

# **Gum Guggul and Some of Its Steroidal Constituents**

## **Review of Toxicological Literature**

**February 2005**

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*Prepared for*

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National Institute of Environmental Health Sciences (NIEHS)  
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### Abstract

Gum guggul and its constituents are increasingly being used as dietary supplements. Biological effects have been demonstrated on lipid metabolism, thyroid hormone homeostasis, female reproductive tissues, and endogenous nuclear hormone receptors. Gum guggul is the oleoresin of *Commiphora mukul*, a plant that is native to India, and its extracts include compounds known for their hypolipidemic properties—the *Z*- and *E*- isomers of guggulsterone and its related guggulsterols. *C. mukul* has been used as an inactive pharmaceutical ingredient, binding agent, anti-obesity agent, and cholesterol-reducing agent. Gum guggul is used in incense, lacquers, varnishes, and ointments, as a fixative in perfumes, and in medicine. Therapeutic uses include treatment of nervous diseases, leprosy, muscle spasms, ophthalmia, skin disorders, ulcerative pharyngitis, hypertension, ischaemia, and urinary disorders. Clinical studies of guggul have reported it has cholesterol-reducing effects, however, the first randomized controlled clinical trial of guggulipid done outside of India, reported that standardized doses failed to decrease the levels of low-density lipoprotein cholesterol in healthy adults with hyperlipidemia. Products containing gum guggul or its constituents which are marketed as dietary supplements must adhere to the Federal Food, Drug, and Cosmetic Act. Human exposure to gum guggul most often occurs from ingesting herbal remedies or pharmaceuticals and from the use of cosmetics. Side effects include skin rashes, irregular menstruation, diarrhea, headache, mild nausea, and with very high doses, liver toxicity. In mice, gum guggul extract significantly increased serum triiodothyronine and decreased hepatic lipid peroxidation. In rats, gum guggul and its acid fraction caused significant increases in absolute and relative weights of the ovaries, uterus, and cervix. Gugulipid<sup>®</sup> significantly increased the levels of catecholamine and the activity of dopamine  $\beta$ -hydroxylase in normal rabbits and decreased those in cholesterol-fed rabbits. It contributed to increasing the levels of catecholamine in hypercholesteremic rabbits and norepinephrine, dopamine, and dopamine  $\beta$ -hydroxylase activity in the heart and brain tissues of rhesus monkeys.

## Executive Summary

### Nomination

Gum guggul extract was nominated by the NIEHS for toxicological characterization based on its expanding use as a dietary supplement and a lack of available information to adequately assess safe use in humans. Demonstrated biological effects of gum guggul extracts on lipid metabolism, thyroid hormone homeostasis, female reproductive tissues, endogenous nuclear hormone receptors and the potential for serious drug interactions highlight the need for further study.

### Nontoxicological Data

Gum guggul is the oleoresin of the plant *Commiphora mukul*, a plant native to India. Extracts of the oleoresin include compounds known for their hypolipidemic properties, on which this report focuses—the *Z*- and *E*- isomers of guggulsterone and its related guggulsterols: guggulsterol I, guggulsterol-II, guggulsterol-III, guggulsterol IV, guggulsterol V, and guggulsterol VI. A standardized extract of the guggulsterones offered by Sabinsa Corp. has the trademarked name Gugulipid<sup>®</sup>.

Other gum guggul chemicals were reported to be biologically active: Myrrhanol A [350809-42-6] and myrrhanone A [350809-44-8] showed anti-inflammatory activity in adjuvant-induced, air-pouch granuloma of mice, and two ferulic acid esters, (*Z*)-5-tricosene-1,2,3,4-tetraol [375798-03-1] and (*Z*)-5-tetracosene-1,2,3,4-tetraol [375798-04-2], were reported to have antitumor properties. No published toxicology studies were located for myrrhanol A and myrrhanone A. No attempt was made to locate and compile literature on other constituents.

Crude gum guggul was found to contain 2% guggulsterones. Its ethyl acetate extract contains 4% to 4.5% guggulsterones. The neutral subfraction contains 4.2% to 4.7% guggulsterones. The ketonic subfraction of the neutral subfraction contains 35% to 40% guggulsterones, from which the 10% *E*- and *Z*-guggulsterones are derived.

Concentrations of guggulsterones in gum guggul may be determined by thin layer chromatography (TLC) and high performance liquid chromatography/mass spectrometry (HPLC/MS) and by a colorimetric method. The structures of the guggulsterones were elucidated by NMR (nuclear magnetic resonance) spectrometry.

### Production and Commercial Availability

Several companies supply gum guggul in bulk through the Internet. Ayurveda Holistic Center of Bayville, N.Y., and India supplies the resin. Lotus Natural Health and Healing Center of East Hanover, N.J., offers 0.5-lb quantities of guggulu (*C. mukul* [gugal]), presumably the resin. Banyan Trading Co. of Albuquerque, N.M., and India supplies guggulu, presumably the resin, in bulk. Monterey Bay Spice Company supplies gum guggul pieces weighing 5 to 25 pounds and gum guggul powder in 5 to 24 pound quantities.

Two producers have bases in both India and the United States: Sabinsa Corporation, maker of Gugulipid<sup>®</sup>, and Xechem International, which produces the nutritional product Gugulon<sup>™</sup> through its XetaPharm Inc. subsidiary.

Several suppliers of supplements containing gum guggul extracts can be found on the Internet, including iHerb.com, Vitacost.com, America's Finest Inc. of Piscataway, NJ, Wellness Works LLC. Several others are listed by Hess. The National Institute of Ayurvedic Medicine sells Ayurvedic formulations—gum guggul combined with other herbs. Neelam Exim Pvt. Ltd. sells a Royal Slim Herbal capsule containing medohar gugal from *Balsamodendron mukul*. However, commercially available gum guggul supplements subjected to HPLC were found to contain significantly lower guggulsterone concentrations than claimed.

### Production Processes

The tree is tapped for the oleoresin. The oleoresin is collected by making a circular incision on the main stem, no thicker than the bark. One article proposed an improvement to tapping methods for *C. wightii* in which ethephon (2-chloroethylphosphonic acid) was applied to the tree 48 hours before tapping.

The resin is extracted from *C. mukul* by steam distillation. The solids that remain are removed by filtering through a 100 µm mesh. The remaining water is evaporated under a vacuum, and the concentrated aqueous extracts were lyophilized, resulting in a fine powder.

### Uses

#### *Traditional Uses*

Gum guggul is used as incense, to make lacquers, varnishes, and ointments, as a fixative in perfumes, and in medicine.

Traditional (Indian) uses of *C. mukul* include as an anti-inflammatory, antispasmodic, carminative, emmenagogue, hypoglycemic, alterative, antiseptic, aperitif, astringent, sedative, stomachic, carminative, diaphoretic, diuretic, expectorant, antispasmodic, antisympurative, aperient, expectorant, a thyroid stimulant, anthelmintic, depurative, vulnerary, antiseptic, demulcent, aphrodisiac, stimulant, liver tonic, detergent, anti-spasmodic, hematinic, diuretic, and lithonotriptic.

Gum guggul has been used to treat dysmenorrhea, dyspepsia, endometritis, hypercholesteremia, hypertension, impotence, bronchitis, caries, catarrh, gingivitis, hay fever, hysteria, inflammation, laryngitis, lochia, mania, pharyngitis, phthisis, pyorrhea, rheumatism, sores, sore throat, stimulant, tonsillitis, tumors, wounds bone fractures, gout, scrofula, sciatica, facial paralysis, diplegia, leprosy, leucoderma, pectoral disorders, otorrhea, epilepsy, fever, strangury, hemorrhoids, dysmenorrheal, amenorrhea, ulcers, anemia, coronary, thrombosis, stomatopathy, pharyngopathy, spermatorrhea, urinary calculus, diabetes, trichosis, to enhance phagocytosis, to increase leukocytes, to induce abortion, and as a tonic for the uterus.

#### *Modern Uses*

Modern therapeutic uses of guggul include nervous diseases, hemiplegia, leprosy, marasmus, muscle spasms, neuralgia, ophthalmia, pyelitis, pyorrhea, scrofula, skin disorders, spongy gums, ulcerative pharyngitis, hypertension, ischaemia, hypertension, and urinary disorders. The Ayurvedic herb *Inula racemosa*, in combination with *C. mukul*, is used to reduce chest pain and dyspnea of angina. Royal Slim with *B. mukul*, is marketed as a weight reducer and fat burner.

Research studies showed that guggul is effective against aspects of cardiovascular disease. Guggul reduced the stickiness of platelets, and Gugulipid<sup>®</sup> was shown to be an efficacious and cost effective treatment of hyperlipoproteinemia. A webpage to sell Gugulon<sup>™</sup> stated it is marketed to help lower cholesterol, decrease high blood pressure, to “strengthen the structural system” and the immune system, to benefit the heart, to lower cholesterol and high blood pressure, and to eliminate toxins.

The crude gum guggul and each of the following fractions containing the *E*- and *Z*-guggulsterones have hypocholesteremic activity: the ethyl acetate extract, the neutral compounds from the extract, the ketonic compounds in the neutral fractions, and that containing the purified *E*- and *Z*-guggulsterones.

#### *Patents*

Several patents have been assigned for guggul uses in cosmetics. *C. mukul* has been used as an inactive pharmaceutical ingredient, as a binding agent, antiobesity agent, and cholesterol-reducing agent. Gugulipid's cognition enhancing effect in Alzheimer's disease model rats/mice, anti-hyperglycemic effect

in streptozotocin-induced diabetic rats, and antifungal effect for dermal conditions have also been examined.

#### Environmental Occurrence and Persistence

Guggulsterones and guggulsterols naturally occur in *C. mukul*, although concentrations vary from 0.75 to 2.35%. In every case, the concentration of the *Z* isomer was more than twice that of the *E* isomer.

*Z*-Guggulsterone is also present in *Ailanthus malabarica* and *A. grandis*, close *C. mukul* relatives. The latter also contains *E*- and *Z*-guggulsterones, guggulsterol I, and cembrene. Guggulsterol III occurs in a marine cnidarian, *Leptogorgia sarmentosa*.

#### Human Exposure

Exposure occurs most often from ingesting herbal remedies and/or pharmaceuticals and from cosmetic use.

A number of guggulsterone-containing products are sold by Sabinsa Corporation under the name Gugulipid<sup>®</sup>. Concentrations of guggulsterones in tablets, capsules, and the raw exudates were found to be lower than claimed by the producers. The actual concentration ranged from 0.92% to 3.8%. Seven formulated products available in the United States were found to have less than the 25 mg guggulsterones claimed on the packaging; the amount of guggulsterones ranged from a negligible amount to 7.8 mg.

Guggul extracts contain 5% to 10% guggulsterone. The Indian Pharmacopeia (IP) recommends a maximum guggulsterone concentration in supplements of 4% to 6% and that Gugulipid<sup>®</sup> be taken in an amount equivalent to 25 mg guggulsterones three times a day. Information about one of its clinical trials stated 400 mg Gugulipid<sup>®</sup> is equivalent to 25 mg guggulsterones/dose, which would be 6.25% guggulsterones. In a clinical trial that effectively treated acne, the dosage was 100 mg guggulsterones daily.

The manufacturers of Gugulon<sup>™</sup> claim it contains 300 mg guggul extract, including 12.5 mg guggulsterones and that it is verified for purity with HPLC. No dosage was suggested.

Some sources marketing products with gum guggul extracts on the Internet listed concentrations and suggested doses. The recommended daily doses vary widely, from 6.25 mg to 132 mg.

#### Regulations

Products containing gum guggul or its constituents and marketed as dietary supplements must adhere to 21 U.S.C. 343(r)(6), Section 403 (r)(6) of the Federal Food, Drug, and Cosmetic Act and not “claim to diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases.”

