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Chemistry and pharmacological profile of *guggul*—A review

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Oleo gum resin secreted by *Commiphora wightii* (A.) Bhandari known as guggul, one of the most reputed drugs in Ayurveda has been extensively studied for its medicinal applications. The plant contains essential oil, mainly consisting of myrecene, dimyrecene and polymyrecene, Z-gugglusterone, E-gugglusterone, gugglusterone-I, gugglusterone-II, and gugglusterone-III. These isolates have been found useful in curing many diseases like rheumatism, arthritis, hyperlipidemia, obesity, inflammation, atherosclerosis, wrinkles, acne and other diseases. The review discusses chemistry and pharmacological activity of *guggul*.

Key Words: Chemistry, *Guggul*, Guggulipid, Gugglusterone, Pharmacology, Obesity, Oleo gum resin, Review, Rheumatism

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The preference for herbal drugs is ever increasing. These drugs produce negligible side effects and enhance its vigour & strength. The present review describes the ingredients derived from *Commiphora wightii* and their novel use in addressing the disease and health problems. *Guggul* or *Gugglu* is an oleo gum resin obtained from plant source with *Commiphora wightii* (A.) Bhandari belonging to family Burseraceae[1]. The plant contains essential oil, mainly consisting of myrecene, dimyrecene and polymyrecene, Z-gugglusterone, E-gugglusterone, gugglusterone-I, gugglusterone-II, and gugglusterone-III. These isolates have been found useful in curing many diseases like rheumatism, arthritis, hyper-lipidemia, obesity, inflammation, atherosclerosis, wrinkles, and acne. *Gugglu* earlier used to grow abundantly in the states of Karnataka, Gujarat and Rajasthan. The production from wild sources requires years of maturing before the plant to start secreting the resin. Gum resin resides in the ducts located in the soft bark of the tree, is obtained through tapping. Circular incisions are made on the main stem, not beyond the thickness of the bark of stem. From these incisions, a pale yellow, aromatic fluid exudes that quickly solidifies to form a golden brown or reddish brown agglomerate of tears or stalactic pieces. Process for the isolation of Z- and E-gugglusterone from the ariel branches of *Commiphora wightii* (*guggul*) is also available[2]. The dried resin has a bitter aromatic taste and a balsamic odour.

Traditional uses

Gugulipid has a long history of use in Ayurveda. The *Atharva Veda* (Fig. 1) is the earliest reference for its medicinal and therapeutic properties[3]. Detailed descriptions regarding its actions, uses and indications as well as the varieties of guggul have been described in numerous Ayurvedic treatises including *Charaka Samhita* (1000 BC), *Sushruta Samhita* (600 BC and *Vagbhata* (7th century AD). In addition, various medical lexicons were written between the 12th and 14th centuries AD. It is responsible for reducing fat, indicated for healing bone fracture to inflammation,

अथर्ववेदः कां. 19 सू 38

न तं यक्ष्मा अरुन्धते नैने शपथो अश्नुते।
यं भेषजस्य गुल्गुलोः सुरभिर्गन्धो अश्नुते ॥ 1॥
विष्वेञ्चस्तस्माद् यक्ष्मो मृगा अश्वो इवेरते
यद् गुल्गुलु सैन्धवं यद् वाप्यार्सि समृद्धियम ॥ 2॥
उभयोरग्रथं नामास्मा अरिष्टतातये ॥ 3॥

Fig. 1—Original Sanskrit verse from *Atharva Veda* that refers to the medicinal values of guggul

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arthritis, atherosclerosis, obesity, and hyperlipidemia[4]. Traditionally, *guggul* is given in the form of *Yog*, wherein *guggul* is mixed with other drugs along with castor oil or Indian clarified butter. The *Yog* could also be prepared by cooking the *guggul* with water, and other herbal drug powder. Popular Ayurvedic formulations containing *guggul* are: *Yograj Gugguluvati, Pachamrit loh guggulu, Kaishore gugguluvayi, Triphla gugglu,* and *Sinhaguggluvati*[5].

