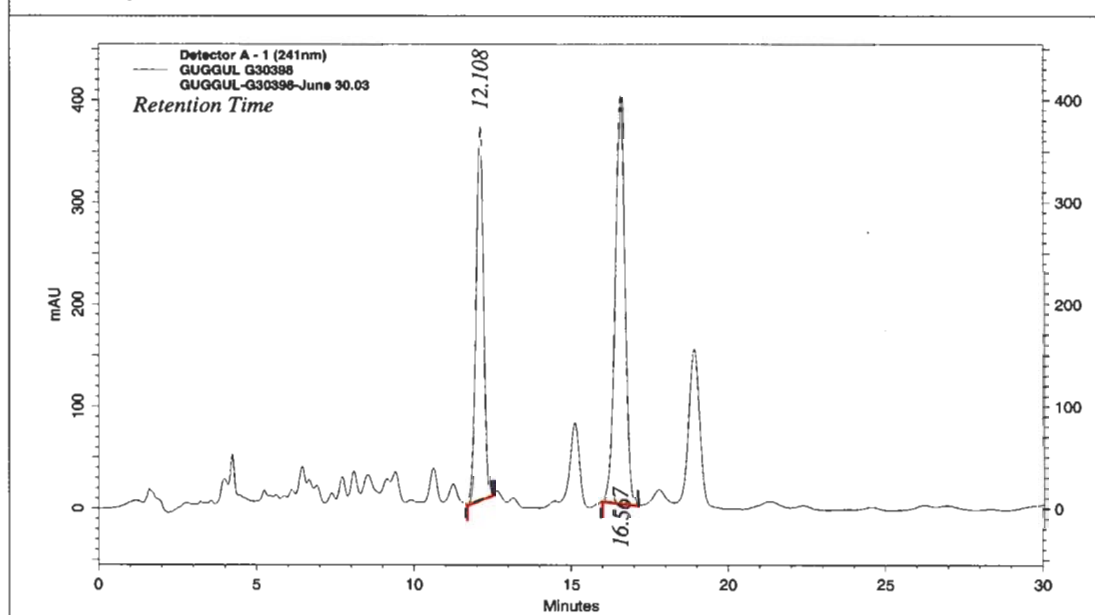


Figure 2 HPLC Analysis of SCFE process gum guggul extract (*Gugulipid*[®]) showing pattern characteristic for the solvent extract



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Vernacular and proprietary names

Sanskrit: Guggula; kou-shikaha
Hindi: Duk, Tej
Mahrati: Gugal
Bengali: Guggul; Mukul
Canarese (Kannada): Guggula
Tamil: Gukkulu; Maisatchi Kungiliyam
Telugu: Maishakshi; Gukkulu
Gujarati: Gugara; Gugal
Arabic: Mogla; Mokhil; Aphalantana
Persian: Bai-jahundana
Sinhala: Rata-dummula
English: Salitree; Gum guggul;
 Indian Bedellium
Gugulipid: Indian Pharmacopoeia (1996)
Gugulipid®: a standardized preparation of E- and Z-guggulsterones produced by Sabinsa Corporation, Piscataway, New Jersey USA

Gugulipid.[®] A Product with a Pedigree.

Since its introduction in 1991, Gugulipid[®] has earned the recognition of being a quality brand ingredient that provides nutritional promise in the area of cardiovascular health.

Research, with its ever increasing knowledge of this subject, indicates there are other "yard-sticks" besides normal values of cholesterol, triglycerides and lipoproteins that impact this multifactorial condition.

Recently, Sabinsa participated

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The growing popularity of Gugulipid[®] has led to the offering of a new, synthetic product standardized for up to 99% guggulsterones with claims that its benefits are similar to the natural extract. This is a failed pharmaceutical drug marketed as a dietary product – the FDA's definition of adulteration. Accept no substitutes.



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with the National Institutes of Health (NIH) in a US clinical trial involving Gugulipid – with the protocol reviewed by the FDA for safety. The enduring benefits of Gugulipid as a dietary contributor to cardiovascular fitness further sustain the promise that began so many years ago. Sabinsa's patented composition of Gugulipid stands alone as the "product with a pedigree."



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