A search of the Code of Federal Regulations website for “guggul,” “gugul,” and “gugulipid” revealed no other U.S. government regulations pertaining to gum guggul.

### **Toxicological Data**

#### Human Data

Reported side effects were not significant in clinical studies of gum guggul. When subjects were given 400 mg Gugulipid<sup>®</sup> three times a day for a month (75 mg guggulsterones total), there were no adverse effects on blood glucose, liver function, blood urea levels, hematological parameters, or electrocardiogram results. The only adverse effect reported was epigastric fullness in one patient.

Traditional Ayurvedic treatments for obesity were administered in a clinical trial to determine their effectiveness. All of the formulations contained gum guggul among its herbal ingredients. Each group

except controls were administered triphala guggul (138 mg gum guggul). Group I was administered gokshuradi guggul (35 mg gum guggul); Group II, sinhanad guggul (15 mg gum guggul); Group IV, chandraprabha vati (57.6 mg gum guggul); and Group III, placebo tablets as a control. Guggulsterone amounts were not given, but in analyses of gum guggul from trees grown in five locations in India, the total percentage of guggulsterones ranged from 0.75 to 2.35%. The 70 participants experienced a few minor side effects such as nausea and mild diarrhea (eight in treatment groups, two in control group).

In other studies reporting no significant side effects, adult obese patients were administered medohar, a guggulu formulation, for 30 days for weight loss, and patients with primary hyperlipidemia received guggulipid three times a day for six weeks.

More side effects have been associated with the crude gum guggul. These include skin rashes, irregular menstruation, diarrhea, headache, mild nausea, and with very high doses, liver toxicity.

Caution is recommended when using guggul in people with liver disease, inflammatory bowel disease, or diarrhea. It should not be used during pregnancy and it can cause diarrhea, hiccups, apprehension, and restlessness. Gum guggul possibly interacts with several drugs.

#### Acute Toxicity

In rats exposed to Guggulipid (route not provided), the LD<sub>50</sub> was 1.6 g/kg (5.12082 mmol/kg). In mice administered *C. mukul* extract intraperitoneally, the LD<sub>50</sub> was 750 mg/kg (2.400384 mmol/kg).

#### Short-term and Subchronic Exposure

The seven-day toxic low dose TD<sub>L0</sub> for gum guggul was 1,400 mg/kg.

In a study investigating the effects of gum guggul on thyroid hormone levels in mice, the extract (0.2 g/kg ethanolic extract of gum guggul with 45.29% guggulipid and 11.50% guggulsterones) significantly increased serum triiodothyronine (T<sub>3</sub>) and significantly decreased hepatic lipid peroxidation when given by gastric intubation for 15 days. The extract was not found to be hepatotoxic, but was antiperoxidative. In a similar study where mice were administered a mixture containing 0.2 g/kg ethanolic extract, 1.4 g/kg ashvagandha root extract, and 2.5 mg/kg bauhinia bark extract by gastric intubation for 30 days, serum concentrations of T<sub>3</sub>, T<sub>4</sub> and the T<sub>3</sub>/T<sub>4</sub> ratio were significantly higher for the treatment group than in controls. Hepatic lipid peroxidation did not decrease. The activity of two cytosolic defense enzymes, dismutase and catalase, increased, suggesting a hepatoprotective effect.

#### Synergistic/Antagonistic Effects

Guggulipid decreased the serum level of the drugs Diltiazem and Propranolol. When combined with some thyroid medications, Z-guggulsterone increased the uptake of iodine by the thyroid gland as well as oxygen uptake in the liver and bicep tissues. Guggul may potentiate the effects of aspirin, nonsteroidal anti-inflammatory drugs, and warfarin.

Guggulsterone was found to be a bile acid receptor and farnesoid X receptor (FXR) antagonist both *in vitro* and *in vivo*.

#### Reproductive and Teratological Effects

Gum guggul and its acidic fraction were administered to rats in order to observe its effects on the female reproductive system. Three groups of 12 adult female albino rats with normal estrous cycles were dosed orally once a day for seven days while in heat. Group I received 0.1% gum acacia in water while Group II and Group III received a 20 mg/100g emulsion of gum guggul and 2 mg/100g of its acid fraction, respectively. Both gum guggul and its acid fraction caused significant increases in absolute and relative weights of the ovaries, uterus, and cervix. Relative vagina weights for the rats treated with the acid

fraction alone were significantly higher than with either controls or with gum guggul-treated rats (0.70 mg/g).

The reproductive tissues in the rats were analyzed for levels of glycogen, sialic acid, and proteins. The glycogen levels in the ovaries, uterus, and cervix increased in rats treated with the oleoresin and its acid fraction. Gum guggul increased sialic acid levels in these three organs; the acid fraction increased its levels in the ovaries and uterus but not in the cervix. These findings were significant. Higher protein levels in treated rats were not significant.

#### Other Data

##### *Thyroid Effects*

Gugulipid<sup>®</sup> increased thyroid hormone production. Both thyroid-stimulating immuno-globulin substance and petroleum ether extract of gum guggul increased synthesis and release of thyroid hormone from mice thyroid gland *in vitro*.

##### *Cholesterol-Lowering Effects*

Clinical studies of guggul have shown its cholesterol-reducing effect. However, in a more recent study, the first randomized controlled clinical trial of gugulipid done outside of India, standardized doses (1000 or 2000 mg, containing 2.5% guggulsterones) failed to decrease the levels of low-density lipoprotein cholesterol (LDL-C) in healthy adults with hyperlipidemia eating a typical Western diet. Furthermore, there were no significant changes in total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, or very LDL-C levels, and hypersensitivity rash was reported for six participants out of 67 patients.

Gugulipid<sup>®</sup> inhibited liver cholesterol biosynthesis and increased excretion of bile acids and cholesterol in the feces. It stimulated the binding activity of LDL receptors in the liver membrane, causing the rapid catabolism of LDL, which is responsible for its hypolipidemic activity.

Guggulsterone is a potent FXR antagonist both *in vitro* and *in vivo*. In contrast, it enhanced FXR agonist-induced transcription of bile salt export pump (BSEP), a major hepatic bile acid transporter, in cells and animals. Furthermore, guggulsterone activated the estrogen receptor alpha isoform, progesterone receptor, and pregnane X receptor, and activation of the pregnane X receptor induced the expression of CYP3A genes in both rodent and human hepatocytes, which causes herb-drug interactions, but inhibited the human CYP7A1 gene.

##### *Other Effects*

Guggulsterones were comparable to cardioprotective drugs propranolol and nifedipine in protecting from myocardial necrosis induced by isoproterenol in rats. Gugulipid<sup>®</sup> significantly increased the levels of catecholamine and the activity of dopamine  $\beta$ -hydroxylase in normal rabbits and decreased those in cholesterol-fed rabbits. Additionally, it helped increase catecholamine levels in hypercholesteremic rabbits and the levels of norepinephrine, dopamine, and dopamine  $\beta$ -hydroxylase activity in the heart and brain tissues of rhesus monkeys.

Bioactive constituents from gum guggul (*C. wightii*), identified as ferulates, showed significant cytotoxicity *in vitro*, decreasing cell viability in MCF-7 (breast) tumor cells, PC-3 (prostate) tumor cells, and in parental and transfected P388 cells.

#### **Structure-Activity Relationships**

Compounds closely related to guggulsterones are other steroids, including cholesterol and steroid hormones.



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## 1.0 Basis for Nomination

Gum guggul extract was nominated by the NIEHS for toxicological characterization based on its expanding use as a dietary supplement and a lack of available information to adequately assess safe use in humans. Demonstrated biological effects of gum guggul extracts on lipid metabolism, thyroid hormone homeostasis, female reproductive tissues, endogenous nuclear hormone receptors and the potential for serious drug interactions highlight the need for further study.

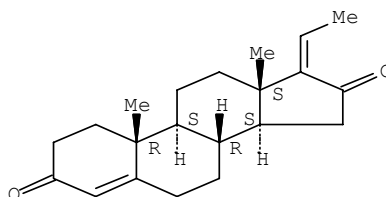
## 2.0 Introduction

### 2.1 Guggulsterones, Gum Guggul, and *Commiphora mukul*

#### 2.1.1 Guggulsterones

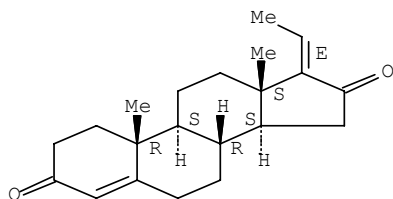
Gum guggul is the oleoresin of the plant *Commiphora mukul* (Bradshaw et al., undated). Extracts of the oleoresin include compounds known for their hypolipidemic properties, on which this report focuses—the Z- and E-isomers of guggulsterone and its related guggulsterols (Pioneer Enterprise, 2000).

Guggulsterone; Gugulipid (unspecified geometry)  
[95975-55-6]

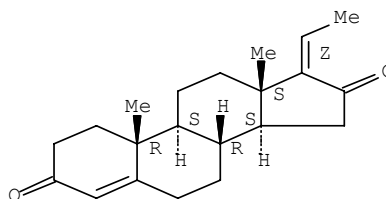


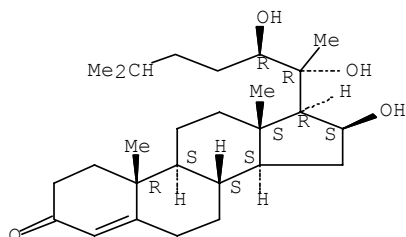
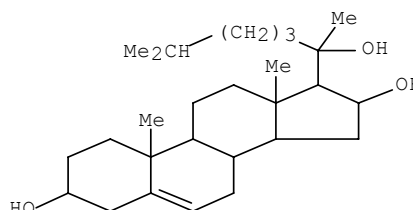
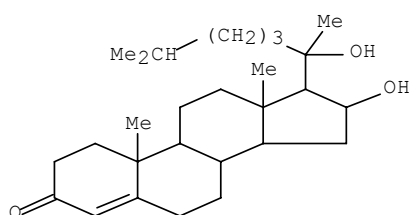
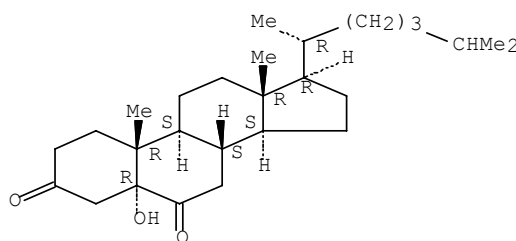
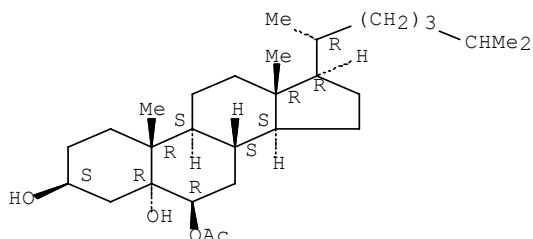
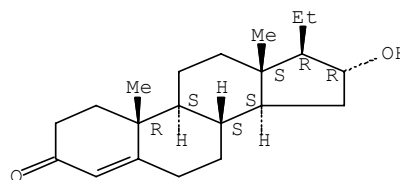
A standardized extract of the guggulsterones offered by Sabinsa Corp (2000) has the trademarked name Gugulipid<sup>®</sup>.