Phytochemistry

The oleoresin contains 0.37% essential oil, containing mainly myrecene, dimyrecene and polymyrecene. Solvent extraction, hydrolysis and column chromatography over silica gel of *guggul* resin identifies a number of compounds such as diterpene hydrocarbon, a diterpene alcohol, Z-guggulsterone, E-guggulsterone, guggulsterol-I guggulsterol-II & guggulsterol-III, cholesterol, sesamin and camphorene[6-12]. Solvent extraction using ethyl acetate separates the oleo-gum-resin into two parts, i.e. gum and resin (Fig. 2). The gum insoluble in ethyl acetate is chemically characterized as carbohydrate. The resinous portion dissolves in ethyl acetate and possesses both anti-inflammatory and lipid-lowering properties. It was further separated into acidic, basic, and neutral fraction that comprised approximately 4%w/v, 0.3%w/v, and 95%w/v of the ethylacetate soluble resin, respectively. The basic fraction is devoid of any activity, while acidic fraction possesses significant anti-inflammatory activity; the neutral fraction possesses lipid-lowering activity. The lipid-lowering activity is found in ketonic fraction, which is a complex mixture of chemical compounds belonging to steroids (Fig. 3).

Pharmacological Activity

Hyperlipidemia, also known as hyperlipoproteinemia or high cholesterol, is a disorder characterized by abnormally high concentrations of lipids (fats) in the blood that are correlated with the development of atherosclerosis, the underlying cause of coronary heart disease (CHD) and stroke. Hyperlipidemia is caused by abnormal lipid and lipoprotein metabolism. *Commiphora mukul* Engl. has long been used for the treatment for hyperlipidaemiain the form of a gum resin, guggulipid[13]. The lipid lowering activity of *guggul* was first reported and an active lipid lowering agent, a