*E*-Guggulsterone  
[39025-24-6]

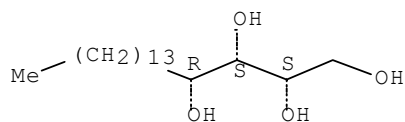
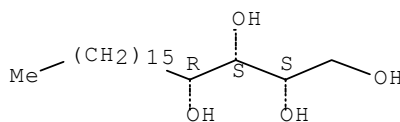


*Z*-Guggulsterone  
[39025-23-5]



Guggulsterol I  
[39025-25-7]Guggulsterol-II  
[39025-26-8]Guggulsterol-III  
[39025-27-9]Guggulsterol IV  
[20281-70-3]Guggulsterol V  
[6120-71-4]Guggulsterol VI  
[61391-01-3]

A search was done on these two tetrols, but no references describing biological activity were found.

Guggultetrol-18; 1,2,3,4-octadecanetetrol  
[105368-62-5]Guggultetrol-20; eicosan-1,2,3,4-tetrol  
[105368-60-3]

No search was done on other steroids named as gum guggul components, such as cholesterol [57-88-5]; 20(*S*)-hydroxypregn-4-en-3-one [No CAS RN located]; *Z*-guggulsterol [No CAS RN located]; and 20(*R*)-hydroxypregn-4-en-3-one [No CAS RN located]. The latter two were only named in one source located (Dev, 1983).

### 2.1.2 Gum Guggul

Gum guggul (trunk with the gum)



Image from Sabinsa Corp. (2000)

Gum guggul is the oleoresin of the plant *Commiphora mukul* (Bradshaw et al., undated), located in ducts in the soft underbark (Sabinsa Corp., 2000). The oleoresin is yellowish, collected when the sap is tapped and a pale yellow, aromatic fluid flows out that turns into an “agglomerate of tears or stalactic pieces” that are reddish brown, golden brown, or dull green (Sabinsa Corp., 2000; Sears Phytochem Ltd., undated). About 700 to 900 g resin come from each four- to six-foot-tall tree (Sabinsa Corp., 2000).

Synonyms for the oleoresin include Indian bdellium (Sears Phytochem Ltd., undated), aflatan, moql, moqlearzaqi, mukularahi, gugal, guggul, mukul, ranghanturb, guggala, gugal, goggle, gulag, boejahudan, gugali, gugar, bhavbhishtha, bhutahara, devadhupa, deveshta, dhurta, divya, kumbholu, kumbholukhalaka, kunti, mahishaksha, mahishakshaka, marudishta, nishadhaka, palankasha, pavandvishta, pura, puta, rakshoha, sarvasaha, shamhava, shiva, uddipta, ulukhalaka, usha, vayughna, ranghanturb, jatayu, javayu, ratadummula, maishakshi, mahisaksh, maisakshi (Sarasvati Sindhu, undated), juggulu (Sharma et al., 1983), guggulu (Lotus Natural Health and Healing Center, 1999), “Gugal, the oleoresin” (Atal et al., 1975), “Guggal, the oleo-gum resin from *C. wightii*” (Bhatt et al., 1989), “guggulu (resin from *C. Mukul*)” (Patil et al., 1972), and palnkash (AyuHerbal.com, undated).

Sources may differentiate between essential oil, gum, and resin. One source states that resin can be separated from the gum either by hot expression at 120 to 130 °C, with a yield of 51%, or by solvent extraction, with a yield of 61%. It defined the commercially available gum guggul as “the purified resin” (Sears Phytochem Ltd., undated). This explains why many sources call the resin “oleoresin of gum guggul” (RTECS RK1930000, 2001). Throughout this document, oleoresin of *C. mukul* will usually be called gum guggul.

### 2.1.3 Ayurvedic Medicines with Gum Guggul

Ayurvedic medicines containing gum guggul often contain guggulu in their names, such as in Shunthi-guggulu (AsiaPulse News, 2001), yogaraja guggulu (Alam et al., 1986; cited by CCRAS, undated), sunthi-guggulu (Prem Kishore, et al., 1982; cited by CCRAS, undated), kaishor guggulu, kanchanar guggulu, punarnavadi guggulu, simhanad guggulu, triphala guggulu, (Gershon, 1998), gokshuradi guggulu (Ayurvedica.net, undated), and guggulu thiktaka (Venkataraghavan et al., 1975; cited by CCRAS, undated). For example, triphala guggulu includes gum guggul, dried fruits from three plants—*Terminalia chebula* Retz., *T. belerica*

Roxb., and *Embilica officinalis* Gaertn.—and the dried, unripe fruit of *Piper longum* Linn. (Paranjpe et al., 1990).

#### 2.1.4 *Commiphora mukul*



Images from Sabinsa Corp. (2000) and Pioneer Enterprise (2000)

Native to India (Bradshaw et al., undated), *C. mukul* grows wild in the Indian states of Rajasthan, Gujarat, Karnataka, Rajasthan, Rajputana, Bellari, Baluchistan, Assam, Berar, and Mysore, and in Afghanistan, Arabia, and northeast Africa in rocky dry areas (AyuHerbal.com, undated; Sabinsa Corp., 2000; Varier, 1994; Atal et al., 1975). The tree is four to six feet tall, thorny, and free of foliage most of the year with ash-colored bark that flakes off in a rough way. The underbark also comes off easily (Bradshaw et al., undated). It has also been described as a shrub (Pioneer Enterprise, 2002). A physical description of the tree, from two sources, follows:

**Branches:** “spirally ascending” (Pioneer Enterprise, 2002), “spinescent ... young parts glandular, pubescent” (Varier, 1994).

**Leaves:** “one to three foliate” (Pioneer Enterprise, 2002).

**Leaflets:** “sessile to subsessile, terminal ones the largest, rhomboid to ovate in shape, irregularly toothed margin” (Pioneer Enterprise, 2002), “leaves alternate, one to three foliate, obovate, serrate-toothed in the upper parts ... lateral leaflets when present only less than half the size of the terminal ones” (Varier, 1994).

**Flowers:** “small, brown to pink, unisexual” (Pioneer Enterprise, 2002), “flowers small, brownish red, polygamous in fascicles” (Varier, 1994).

**Calyx:** “glandular hairs, forming cylindrical cap” (Pioneer Enterprise, 2002).

**Petals:** “for to five times as long as sepal” (Pioneer Enterprise, 2002).

**Stigma:** “eight to ten, inconspicuously bilobed” (Pioneer Enterprise, 2002).

**Stamens:** “eight to ten, alternately long and short” (Varier, 1994).

**Fruit:** “drupe, red ovate, acuminate in shape, with 2-celled-store, rarely four-valved” (Pioneer Enterprise, 2002), “red when ripe” (Varier, 1994).

In the published journal literature, the source plant for gum guggul is a member of the Burseraceae family, named variously as *Commiphora mukul* (Bajaj and Dev, 1982), *C. wightii* (Sharma, 1994), and *Balsamodendron mukul* (Sarasvati Sindhu, undated). A few sources stated they are names for the same plant (e.g., Sabinsa Corp., 2000); however, *Indian Medicinal Plants: A Compendium of 500 Species* (Varier, 1994) describes two different plants (one with alternate leaves and one with opposite leaves) with different geographical distribution and different but overlapping uses.

The classification and nomenclature of Burseraceae, particularly the *Boswellia* and *Commiphora* genera, have been called “taxonomically difficult.” The drought-tolerant plants are leafless for most of the year and are thus difficult to identify (Gachathi, 1997). Confusion is caused by *Boswellia serrata*, also an Ayurvedic plant and member of the Burseraceae family, called gugal, guggul, or salai guggal. Like *C. mukul*, *B. serrata* exudes a medically valuable resin, and its uses overlap with those of gum guggul (Dehlvi Remedies, undated; Sane et al., 1998; Shah and Gopal, 1985).

Other names for *C. mukul* include Indian bdellium tree (Sears Phytochem Ltd., undated), juggulu (Sharma et al., 1983), gugal, guggul, mahisaksagululu, gugguluh, mahisaksah, gukkulu, and mahisaksi (Varier, 1994).

### 2.1.5 Other Gum Guggul Constituents

Other gum guggul chemicals were reported to be biologically active: Myrrhanol A [350809-42-6] and myrrhanone A [350809-44-8] showed anti-inflammatory activity in adjuvant-induced, air-pouch granuloma of mice (Kimura et al., 2001), and two ferulic acid esters, (*Z*)-5-tricosene-1,2,3,4-tetraol [375798-03-1] and (*Z*)-5-tetracosene-1,2,3,4-tetraol [375798-04-2], were reported to have antitumor properties (Majeed et al., 2001) (The author is the president and CEO of Sabinsa Corp.). No published toxicology studies were located for myrrhanol A and myrrhanone A. No attempt was made to locate and compile literature on other constituents.

Other types of chemicals that were named as gum guggul constituents with no mention of biological activity were a tetrol, nonadecan-1,2,3,4-tetrol [No CAS RN given], lignans and terpenes. The lignans named included some for which no CAS RNs were located, including guggullignan I; guggullignan II; octadecane-1,2,3,4-tetraol-1-yl 3-(4-hydroxy-3-methoxyphenyl) propanoate, ferulic acid [1135-24-6], and sesamin [607-80-7] (Dev, 1983; Patil et al., 1972). The terpenes included mukulol [41943-03-7]; allylcembrol I [39012-00-5]; cembrene A [31570-39-5] (Dev, 1983); cembrene [20016-72-2];  $\alpha$ -camphorene I [532-87-6] (Rücker, 1972); myrcene [123-35-3], and dimyrcene (AyuHerbal.com, undated).

One source lists the components of the essential oil of *C. mukul* and their percentages by weight: (Saxena and Sharma, 1998):  $\alpha$ -pinene, 4.75%; myrcene, 3.50%; eugenol, 14.70%, cadinene, 5.50%; geraniol, 6.20%; methyl heptanoate, 17.50%; (+)- $\alpha$ -phellandrene, 5.50%; (+)-limonene, 6.50; ( $\pm$ )-bornyl acetate, 7.30%; ( $\pm$ )-linalool, 8.70%; methyl chavicol, 5.40%;  $\alpha$ -pineol, 4%; 1,8-cineole (eucalyptol), 3.5%; and unidentified compounds.

## 2.2 Chemical Identification and Analysis

Guggulsterone ( $[C_{21}H_{28}O_2]$ ; mol. wt. = 312.45) is also called:

Pregna-4,17(20)-diene-3,16-dione (7CI, 9CI)

Gugulipid

*E*-Guggulsterone ( $[C_{21}H_{28}O_2]$ ; mol. wt. = 312.45) is also called:

Pregna-4,17(20)-diene-3,16-dione, (17*E*)- (9CI)

(-)-(*E*)-Guggulsterone

Guggulsterone E

*Z*-Guggulsterone ( $[C_{21}H_{28}O_2]$ ; mol. wt. = 312.45) is also called:

Pregna-4,17(20)-diene-3,16-dione, (17*Z*)- (9CI)

(17*Z*)-Guggulsterone

Guggulsterol I ( $[C_{27}H_{44}O_4]$ ; mol. wt. = 432.64) is also called:

Cholest-4-en-3-one, 16,20,22-trihydroxy-, (16 $\beta$ ,22*R*)- (9CI)

Guggulsterol-II<sup>1</sup> ( $[C_{27}H_{46}O_3]$ ; mol. wt. = 418.65) is also called:

Cholest-5-ene-3,16,20-triol, (3 $\beta$ ,16 $\beta$ ,20 $\chi$ )- (9CI)

Guggulsterol-III<sup>1</sup> ( $[C_{27}H_{44}O_3]$ ; mol. wt. = 416.64) is also called:

Cholest-4-en-3-one, 16,20-dihydroxy-, (20 $\chi$ )- (9CI)

Guggulsterol IV ( $[C_{27}H_{44}O_3]$ ; mol. wt. = 416.64) is also called:

Cholestane-3,6-dione, 5-hydroxy-, (5 $\alpha$ )- (9CI)

5 $\alpha$ -Cholestane-3,6-dione, 5-hydroxy- (6CI, 8CI)

5-Hydroxy-5 $\alpha$ -cholestan-3,6-dione

5 $\alpha$ -Cholestane-5 $\alpha$ -ol-3,6-dione

5 $\alpha$ -Hydroxycholestane-3,6-dione

Guggulsterol V ( $[C_{29}H_{50}O_4]$ ; mol. wt. = 462.70) is also called:

Cholestane-3,5,6-triol, 6-acetate, (3 $\beta$ ,5 $\alpha$ ,6 $\beta$ )- (9CI)

5 $\alpha$ -Cholestane-3 $\beta$ ,5,6 $\beta$ -triol, 6-acetate (6CI, 7CI, 8CI)

Guggulsterol VI ( $[C_{21}H_{32}O_2]$ ; mol. wt. = 316.48) is also called:

Pregna-4-en-3-one, 16-hydroxy-, (16 $\alpha$ )- (9CI)

16 $\alpha$ -Hydroxypregna-4-en-3-one

<sup>1</sup>The use of hyphens in some of the guggulsterol names is consistent between Registry records and STN abstracts.



Gum guggul is fractionated in the following steps:

1. It is mixed with ethyl acetate to yield a soluble fraction (~45%) and an insoluble fraction (~55%).
2. The soluble portion is subfractionated into acid (4%), basic (1%), and neutral (95%) fractions. The acid fraction contains compounds associated with anti-inflammatory activity—ferulic acid and related compounds, phenols, and other aromatic acids.
3. The neutral fraction is divided into ketonic (12%) and nonketonic (88%) subfractions. The nonketonic, inactive subfraction contains fatty alcohols, diterpenes, and lignans.
4. The neutral ketonic fraction is known as guggulipid. Besides *E*- and *Z*-guggulsterones, it contains other C21 and C27 sterols and other esters (Bradshaw et al., undated).

The crude gum guggul was found to contain 2% guggulsterones. Its ethyl acetate extract contains 4% to 4.5% guggulsterones. The neutral subfraction contains 4.2% to 4.7% guggulsterones. The ketonic subfraction of the neutral subfraction contains 35% to 40% guggulsterones, from which the 10% *E*- and *Z*-guggulsterones are derived (Mesrob et al., 1998). Details of the extraction process are found in Bajaj and Dev (1982) as shown in **Figure 1**.

Guggulsterol IV and guggulsterol V were isolated from the neutral fraction of gum guggul after saponification of the chloroform extract (Purushothaman and Chandrasekharan, 1976).

“The commercial product contains about 4.65% foreign matter and about 1.45% of an aromatic oil besides gum and resin.” It is transparent in thin films but translucent or opaque in bulk (Sears Phytochem Ltd., undated).

*C. mukul* was among herbs analyzed by flame AAS (atomic absorption spectrophotometry) and ICP-AES (inductively coupled plasma-atomic emission spectroscopy) to determine its elemental composition. The plant parts analyzed were not given in the abstract (Siddiqui et al., 1990).

Concentrations of guggulsterones in gum guggul may be determined by thin layer chromatography (TLC) and high performance liquid chromatography/mass spectrometry (HPLC/MS) (Hung et al., 1996) and by a colorimetric method (Rangari and Donglikar, 1994). The structures of the guggulsterones were elucidated by nuclear magnetic resonance (NMR) spectrometry (Purushothaman and Chandrasekharan, 1976).

The guggulsterones in gum guggul, in commercial tablets, and in commercial capsules were detected and determined quantitatively by HPLC with a PDA (photo-diode array) detector. Liquid chromatography-MS (LC-MS) of the commercial products was compared with those of *E*- and *Z*-guggulsterones. The validated quantitation range of HPLC was 15 to 85 µg/mL for *E*-guggulsterone and 25 to 130 µg/mL for *Z*-guggulsterone (Mesrob et al., 1998). In addition, guggulsterones were determined in human serum (Singh et al., 1995). Guggulsterones were determined in a synthetic mixture using LC. The stationary phase was a Symmetry C18 steel column with a Sentry C<sub>18</sub> guard column, and the mobile phase was acetonitrile-water (46 + 54, v/v) degassed under vacuum with an in-line degasser. The retention time was 8 minutes for the *E* isomer, 11 minutes for the *Z* isomer (Nagarajan et al., 2001).

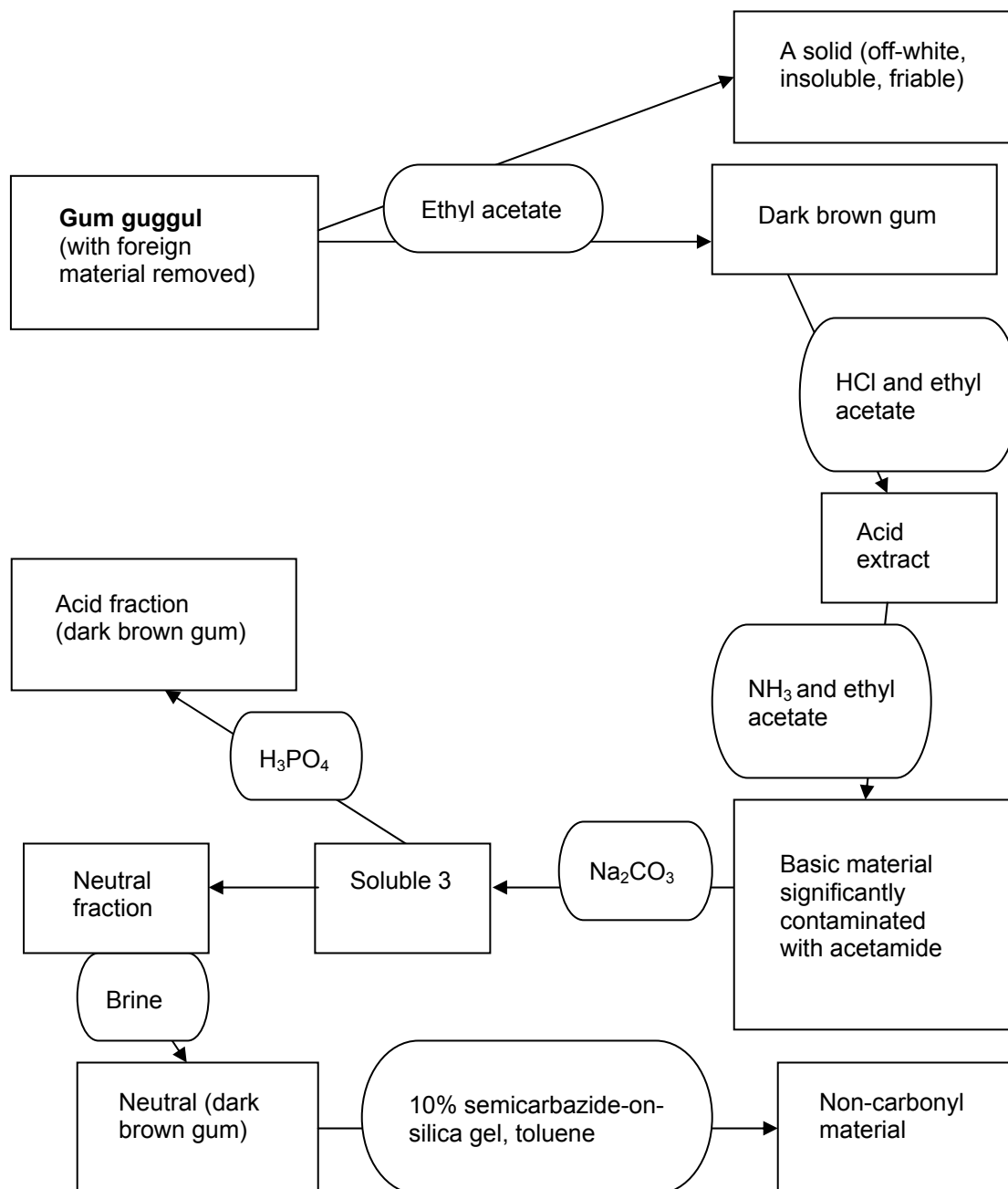
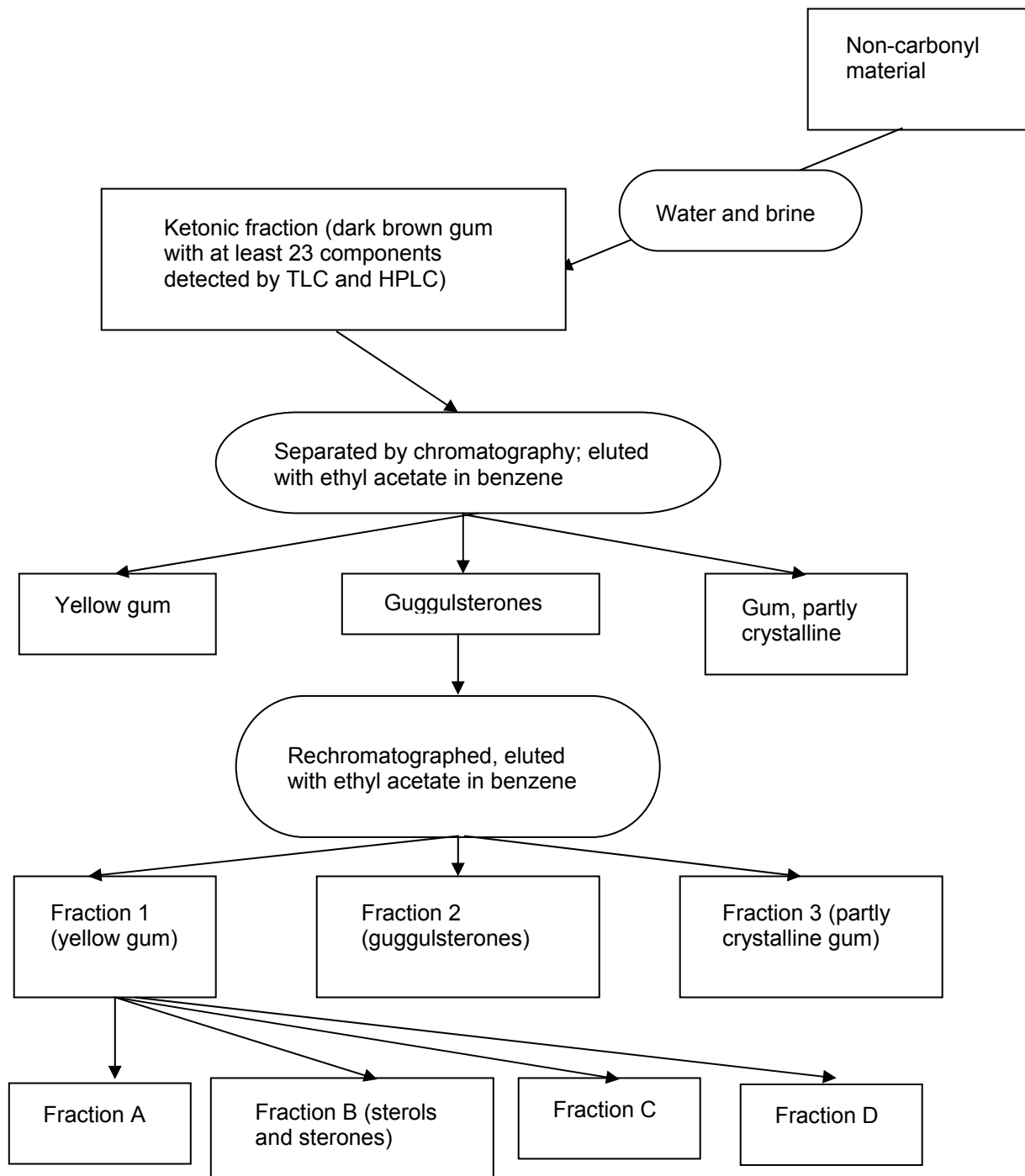


Figure 1. Extraction of Steroids from Gum Guggul



**Figure 1. Extraction of Steroids from Gum Guggul (continued)**

Abbreviations: HPLC = high-performance liquid chromatography; TLC = thin layer chromatography

Source: Bajaj and Dev (1982).