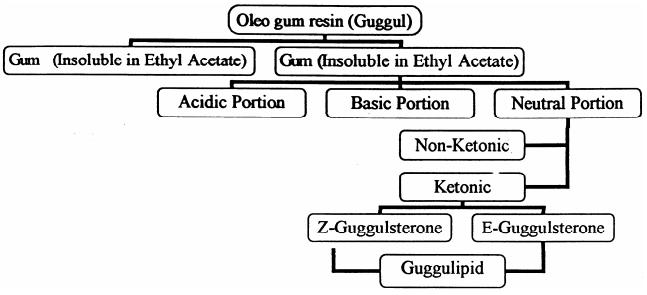

Fig. 2—Separation of the Chemical Constituents of Guggul

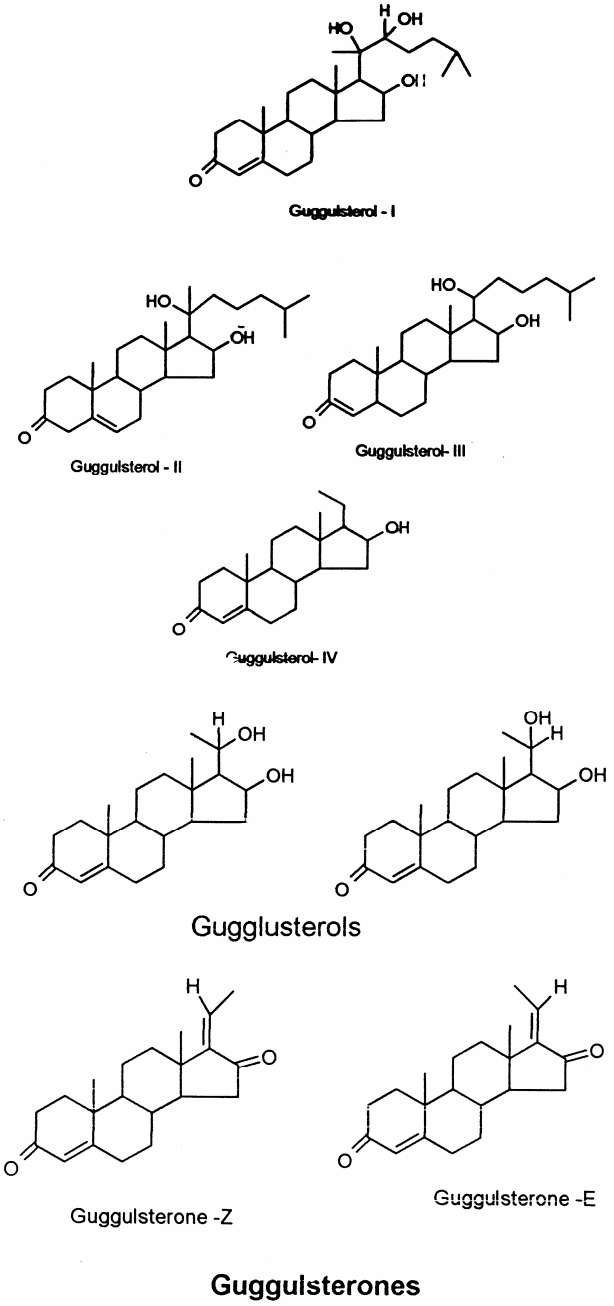

Fig. 3—Structures of Guggulsterone

standardized fraction from ethyl acetate extract of *guggul* gum containing guggulsterone mixed with some other steroids, diterpene, esters and higher alcohols named as guggulipid was developed[14–16]. The hypolipidemic activity could be attributed to several mechanisms including inhibition of cholesterol biosynthesis and enhancement in cholesterol degradation and/ or excretion. *Guggul* compounds are antagonist ligands for bile acid receptor called farnesoid X receptor (FXR), which is an important regulator of cholesterol homeostasis[17]. It is likely that this effect accounts for the hypolipidemic activity of these phytosteroids. Guggulsterone have the capability of inhibiting oxidative modification of LDL.

Guggul markedly inhibits liver cholesterol biosynthesis[18]. This causes interference in lipoprotein formation and lipid turnover (Fig. 4). *Guggul* increases fecal excretion of bile acids (cholic and deoxycholic acids) & cholesterol and lowers intestinal absorption of fat and cholesterol[19]. *Guggul* stimulates the LDL receptor binding activity in hepatocytes and enhances its catabolism. It also inhibits oxidative modification of LDL due to its constituent gugglusterone[20]. Protective and antioxidant properties of *Guggul* also play a part in its lipid lowering activity and reduce lipid peroxides, xanthine oxidase, and increases superoxide dismutase[21]. *Guggul* has been found to have the capacity to enhance production of thyroxin (T4), triidothyronine (T3) (thermogenic activity), which also account for its lipid lowering activity[22]. Thyroid hormones increase metabolism of carbohydrates, enhance protein synthesis, and stimulate use and breakdown of lipids. A keto steroid, 2-gugglusterone was found to counteract the thyroid suppressant activity of carbimazole[23]. Preclinical studies have reported *guggul's* effect on biogenic amines, catecholamine and dopamine liable to attribute to its lipid lowering properties[24]. It has been noted for helping the hypercholesterolemic β rabbits to recover the decrease in catecholamine synthesis. *Guggul* significantly lowers serum triglycerides and cholesterol as well as LDL and VLDL cholesterol[25].

Atherosclerosis or hardening of the arteries results from build up of cholesterol on the interior blood vessel walls. It is the LDL that leads to this build-up

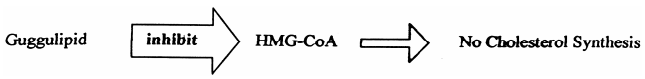

Fig. 4—Blockade of Cholesterol Synthesis

and HDL takes the cholesterol back to the liver. Guggulipids have been found having capacity to lower the VLDL, LDL and triglycerides with simultaneously raising the HDL revealing that *Guggul* is useful in providing protection against atherosclerosis[26]. The effect is proclaimed to resulting out from the *Guggul's* action on liver and thyroid, wherein, thyroid is stimulated to increase body's metabolic rate and the liver is stimulated to metabolize LDL cholesterol. *Guggul* being antioxidant helps stop the oxidation of cholesterol and subsequent hardening of the arteries. Moreover, g*uggul* has also been shown to reduce the stickiness of platelet, another effect that lowers the risk of coronary artery disease[27].

Obesity is the most prevalent problem characterized by the deposit of fat cells and influenced by caloric intake, metabolism and genetic predisposition. *Guggul* increases thyroid stimulation, improves digestion, and accelerates metabolism to pass the food along the GIT tract quickly[28]. It also prevents the transformation of undigested carbohydrates into triglycerides and reduces cholesterol in blood by metabolizing the existing fatty acid. *Guggul* is considered to be a well-established fat burning agent. *Shuddha guggul* and *Ayurslim* are the example of proprietary antiobesity products. Dietary supplements containing *guggul* patented in United States claim reduction in the build-up of body fat other than associated with medical problems of the endocrine or neuroendocrine system[29]. Lipophilic extract, when combined with a mixture of phosphate salts demonstrates outstanding weight loss, fat loss and mood elevating properties[30]. A combination of *guggul*, phosphate salts, hydroxycitrate and tyrosine, coupled with exercise has been found in double blind trial to improve the mood with a tendency of weight loss in overweight adults[31]. *Guggul* has antioxidant effect because of its active constituent gugglusterone, which inhibits the generation of oxygen free radical[32, 33]. Several studies have revealed cardioprotective abilities of *guggul* including increased fibrinolytic activity and decreased the platelet adhesive index[34-39]. Guggulipid is effective against myocardial infarction and known to cause thyrogenic effect. Guggulsterone inhibits platelets aggregation and provide protection against myocardial ischemia induced by isoproterenol.