*E*- and *Z*-Guggulsterones in gum guggul were profiled using ultraviolet (UV) monitoring (Mesrob et al., 1998). Guggulsterols in gum guggul were identified by <sup>1</sup>HNMR, and spectrometers and spectrophotometers were used to gather spectral and analytical data (Bajaj and Dev., 1982).

## 2.3 Physical-Chemical Properties

### 2.3.1 Physical-Chemical Properties of Gum Guggul, the Oleoresin of *Commiphora mukul*

Property	Information	Reference(s)
Physical State	Viscous, moist; dry powder or granules	AyuHerbal.com (undated); Sears Phytochem Ltd. (undated) <sup>1</sup>
Odor	Fragrant; acrid	AyuHerbal.com (undated); Varier (1994)
Taste	Bitter	Varier (1994)
Feel	Astringent, thermogenic	Varier (1994)
Color	Off-white or pale yellow; dusty	AyuHerbal.com (undated); Sears Phytochem Ltd. (undated) <sup>1</sup> ; Varier, 1994)
Solubility	In water	Pioneer Enterprise (2002) <sup>2</sup>
	≥60% w/w	
	In alcohol	
	≥40% w/w	
	In petroleum ether, ethyl acetate, castor oil, drying oils, and turpentine.	Sears Phytochem Ltd. (undated) <sup>1</sup>
pH (1% w/v solution)	5 to 7	Pioneer Enterprise (2002) <sup>2</sup>
Loss upon drying at 105 °C	≤5% w/w	Pioneer Enterprise (2002) <sup>2</sup>
Moisture content by K.F.	≤5% w/w	Pioneer Enterprise (2002) <sup>2</sup>
Ash content	≤5% w/w	Pioneer Enterprise (2002) <sup>2</sup>
Sulphated ash content	≤5% w/w	Pioneer Enterprise (2002) <sup>2</sup>
Gugulipid concentrations in ethyl acetate extract	≥25%	Sears Phytochem Ltd. (undated) <sup>1</sup>
Guggulsterones by HPLC	≥2.5%	Sears Phytochem Ltd. (undated) <sup>1</sup>
Assay of guggulsterones by HPLC and HPTLC	≥3%	Pioneer Enterprise (2002) <sup>2</sup>
Heavy metals concentration	≥20 ppm	Sears Phytochem Ltd. (undated) <sup>1</sup>
Total bacterial count (CFU/g)	≤800	Pioneer Enterprise (2002) <sup>2</sup>
Total fungal count (CFU/g)	≤500	Pioneer Enterprise (2002) <sup>2</sup>
Microbial pathogens	None	Pioneer Enterprise (2002) <sup>2</sup>

<sup>1</sup>Based on commercially available products, i.e. Gugulipid®.

<sup>2</sup>Whether source is crude or refined gum guggul is unclear.

Abbreviations: CFU = colony-forming unit(s); HPLC = high performance liquid chromatography; HPTLC = high performance thin layer chromatography; K.F. = Karl Fischer titration; w/w = weight/volume; W/w = weight/weight.

The oleoresin “burns in fire, melts in the sun, and forms a milky emulsion with hot water” (AyuHerbal.com, undated). It mixes well with vegetable waxes, stearic acids, and resin [*sic*] (Sears Phytochem Ltd., undated).

**2.3.2 Physical-Chemical Properties of *E*-Guggulsterone and *Z*-Guggulsterone**

Property	Information	Reference(s)
Physical State	white solid	BIOMOL Res. Lab (undated)
Water solubility	<0.01 M	Registry (2002) <sup>1</sup>
Soluble in	DMSO	BIOMOL Res. Lab (undated)
Log of the octanol-water partition coefficient (log K <sub>ow</sub> , Log P)	3.646±0.287	Registry (2002) <sup>1</sup>
Ultraviolet (UV) detection	242 nm 245 nm 254 nm	Nagarajan et al. (2001); Mesrob et al. (1998); Sharma (1994)

<sup>1</sup>Calculated based on structure**2.3.3 Physical-Chemical Properties Guggulsterol I**

Property	Information	Reference(s)
Water solubility	<0.01 M	Registry (2002) <sup>1</sup>
Log of the octanol-water partition coefficient (log K <sub>ow</sub> , Log P)	3.973±0.342	Registry (2002) <sup>1</sup>

<sup>1</sup>Calculated based on structure**2.3.4 Physical-Chemical Properties Guggulsterol-II**

Property	Information	Reference(s)
Water solubility	<0.01 M	Registry (2002) <sup>1</sup>
Log of the octanol-water partition coefficient (log K <sub>ow</sub> , Log P)	5.975±314	Registry (2002) <sup>1</sup>

<sup>1</sup>Calculated based on structure**2.3.5 Physical-Chemical Properties Guggulsterol-III**

Property	Information	Reference(s)
Water solubility	<0.01 M	Registry (2002) <sup>1</sup>
Log of the octanol-water partition coefficient (log K <sub>ow</sub> , Log P)	5.489±0.314	Registry (2002) <sup>1</sup>

<sup>1</sup>Calculated based on structure**2.3.6 Physical-Chemical Properties Guggulsterol V**

Property	Information	Reference(s)
Water solubility	<0.01 M	Registry (2002) <sup>1</sup>
pKa	13.86±0.20	Registry (2002) <sup>1</sup>
Log of the octanol-water partition coefficient (log K <sub>ow</sub> , Log P)	7.794±0.338	Registry (2002) <sup>1</sup>

<sup>1</sup>Calculated based on structure**2.3.7 Physical-Chemical Properties Guggulsterol VI**

Property	Information	Reference(s)
Water solubility	<0.01 M	Registry (2002) <sup>1</sup>
Log of the octanol-water partition coefficient (log K <sub>ow</sub> , Log P)	4.4±0.279	Registry (2002) <sup>1</sup>

<sup>1</sup>Calculated based on structure

## 2.4 Production and Commercial Availability

### 2.4.1 Growing and Harvesting

One source mentions guggul from “*C. wightii* (Arnott). Bhandari (Syn *C. mukul*)” being harvested from a herbal farm in the Indian state of Rajasthan (Sharma, 1994).

### 2.4.2 Bulk Suppliers

Several companies supply gum guggul in bulk through the Internet. Ayurveda Holistic Center (2000) of Bayville, NY, and India supplies the resin. Lotus Natural Health and Healing Center (1999) of East Hanover, NJ, offered 0.5-lb quantities guggulu (*C. mukul* [gugal]) for \$16.50/0.5 pound, presumably the resin. Banyan Trading Co. (undated) of Albuquerque, NM, and India supplies guggulu, presumably the resin. The website stated, “we work only with practitioners on a wholesale basis.” Metro Exporters (undated) of India seems to be a bulk supplier of “gugal extract”; no details are given. Monterey Bay Spice Company (undated) supplies gum guggul pieces weighing 5 to 25 pounds for \$5.85/pound and 5 to 24 pounds gum guggul powder for \$6.21/pound.

Z-Guggulsterone, with a purity of ~95%, is available from Sigma-Aldrich (St. Louis, MO); availability and pricing were not available (Sigma-Aldrich, 2002).

### 2.4.3 Extract Producers

Two producers have bases in both India and the United States: Sabinsa Corporation (2000), maker of Gugulipid<sup>®</sup> (Whole Foods Magazine, 1998), and Xechem International (2000), which produces the nutritional product Gugulon<sup>™</sup> through its XetaPharm Inc. subsidiary. A standardized fraction from gugulipid from *C. wightii* is now being marketed as Guglip<sup>®</sup>, CIPLA (Indian Institute of Science, undated).

### 2.4.4 Supplement Suppliers

Several suppliers of supplements containing gum guggul extracts can be found on the Internet, including iHerb.com (2002), Vitacost.com (2002), America’s Finest Inc. of Piscataway, NJ (Health Products Business, 2000), and Wellness Works LLC (2001). Several others are listed by Hess (2002). The National Institute of Ayurvedic Medicine (Gershon, 1998) sells Ayurvedic formulations—gum guggul combined with other herbs. Neelam Exim Pvt. Ltd. (undated) sells a Royal Slim Herbal capsule containing medohar gugal from *Balsamodendron mukul*. However, commercially available gum guggul supplements subjected to HPLC were found to contain significantly lower guggulsterone concentrations than claimed (See **Section 7.0**) (Mesrob et al., 1998; Najarajan et al., 2001).

## 3.0 Production Processes

The tree is tapped for the oleoresin. The oleoresin is collected by making a circular incision on the main stem, no thicker than the bark (Sabinsa Corp., 2000). One article proposed an improvement to tapping methods for *C. wightii* in which ethephon (2-chloroethylphosphonic acid) was applied to the tree 48 hours before tapping. The article noted the yield of resin was higher in April and May than in December and January (Bhatt et al., 1989), although another source stated the tree is tapped in winter (Sabinsa Corp, 2000).

A source described extraction of *C. mukul* resin by steam distillation. The solids that remain were removed by filtering through a 100 µm mesh. The remaining water was evaporated under a vacuum, and the concentrated aqueous extracts were lyophilized, resulting in a fine powder (Duwiejua et al., 1992).

A pharmacologically active synthetic stereoisomeric mixture of guggulsterones can be synthesized by the epoxidation 16-dehydropregnenolone acetate with hydrogen peroxide to provide 16,17-epoxy-3β-hydroxypregn-5-en-20-one, followed by reduction with hydrazine hydrate to obtain 5,17(20)-pregnadiene-3B,16-diol. The diol is then oxidized (Gokaraju et al., 2004).

#### 4.0 Production and Import Volumes

No data were available.

#### 5.0 Uses

##### 5.1 Traditional Uses

Gum guggul is used as incense, to make lacquers, varnishes, and ointments, as a fixative in perfumes, and in medicine (Sears Phytochem Ltd., undated).

In the Ayurvedic, Indian traditional system of medicine, herbs are usually used in combinations (Vitamins-etc.com, 2001). Yogaraj guggulu is traditionally for detoxifying, treating obesity, joint pain, arthritic conditions, muscle aches, rheumatism, and gout. Punavadi guggulu is for detoxifying the kidneys, eliminating fluid, helping heart conditions, and inflammations. Triphala guggulu is for joint pain, arthritic conditions, muscle aches, rheumatism, and weight loss (Gershon, 1998). Commercially available Ayurvedic formulations of guggulu include kaishor guggulu for soothing and cooling soft tissues, joints, and digestive system, supporting the immune system, relieving acne, herpes, and intestinal inflammation. Kanchanar guggulu is used for treating thyroid disease, obesity, skin disorders and as a traditional remedy for sore throat and hemorrhoids. The website (Gershon, 1998) did not state the concentrations of guggulsterones in the 500 mL capsules nor did it list recommended dosages.

Traditional uses of *C. mukul* include as an anti-inflammatory, antispasmodic, carminative, emmenagogue, hypoglycemic (Agricultural Research Service, undated), alterative, antiseptic, aperitif, astringent, sedative, stomachic, carminative, diaphoretic, diuretic, expectorant (Beckstrom-Sternberg and Duke, undated), antispasmodic, antisuppurative, aperient, expectorant, a thyroid stimulant (Vitamins-etc.com, 2001), anthelmintic, depurative, vulnerary, antiseptic, demulcent, aphrodisiac, stimulant, liver tonic, detergent, anti-spasmodic, hematinic, diuretic, and lithonotriptic (Varier, 1994).

Gum guggul is used to treat dysmenorrhea, dyspepsia, endometritis, hypercholesteremia, hypertension, impotence (Agricultural Research Service, undated), bronchitis, caries, catarrh, gingivitis, hay fever, hysteria, inflammation, laryngitis, lochia, mania, pharyngitis, phthisis, pyorrhea, rheumatism, sores, sore throat, stimulant, tonsillitis, tumors, wounds (Beckstrom-Sternberg and Duke, undated), bone fractures (Turner, 2001), gout, scrofula, sciatica, facial paralysis, diplegia, leprosy, leucoderma, pectoral disorders, otorrhea, epilepsy, fever, strangury, hemorrhoids, dysmenorrheal, amenorrhea, ulcers, anemia, coronary, thrombosis, stomatopathy,

pharyngopathy, spermatorrhea, urinary calculus, diabetes, trichosis (Varier, 1994), to enhance phagocytosis, to increase leukocytes (Vitamins-etc.com, 2001), to induce abortion (Baquar and Tasnif, 1967), and as a tonic for the uterus (Beckstrom-Sternberg and Duke, undated).

## 5.2 Modern Uses

Modern therapeutic uses of guggul include nervous diseases, hemiplegia, leprosy, marasmus, muscle spasms, neuralgia, ophthalmia, pyelitis, pyorrhea, scrofula, skin diseases, spongy gums, ulcerative pharyngitis, hypertension, ischaemia, hypertension, hemorrhoids, and urinary tract disorders (AyuHerbal.com, undated; Memorial Sloan-Kettering Cancer Center, 2003). More recently, *C. mukul* was found to be a relatively safe and effective supplement for osteoarthritis of the knee (Singh et al., 2003). The Ayurvedic herb *Inula racemosa*, in combination with *C. mukul*, is used to reduce chest pain and dyspnea of angina (Nutrition for a Living Planet, undated). Royal Slim with *B. mukul* (Neelam Exim. Pvt. Ltd., undated) is marketed as a weight reducer and fat burner.

Research studies showed that guggul is effective against aspects of cardiovascular disease. Guggul reduced the stickiness of platelets (Herbal Pharmacist, undated), and Gugulipid<sup>®</sup> was shown to be an efficacious and cost effective treatment of hyperlipoproteinemia (Ghatak and Asthana, 1995). The standardized fraction from Gugulipid from *C. wightii* (Guglip<sup>®</sup>) may be used to treat hyperlipidemia and atherosclerosis (Indian Institute of Science, undated). A webpage to sell Gugulon<sup>™</sup> stated it is marketed to help lower cholesterol, to decrease high blood pressure, to “strengthen the structural system” and the immune system, to benefit the heart, to lower cholesterol and high blood pressure, and to eliminate toxins (XetaPharm Inc., 2000).

The crude gum guggul and each of the fractions containing the *E*- and *Z*-guggulsterones have hypocholesteremic activity: the ethyl acetate extract, the neutral compounds from the extract, the ketonic compounds in the neutral fractions, and that containing the purified *E*- and *Z*-guggulsterones (Mesrob et al., 1998).

## 5.3 Patents

Several patents have been assigned for guggul uses in cosmetics. Extracts of *C. mukul* were pigmenting agents and melanocyte culture agents and used to manufacture pharmaceutical and cosmetic compositions (Andre et al., 1999 [patent assignee: Parfums Christian Dior, Paris, France]). Antisebum and antioxidant compositions were made using *C. mukul* or *C. wightii* gugulipid components (McCook et al., 1997 [patent assignee: Elizabeth Arden Co., USA]). Cosmetic compounds for skin lightening and antiwrinkle were made from *Commiphora* species (Andre et al., 1997 [patent assignee: Parfums Christian Dior, France]; Zhang et al., 2001, 2002 [patent assignee: Hindustan Lever Limited of the United Kingdom]).

A patent was assigned for a weight control product containing guggul extract and a phosphate salt (Brink, 2000 [patent assignee: Prolab Nutrition of Bloomfield, CN]). *C. mukul* are used in other products for control of body weight and cholesterol Weisspapir and Schwarz, 2002 [patent assignee: Can.]; Gorsek, 2003 [patent assignee: Vitacost.Com, Inc., USA]). As a cholesterol-reducing compound, gugulipid can be added as a supplement to milk (Haber et al., 2004 [patent assignee: Nutrinova Nutrition Specialties & Food Ingredients GmbH, Germany]). Gugulipid's cognition enhancing effect in Alzheimer's disease model rats/mice, anti-hyperglycemic effect in



streptozotocin-induced diabetic rats, and antifungal effect for dermal conditions has also been examined (Pratrap et al., 2002 [patent assignee: Council of Scientific and Industrial Research, India]). As an antiobesity agent, *C. mukul* is added in health foods (Ito, 1996 [patent assignee: Seikosha Kk, Japan]).

*C. mukul* has been used in the roles of inactive pharmaceutical necessities. It was used to make sustained-release tablets of other drugs as a sustaining material (Baveja et al., 1989). Three percent guggul gum mucilage was found to be a suitable binding agent in tablets (Kakrani and Jain, 1981), and a suitable suspending and emulsifying agent for medicines (Kakrani and Varma, 1981). Extracted gum guggul constituents from the *B. mukul* trunk (i.e., myrrhanol A, B, and C, and myrrhanone A and B) have been found useful for the manufacturing of pharmaceuticals for allergy control, chronic arthritis, and inflammation; the triterpenes inhibit production of nitrogen oxide (Kawahara et al., 2002 [patent assignee: Morishita Jintan Co., Ltd, Japan]).

Guggulipids have been deodorized and sometimes decolorized for inclusion in food (e.g., margarine) (Beinford et al., 2002 [patent assignee: Unilever N.V., Netherlands]).

## 6.0 Environmental Occurrence and Persistence

Guggulsterones and guggulsterols naturally occur in *C. mukul*. Gum guggul from plants grown in different locations, four forests and a farm, varied in concentrations of guggulsterones. The total percentage of guggulsterones ranged from 0.75 to 2.35%. In every case, the concentration of the Z isomer was more than twice that of the E isomer (Sharma, 1994).

Z-Guggulsterone, which occurs in *C. mukul*, also occurs in *Ailanthus malabarica* and *A. grandis*, close *C. mukul* relatives (Hung et al., 1996). The latter also contains E- and Z-guggulsterones, guggulsterol I, and cembrene (Hung et al., 1995). Guggulsterol III occurs in a marine cnidarian, *Leptogorgia sarmentosa* (Benvegnu et al., 1982).

## 7.0 Human Exposure

Human exposure occurs primarily from ingesting herbal remedies and/or pharmaceuticals and from cosmetic use. The ethyl acetate extract of gum guggul, specifically its neutral portion, contains the guggulsterones that lower blood cholesterol (Sabinsa, 2000).

When the guggulsterones were extracted from compounded tablets, capsules, and the raw exudates with ethyl acetate, their concentrations were lower than claimed. The raw resins claimed between 3.2% to 20% guggulsterones, while the actual range was 0.92% to 3.8%. Of seven formulated products available in the United States that were examined, each sample that claimed to have 25 mg guggulsterones had less. The amount of guggulsterones ranged from a negligible amount to 7.8 mg (Mesrob et al., 1998).

Sabinsa Corporation (2000) products include: Gugulipid<sup>®</sup> Granules, standardized for at least 2.5% Z- and E-guggulsterones for preparing tablets; Gugulipid<sup>®</sup> 40 mesh, standardized for at least 2.5% Z- and E-guggulsterones for preparing capsules; and Gugulipid<sup>®</sup> Soft Extract, standardized for at least 7.5% Z- and E-guggulsterones for preparing soft gels. The Ultra Guggalow product incorporates Gugulipid<sup>®</sup> (DRB Vitamins, 2000).

Guggul extracts contain 5% to 10% guggulsterone (Turner, 2001). The Indian Pharmacopeia (IP) recommends a maximum guggulsterone concentration in supplements of 4% to 6% and that Gugulipid<sup>®</sup> be taken in an amount equivalent to 25 mg guggulsterones three times a day (Indian Pharmacopoeia, 1996; cited by Sabinsa, 2000). Information about one of its clinical trials stated 400 mg Gugulipid<sup>®</sup> is equivalent to 25 mg guggulsterones/dose, which would be 6.25% guggulsterones. Yet elsewhere in the same source, the Sabinsa Corp. site stated Gugulipid is standardized to contain at least 2.5% guggulsterones and that “the Indian Pharmacopeia limits the maximum level of guggulsterones (E and Z) to 4% to 6% in a soft extract.” AltDiabetes.com (2000) and Healthnotes, Inc. (2000) echo this recommendation of 75 mg guggulsterones/day. Turner (2001) recommended 25 mg guggulsterone for decreasing atherosclerosis risk or losing weight. In a clinical trial that effectively treated acne, the dosage was 100 mg guggulsterones daily (Prima Communications Inc., 2001). Doses of gugulipid containing 25 mg guggulsterone were also effective in treating patients with nodulocystic acne (LoweringCholesterol.net [Natural Pharmacy], 2004).

The manufacturers of Gugulon<sup>™</sup> claim it contains 300 mg guggul extract, including 12.5 mg guggulsterones and that it is verified for purity with HPLC. No dosage was suggested (XetaPharm Inc., 2000).

Some sources marketing products with gum guggul extracts on the Internet listed concentrations and suggested doses, listed in **Table 1**. The recommended daily doses vary widely, from 6.25 mg to 132 mg.

Many sources marketing gum guggul on the Internet did not quantify the amount of guggulsterones their products contain, including Ayurvedica.net (undated), which offers different herbal formulations containing “guggulu”; Batra Medicos (undated), which offers *C. mukul* as a leaf and as tablets combined with different herbs or by itself; and National Institute of Ayurvedic Medicine, which supplies different guggulu oleoresin gum supplements (Gershon, 1998).

## **8.0 Regulatory Status**

Products containing gum guggul or its constituents and marketed as dietary supplements must adhere to 21 U.S.C. 343(r)(6), Section 403 (r)(6) of the Federal Food, Drug, and Cosmetic Act and not “claim to diagnose, mitigate, treat, cure, or prevent a specific disease or class of diseases” according to a May 15, 2001, warning letter to a representative of the company Amrita Veda about two products that did not contain gum guggul. However, two guggulu products were included in a list of statements of nutritional support that the company provided (Foret, 2001).

In a search of the FDA website, several notification letters from firms marketing gum guggul-containing dietary supplements were located. Health claims apparently not allowed under Section 403 (r)(6) were being made about gum guggul-containing products marketed as dietary supplements. No FDA responses to these letters were located (FDA Internet search for guggul\* and gugul\*, June 20, 2002).

A search of the Code of Federal Regulations website for “guggul,” “gugul,” and “gugulipid” revealed no other U.S. government regulations pertaining to gum guggul.