With a topical administration of a preparation containing guggulsterone-enriched fraction of *guggul*, benign prostatic hypertrophy with symptoms of dysuria, diurnal & nocturnal pollakiuria and urinary

retention have been treated[40]. *Guggulu* has been extensively studied in inflammation and pain in bones, joints, muscles and related connective tissues[41–44]. The aqueous extract significantly inhibited both the maximal edema response and the total edema response during 6 hrs of carrageenan-induced rat paw edema. Fraction containing gum-*guggul* (acidic fraction of ethyl acetate extract) in experimental arthritis decreased the thickness of the joint swelling during the course of drug treatment[42]. Myrrhanol A, a new triterpene isolated from *guggul* displayed a potent anti-inflammatory effect on exudative pouch fluid, angiogenesis, and granuloma weights in adjuvant-induced air-pouch granuloma of mice[43]. Activation of NF-kappa B has been closely linked with inflammatory diseases affected by guggulsterone[45]. Guggulsterone suppressed DNA binding of NF-kappa B induced by tumor necrosis factor (TNF), phorbol ester, okadaic acid, cigarette smoke condensate, hydrogen peroxide, and interleukin-1. NF-kappa B activation was not cell type-specific, because both epithelial and leukemia cells were inhibited. Guggulsterone also suppressed constitutive NF-kappa B activation expressed in most tumour cells. Through inhibition of IkappaB kinase activation, this steroid blocked Ikappa Balpha phosphorylation and degradation, thus suppressing p65 phosphorylation and nuclear translocation. NF-kappa B-dependent reporter gene transcription induced by TNF, TNFR1, TRADD, TRAF2, NIK, and IKK was also blocked by guggulsterone but without affecting p65-mediated gene transcription. In addition, guggulsterone decreased the expression of gene products involved in anti-apoptosis, proliferation and metastasis, this correlated with enhancement of apoptosis induced by TNF and chemotherapeutic agents. Guggulsterone was found to suppress NF-kappa B regulated gene products, has been attributed for its anti-inflammatory activities[45].

The essential oil, chloroform extract and 7 sesquiterpenoids compounds isolated from the oleo-gum-resin of *guggul* showed a wide range of inhibiting activity against both Gram (+) and Gram (-) bacteria[46]. *Guggul* is one among many plants known for immunomodulatory properties[47]. It provides effective support to immune functions ensuring an optimal response. The best level of resistance is indicated by normalization of leukocyte function through improved phagocytosis. The defense mechanism of the body is enhanced through increased white blood cell production. Fraction containing guggulsterones have been found to be particularly useful in the treatment of allergic dermatitis. Guggulipid and alcoholic fractions thereof possess a rare quality of providing a dual benefit for skin care, i.e. antisebum and antioxidant activity. The compositions provide control of sebum secretion from sebocytes, improved oil control and improved skin feel, prevent shine and stickiness, protect skin from damaging free radical activity, which results in reduced appearance of wrinkles and aged skin, improved skin colour, treatment of photo aged skin, improvement in skin's radiance, healthy and youthful appearance of the skin[45].

Skin is subject to abuse by many extrinsic (environmental) factors as well as intrinsic (aging) factors. *Guggul* has ability of promoting synthesis of intracellular triglycerides or lowering degradation of intracellular triglycerides, and thereby, reducing depth of large and small wrinkles and giving the skin a smooth appearance. The extracts showed stimulating activity on lipogenesis inside the fibroblasts, leading to better contact with the extra cellular protein network, toning the dermis and thereby reducing the depth of wrinkles[49]. Anti-inflammatory activity of guggulipid and a guggulsterone-enriched fraction have been reported[40,50]. An appetite suppressant toothpaste formulation, containing Guarana, green tea, myrrh, guggulipid and black current seed oil suppresses the users' appetite while promoting intraoral cleanliness. The toothpaste composition includes toothpaste base ingredients; and at least one of appetite suppressant and appetite depressant herbs[51]. Molecules derived from guggulipid extract are reported to be capable of reducing insulin resistance in humans[52]. Guggulipid extract has also been reported to activate PPAR gamma receptors. PPAR gamma is a known member of the peroxisome proliferator activated receptor (PPAR) subset of the nuclear hormone receptor superfamily. PPAR gamma has been characterized as an important regulator of lipid metabolism. PPAR gamma is suggested as playing a role in insulin sensitivity and other biological activities including effects on inflammation, cancer, cognition and cellular differentiation. *Guggul* could function as a drug carrier or excipient[53].

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