**Table 1. Concentration of *Z*- and *E*-Guggulsterones in Various Herbal Products<sup>1</sup>**

Product and manufacturer	Content, type of extract/dosage form (mg)	<i>Z</i> - and <i>E</i> -Guggulsterones concentration (%)	Dosage forms/serving	Guggulsterones/serving (mg)	Recommended daily dosage (mg guggulsterones)	Source
Guggulipid Standardized Extract	250 standardized	2.5	1	6.25	6.25, 12.5, 18.75 or 25	Wellness Works LLC™ (2001)
Policosanol Cholesterol Complex, Source Naturals	100 Gugulipid®	2.5	3	2.5	7.5	iHerb.com (2002)
Cholesterol Support (with Tocotrienols, Policosanol), Now Foods	220, standardized	10	3	22	132	iHerb.com (2002)
Opti-Guggul, AOR, Jarrow Formulas	500	4	1	20	60	iHerb.com (2002)
GugulPlus, Enzymatic Therapy	250, standardized	2.5	1	6.25	18.75	iHerb.com (2002)
Ultra Guggulow, Doctor's Best	1,000, standardized	2.5	1	25	75	iHerb.com (2002)
Choles-Response, Source Naturals	100, standardized	2.5	3	2.5	7.5	iHerb.com (2002)
Circu-Pressure, BioChem, Country Life	500	2.5	2	12.5	25	iHerb.com (2002)
GUGULIN, Ayurved Formulas	250	18	1	45 <sup>2</sup>	90	iHerb.com (2002)
Nutri Chol-less (Formula XIII), Country Life	100, standardized	2.5	2	2.5	10	iHerb.com (2002)
Guggalip Nut Herbal Complex, InterPlexus	300, standardized	8.3	1	25	75	Vitacost.com (2002)
Gugulmax, Nature's Herb	1,000, standardized	2.5	1	25	25, 50,75	Vitacost.com (2002)

<sup>1</sup>1 mg = 0.0032 mmol *Z*- or *E*-guggulsterones.

<sup>2</sup>by HPLC (high performance liquid chromatography)

## 9.0 Toxicological Data

### 9.1 General Toxicology

#### 9.1.1 Human Data

Reported side effects were not significant in clinical studies of gum guggul. When subjects were given 400 mg Gugulipid<sup>®</sup> three times a day for a month (75 mg guggulsterones total), there were no adverse effects on blood glucose, liver function, blood urea levels, hematological parameters, or electrocardiogram results. The only adverse effect reported was epigastric fullness in one patient (Agarwal et al., 1986; cited by Sabinsa Corp., 2000).

Traditional Ayurvedic treatments for obesity were administered in a clinical trial to determine their effectiveness for weight loss. All of the formulations contained gum guggul among its herbal ingredients. Each group except controls were administered triphala guggul (138 mg gum guggul). Group I was administered gokshuradi guggul (35 mg gum guggul); Group II, sinhanad guggul (15 mg gum guggul); Group IV, chandraprabha vati (57.6 gum guggul); and Group III, placebo tablets as a control. The 70 participants experienced a few minor side effects such as nausea and mild diarrhea (eight in treatment groups, two in control group) (Paranjpe et al., 1990). Guggulsterone amounts were not given, but in analyses of gum guggul from trees grown in five locations in India, the total percentage of guggulsterones ranged from 0.75 to 2.35% (Sharma, 1994).

In other studies reporting no significant side effects, adult obese patients were administered medohar, a guggulu formulation, for 30 days for weight loss (Bhatt et al., 1995), and patients with primary hyperlipidemia received gugulipid three times a day for six weeks (Anand and Kapoor, 1984). In a double-blind study, a combination of guggul, phosphate salts, hydroxycitrate, and tyrosine slightly improved weight loss as well as the mood of obese patients (LoweringCholesterol.net [Natural Pharmacy], 2004).

A standardized gugulipid extract had a few side effects, including minor gastrointestinal disturbances, such as dyspepsia, fullness (Sabinsa Corp., 2000).

More side effects are associated with the crude gum guggul. These include skin rashes, irregular menstruation, diarrhea, headache, mild nausea, eructation, hiccough, and with very high doses, liver toxicity (Satyavati, 1966 [cited by Sabinsa Corp., 2000]; Turner, 2001; Memorial Sloan-Kettering Cancer Center, 2003).

Caution is recommended when using guggul in people with liver disease, inflammatory bowel disease, or diarrhea (Healthnotes, Inc., 2000). It should not be used during pregnancy and it can cause diarrhea, hiccups, apprehension, and restlessness. Gum guggul possibly interacts with several drugs (Nutrition for a Living Planet, undated).

In a phase I tolerability study of Yogaraj-guggulu (containing 39.87% guggulu) with male volunteers (22-28 years old), general tolerability was “good” at doses up to 9 g/day. Three volunteers reported diarrhea; whether intestinal parasites were irritated by Yogaraj-guggulu were not determined. One subject developed rash and pruritus, which was probably not drug-related since a rechallenge dose failed to reproduce the symptoms and the patient had a past history of

urticaria. Another subject had stomatitis; he, however, also had a history of recurrent stomatitis (Antarkar et al., 1984).

In the SN/AEMS (Special Nutritionals Adverse Event Monitoring System) web report, adverse effects of “guggul”-containing products were “hospitalization for fluid retention” and “swelling of the extremities, a total body rash, and hives.” Another product called “guggal” was linked to “weakness, myopathy” (FDA/CFSAN, 1998).

### 9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics

No data were available.

### 9.1.3 Acute Exposure

Acute toxicity values for gum guggul and its constituents are presented in **Table 2**.

**Table 2. Acute Toxicity Values for Gum Guggul, Constituents**

Route	Species (sex and strain)	Constituent	LD <sub>50</sub>	Reference(s)
n.p.	Rat, sex and strain n.p.	Gugulipid	1.6 g/kg (5.12082 mmol/kg)	Bradshaw et al. (undated)
i.p.	Mouse, sex and strain n.p.	<i>C. mukul</i> extract, excluding roots	750 mg/kg (2.400384 mmol/kg)	Indian Journal of Experimental Biology (1973); cited by RTECS GK1189000 (2001)

Abbreviations: i.p. = intraperitoneal; LD<sub>50</sub> = concentration lethal to 50% of test animals; n.p. = not provided

### 9.1.4 Short-term and Subchronic Exposure

In rats dosed for seven days, the toxic low dose TD<sub>Lo</sub> for gum guggul was 1,400 mg/kg (Indian Journal of Experimental Biology, 1978; cited by RTECS RK1930000, 2001).

In a study of the effects of gum guggul on thyroid hormone levels, 20 Swiss albino female mice, about 3 months old, were divided into groups of ten and either administered 0.2 g/kg ethanolic extract of gum guggul with 45.29% gugulipid and 11.50% guggulsterones or 0.1 mL saline as controls, each by gastric intubation for 15 days. On the last day, blood was collected, and livers were removed, cleaned, and processed for biochemical analysis. The extract significantly increased serum triiodothyronine (T<sub>3</sub>) and significantly decreased hepatic lipid peroxidation. Serum thyroxine (T<sub>4</sub>) is converted to T<sub>3</sub> in the liver, so the researchers conclude that hormone levels and peroxidation are related. The extract was not found to be hepatotoxic, but was antiperoxidative (Panda and Kar, 1999).

The effects of a combination of gum guggul and other plant extracts on thyroid hormone levels were studied in two groups of eight 3-month-old Swiss albino female mice. The experimental group was administered a mixture containing 0.2 g/kg ethanolic extract, 1.4 g/kg ashvagandha root extract, and 2.5 mg/kg bauhinia bark extract, and the control group was administered distilled water, both by gastric intubation each day for 30 days. On the last day, blood was collected, and livers were removed, cleaned, and processed for biochemical analysis. Serum

concentrations of T<sub>3</sub>, T<sub>4</sub> and the T<sub>3</sub>/T<sub>4</sub> ratio were significantly higher in mice administered the plant extract combination than in controls (p <0.01, p <0.001, and p < 0.05). Hepatic lipid peroxidation did not decrease. The activity of two cytosolic defense enzymes, dismutase and catalase, increased, suggesting a hepatoprotective effect (Panda and Kar, 2000).

### 9.1.5 Chronic Exposure

No data were available.

### 9.1.6 Synergistic/Antagonistic Effects

Gugulipid decreased the serum level of the drugs Diltiazem and Propranolol. When combined with some thyroid medications, Z-guggulsterone increased the uptake of iodine by the thyroid gland as well as oxygen uptake in the liver and bicep tissues (Herb-Drug Interaction Handbook, 2001). Guggul may potentiate the effects of aspirin, nonsteroidal anti-inflammatory drugs (e.g., ibuprofen), and warfarin (Memorial Sloan-Kettering Cancer Center, 2003).

Guggulsterone was found to be a bile acid receptor and farnesoid X receptor (FXR) antagonist both *in vitro* and *in vivo* (Urizar et al., 2002; Wu et al., 2002). [See **Section 9.10** for further details.]

### 9.1.7 Cytotoxicity

No data were available.

## 9.2 Reproductive and Teratological Effects

Gum guggul and its acidic fraction were administered to rats in order to observe its effects on the female reproductive system. Three groups of 12 adult female albino rats with a normal estrous cycle were used. The rats were dosed orally once a day for seven days while they were in heat. Group I received 0.1% gum acacia in water while Group II and Group III received a 20 mg/100g emulsion of gum guggul and 2 mg/100g of its acid fraction, respectively. The rats were sacrificed, and their reproductive organs were weighed. Both gum guggul and its acid fraction caused significant increases in absolute and relative weights of the ovaries, uterus, and cervix (p < 0.01 to 0.001). The gum guggul treatment caused decreases in absolute and relative weights of the vagina, which were not significant. The rats treated with the acid fraction alone experienced relative weights of uterus, ovary, and cervix that were lower than with controls and higher than with gum guggul-treated rats. Relative vagina weights for the rats treated with the acid fraction alone were higher than with either controls or with gum guggul-treated rats (0.70 mg/g, a significant increase (p < 0.05) (Amma et al., 1978).

The reproductive tissues in the adult female albino rats were analyzed for levels of glycogen, sialic acid, and proteins. The glycogen levels in the ovaries, uterus, and cervix increased in rats treated with the oleoresin and its acid fraction. Gum guggul increased sialic acid levels in these three organs; the acid fraction increased its levels in the ovaries and uterus but not in the cervix. These findings were significant (p < 0.01 to p < 0.001). Higher protein levels in treated rats were not significant (Amma et al., 1978).

## 9.3 Carcinogenicity

No data were available.

#### 9.4 Initiation/Promotion Studies

No data were available.

#### 9.5 Anticarcinogenicity

No data were available.

#### 9.6 Genotoxicity

No data were available.

#### 9.7 Cogenotoxicity

No data were available.

#### 9.8 Antigenotoxicity

No data were available.

#### 9.9 Immunotoxicity

No data were available.

#### 9.10 Other Data

##### Thyroid Effects

Gugulipid<sup>®</sup> increased thyroid hormone production, activity which may be responsible for its lipid lowering properties (Sabinsa Corp., 2000). Both thyroid-stimulating immunoglobulin substance (LATS) and petroleum ether extract of gum guggul increased synthesis and release of thyroid hormone from mice thyroid gland *in vitro* (Singh and Prasad, 1998).

##### Cholesterol-Lowering Effects

In clinical studies of guggul for reducing cholesterol, individuals receiving guggul (100 mg of guggulsterones daily) after following a healthy diet for 12 weeks showed a 11.7% decrease in total cholesterol. There was a 12.7% decrease in low-density lipoprotein (LDL) and a 12% decrease in triglycerides (Singh et al., 1994). In another study, 40 heart disease patients given guggulipid (4.5 g) twice daily experienced a 21.75% decrease in blood fats, which included LDL, very LDL (VLDL), and triglycerides, as well as a reduction in platelet stickiness. In addition, there was a 35% increase in high-density lipoprotein cholesterol (HDL-C) (LoweringCholesterol.net [Natural Pharmacy], 2004). In the first randomized controlled clinical trial of guggulipid done outside of India, however, standardized doses (1000 or 2000 mg, containing 2.5% guggulsterones) failed to decrease the levels of LDL-C in healthy adults with hyperlipidemia eating a typical Western diet. Instead, levels were elevated by 4 and 5% at the low and high doses, respectively. Furthermore, there were no significant changes in total cholesterol, HDL-C, triglycerides, or VLDL-C levels, and hypersensitivity rash was reported for six participants out of 67 patients (Szapary et al., 2003). In a recent study, *C. mukul* and guggulsterone were found to be effective antioxidants against LDL oxidation (Wang et al., 2004).

Liver membrane treated with guggulsterone contains increased amounts of a lipoprotein receptor that binds to particles of LDL (Singh and Kapoor, 1992). Gugulipid<sup>®</sup> inhibited liver cholesterol

biosynthesis and increased excretion of bile acids and cholesterol in the feces. It stimulated the binding activity of LDL receptors in the liver membrane, causing the rapid catabolism of LDL, which is responsible for its hypolipidemic activity (Central Drug Research Institute [India] studies [authors and years n.p.]; Devlin, 1997; Marks, 1990; Orten and Neuhaus, 1982; Schumm, 1988; all cited by Sabinsa Corp., 2000; Badmaev and Majeed, 2000).

Guggulsterone is a potent FXR antagonist both *in vitro* and *in vivo*, inhibiting expression of FXR agonist-induced genes (Urizar and Moore, 2003; Urizar et al., 2002; Wu et al., 2002). In HepG2 cells, it had no effect on FXR activity, but it did inhibit FXR activation by chenodeoxycholid acid, a potent bile acid agonist ligand. *In vivo*, guggulsterone decreased hepatic cholesterol levels in wild-type mice fed a high-cholesterol diet but had no effect in the FXR-null animals. The FXR is required for the cholesterol-lowering activity of guggulsterone (Urizar et al., 2002). In contrast, guggulsterone enhanced FXR agonist-induced transcription of bile salt export pump (BSEP), a major hepatic bile acid transporter, in cells and animals. In HepG2 cells, in the presence of an FXR agonist, guggulsterone enhanced BSEP expression by 400-500% of that induced by an FXR agonist alone. In rats, it also increased BSEP mRNA in a dose-dependent manner, lowering serum triglyceride and increasing serum HDL levels (Cui et al., 2003). Furthermore, guggulsterone activated the estrogen receptor alpha isoform, progesterone receptor, and pregnane X receptor, and activation of the pregnane X receptor induced the expression of CYP3A genes in both rodent and human hepatocytes, which causes herb-drug interactions, but inhibited the human CYP7A1 gene (Brobst et al., 2004; Owsley and Chiang, 2003).

#### Other Effects

Guggulsterones were comparable to cardioprotective drugs propranolol and nifedipine in protecting from myocardial necrosis induced by isoproterenol in male albino Charles-Foster rats (Chander et al., 2003; Kaul and Kapoor, 1989). Gugulipid<sup>®</sup> significantly increased the levels of catecholamine and the activity of dopamine  $\beta$ -hydroxylase in normal rabbits and decreased those in cholesterol-fed rabbits. Additionally, it helped increase catecholamine levels in hypercholesteremic rabbits (Central Drug Research Institute [India] studies [authors and years n.p.]; Devlin, 1997; Marks, 1990; Orten and Neuhaus, 1982; Schumm, 1988; all cited by Sabinsa Corp., 2000; Badmaev and Majeed, 2000). Gugulipid<sup>®</sup> increased the levels of norepinephrine, dopamine, and dopamine  $\beta$ -hydroxylase activity in the heart and brain tissues of rhesus monkeys in a dose-dependent manner (Srivastava et al., 1984; cited by Sabinsa Corp., 2000). In lipopolysaccharide (LPS)-activated murine macrophages J774.1 *in vitro*, E- and Z-guggulsterones were the most potent inhibitors of nitric oxide (NO) production, followed by myrrhanol A and myrrhanone A (Meselhy, 2003).

Bioactive constituents from gum guggul (*C. wightii*), identified as ferulates, showed significant cytotoxicity *in vitro*, decreasing cell viability in MCF-7 (breast) tumor cells, PC-3 (prostate) tumor cells, and in parental and transfected P388 cells (Zhu et al., 2001, 2002). The ferulates compounds have been used in compounds and methods for prevention and treatment of abnormal cell growth and proliferation of inflammation, neoplasia, and cardiovascular disease (Majeed et al., 2001).



## 10.0 Structure-Activity Relationships

No studies systematically investigating structure-activity relationships of guggulsterones were located. Compounds closely related to guggulsterones are other steroids, including cholesterol and steroid hormones; a discussion of the biological activities of these compounds is beyond the scope of this document.

## 11.0 Online Databases and Secondary References

### 11.1 Online Databases

#### Chemical Information System Files

SANSS (Structure and Nomenclature Search System)

TSCATS (Toxic Substances Control Act Test Submissions)

#### DIALOG Files

CEH (Chemical Economics Handbook)

DIODENES (DIODENES<sup>®</sup>—FDA Regulatory Updates)

#### National Library of Medicine Databases

EMIC and EMICBACK (Environmental Mutagen Information Center)

#### STN International Files

AGRICOLA	EMBASE	NTIS
BIOSIS	ESBIOBASE	PROMT
CA	HSDB	Registry
CABA	MEDLINE	RTECS
CAPLUS	NAPRALERT	TOXCENTER

TOXLINE includes the following subfiles:

Toxicity Bibliography	TOXBIB
International Labor Office	CIS
Hazardous Materials Technical Center	HMTC
Environmental Mutagen Information Center File	EMIC
Environmental Teratology Information Center File (continued after 1989 by DART)	ETIC
Toxicology Document and Data Depository	NTIS
Toxicological Research Projects	CRISP
NIOSH <sup>®</sup>	NIOSH
Pesticides Abstracts	PESTAB
Poisonous Plants Bibliography	PPBIB
Aneuploidy	ANEUPL
Epidemiology Information System	EPIDEM
Toxic Substances Control Act Test Submissions	TSCATS
Toxicological Aspects of Environmental Health	BIOSIS
International Pharmaceutical Abstracts	IPA
Federal Research in Progress	FEDRIP
Developmental and Reproductive Toxicology	DART

### Databases Available on the Internet

Code of Federal Regulations (CFR), National Archives and Records Administration

### In-House Databases

Current Contents on Diskette®

The Merck Index, 1996, on CD-ROM

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**Appendix A: Units and Abbreviations**

°C = degrees Celsius

µg/L = microgram(s) per liter

µg/m<sup>3</sup> = microgram(s) per cubic meter

µg/mL = microgram(s) per milliliter

µM = micromolar

bw = body weight

F = female(s)

FXR = farnesoid X receptor

g = gram(s)

g/mL = gram(s) per milliliter

h = hour(s)

HDL = high-density lipoprotein

HPLC = high performance liquid chromatography

i.p. = intraperitoneal(ly)

kg = kilogram(s)

L = liter(s)

lb = pound(s)

LC = liquid chromatography

LD<sub>50</sub> = lethal dose for 50% of test animals

LDL = low-density lipoprotein

M = male(s)

mg/kg = milligram(s) per kilogram

mg/m<sup>3</sup> = milligram(s) per cubic meter

mg/mL = milligram(s) per milliliter

min = minute(s)

mL/kg = milliliter(s) per kilogram

mm = millimeter(s)

mM = millimolar

mmol = millimole(s)

mmol/kg = millimoles per kilogram

mol = mole(s)

mol. wt. = molecular weight

MS = mass spectrometry

NIEHS = National Institute of Environmental Health Sciences

nm = nanometer(s)

n.p. = not provided

ppm = parts per million

TLC = thin layer chromatography

## Appendix B: Search Description for Gum Guggul

The major search was done July 2, 2002, in the usual biomedical databases: MEDLINE, CANCERLIT, AGRICOLA, NIOSHTIC, CABA, IPA, BIOTECHNO, EMBASE, ESBIODBASE, BIOSIS, TOXCENTER, LIFESCI, and NAPRALERT. Before duplicate removal, there were 377 hits for guggul?, 122 hits for gugul?, nine for gugal?, and 316 for *C. mukul*. Twelve CAS RNs for the sterones, sterols, tetrols, and gugalipid were combined to give 100 records. Only three were not in the set using the names. Since gugal or guggal are mostly used for the resin from *Boswellia serrata*, the six unique records from the gugal? search were examined separately.

Combining the answer sets gave 619 records, which were reduced to 350 upon duplicate removal (number of records per database after duplicate removal in parentheses): MEDLINE (76), CANCERLIT (0), AGRICOLA (29), NIOSHTIC (0), CABA (52), IPA (11), BIOTECHNO (1), EMBASE (42), ESBIODBASE (3), BIOSIS (55), TOXCENTER (9), LIFESCI (0), and NAPRALERT (72).

On July 3, 2002, the same databases were searched using variant names gugal, juggulu, gugglu? and guggal? discovered in the records previously retrieved plus two other *C. mukul* constituents, mukulol and allylcembrol. The 133 records were reduced to 92 upon duplicate removal. Removing records already retrieved using guggul? OR gugul? gave a set of 104 records, which reduced to 75 upon duplicate removal: MEDLINE (12), AGRICOLA (4), CABA (16), IPA (1), EMBASE (4), ESBIODBASE (2), BIOSIS (15), LIFESCIENCE (1), NAPRALERT (20). Most of the resulting new hits were on "Salai guggal" from *B. serrata*.

Use of the variant spellings for guggul retrieved only 15 TOXLINE records on July 2, 2000, which generally duplicated retrievals in the other databases. Other fee-based searches were done in PROMT, SANSS, and RTECS. Extensive Internet searches were done using variant names for guggul and for the source plant. The search engine was generally Google. Some searches were also done on FindArticles.com.

### Guggul Update Search on STN International April 21, 2004

Files MEDLINE, CANCERLIT, NIOSHTIC, CABA, AGRICOLA, EMBASE, ESBIODBASE, BIOTECHNO, IPA, BIOSIS, TOXCENTER, NTIS, NAPRALERT, DIOGENES, and CAPLUS were searched simultaneously. The search statement "guggul? or gugul? OR commiphora(w)mukul" was limited to publications in 2002-2004. A similar strategy was used on PubMed to retrieve the MEDLINE abstracts.

#### Online history:

```
L1          735) SEA GUGUL? OR GUGGUL?
L2          488) SEA COMMIPHORA(W) MUKUL
L3          949) SEA L1 OR L2
L4          210) SEA L3 AND (2002-2004)/PY
L5          102) DUP REM L4 (108 DUPLICATES REMOVED)
L6          102 SOR L5 1-102 TI
```



Number of unique records per database after online and manual duplicate removal (**boldface**) and number of records per database selected for printing in full (*italics*; MEDLINE records already available from PubMed):

102 DUP REM L4 (108 DUPLICATES REMOVED)		
ANSWERS '1-25' FROM FILE MEDLINE	<b>25</b>	
ANSWERS '26-35' FROM FILE CABA	<b>9</b>	<i>2</i>
ANSWER '36' FROM FILE AGRICOLA	<b>0</b>	<i>0</i>
ANSWERS '37-54' FROM FILE EMBASE	<b>16</b>	<i>4</i>
ANSWER '55' FROM FILE ESBIODBASE	<b>1</b>	<i>0</i>
ANSWERS '56-57' FROM FILE IPA	<b>2</b>	<i>1</i>
ANSWERS '58-66' FROM FILE BIOSIS	<b>8</b>	<i>2</i>
ANSWERS '67-68' FROM FILE TOXCENTER	<b>1</b>	<i>0</i>
ANSWERS '69-74' FROM FILE NAPRALERT	<b>4</b>	<i>0</i>
ANSWER '75' FROM FILE DIOGENES	<b>1</b>	<i>1</i>
ANSWERS '76-102' FROM FILE CAPLUS	<b>26</b>	<i>11</i>