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Guggul : An Excellent Herbal Panacea

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ABSTRACT

Guggul, an oleo gum-resin, is a plant exudate of family Burseraceae. In India it is mainly produced by four species i.e. *Commiphora mukul* Engl., *Commiphora wightii* (Arnott.) Bhand., *Commiphora berryi* and *Commiphora agallocha*. Regionally, it is known by different names also. The use of guggul for a wide variety of diseased conditions, including atherosclerosis, hypercholesterolemia, rheumatism, obesity, respiratory diseases, liver disorders, digestive problems, and menstrual irregularities, finds mention in Ayurveda, the ancient Indian system of medicine. Guggul significantly lowers serum triglycerides and cholesterol as well as low-density lipoproteins (LDL or β-lipoproteins) i.e. the bad cholesterol. It elevates the beneficial high-density cholesterol (HDL or α-lipoproteins) i.e. good cholesterol, prevents blood platelet aggregation and breaks up already formed blood clots. Guggul of *Commiphora mukul* Engl./ *Commiphora wightii* (Arnott.) Bhand., on fractionation with moderately non-polar organic solvent and subsequent acid-base fractionations, yield ketonic fractions of two isomers of E- & Z-guggulsterone. Pharmacological studies have revealed that the pure guggulsterone isomers have a pronounced hypolipidemic activity. Even though, the cumulative data from *in vitro*, pre-clinical and clinical studies sufficiently support the therapeutic claims of guggul described in ancient Ayurveda, both larger clinical and longer therapeutical studies are required to be conducted for further strengthening and consolidating such claims. No wonder, if, in near future, Guggul turns out to be the possible panacea for most of the serious chronic ailments presently afflicting the human race.

INTRODUCTION

Guggul, an oleo gum-resin, is a plant exudate of family Burseraceae. Out of 185 existing species of genus *Commiphora* (Family: Burseraceae), guggul is produced in India only by four species i.e. *Commiphora mukul* Engl., *Commiphora wightii* (Arnott.) Bhand., *Commiphora berryi* and *Commiphora agallocha* [1]. Out of these four species, *Commiphora mukul* Engl. and *Commiphora wightii* (Arnott.) Bhand. are good producers of guggul whereas *Commiphora berryi* is usually used as a hedge plant all over South India and regionally known as Mulkiluvai. All other species are found in Africa, Saudi Arabia and their adjoining countries. It is a widely adapted plant, well-distributed in arid regions and propagated both by vegetation and seeds. In India, the main commercial sources of guggul (*Commiphora mukul* Engl./*Commiphora wightii* (Arnott.) Bhand.) are Rajasthan, Gujarat, Madhya Pradesh and Karnataka [2]. Regionally, it is known by different names i.e. gulgulu, guggalu in Malyalam, gukkal, Maishakshi in Tamil, guggal in Telugu, guggul in Bangla, Indian gugguru in Gujarati, guggal in Hindi and Indian Bedellium in English. The use of guggul for a wide variety of diseased-conditions, including atherosclerosis, hypercholesterolemia, rheumatism, obesity, respiratory diseases, liver disorders, digestive problems, and menstrual irregularities, finds mention in Ayurveda, the ancient Indian system of medicine [3]. Even though, the cumulative data from *in vitro*, pre-clinical and clinical studies sufficiently support the therapeutic claims of guggul (*Commiphora mukul* Engl./*Commiphora wightii* (Arnott.) Bhand.) described in ancient Ayurveda, both larger clinical and longer therapeutical studies are required to be conducted for further strengthening and consolidating such claims. Presently, no data on bioavailability, metabolism and pharmacokinetics of guggulsterone in animal models or humans are available. The knowledge of these basic parameters is extremely essential for proper evaluation and appreciation of clinical findings on guggul or guggulsterone. In such a scenario, comprehensive studies for accurate determination of the cumulative effects of these variables on the efficacy of guggul or guggulsterone in the field of therapeutics are eminently necessary [4].

Historical Background

The earliest reference of medicinal and therapeutic properties of guggul (*Commiphora mukul* Engl./*Commiphora wightii* (Arnott.) Bhand.) is in Atharva Veda. Detailed account of guggul as a drug is given in the treatises of of Charaka (1000 B.C.), Sushruta (600 B.C.), Vagbhata (17th century A.D.) and various Nighantus written in India between 12th and 14th centuries[5-6]. In fact, the herb is mentioned as early as from 3000 to 10,000 years ago in the Vedas, the holy scriptures of India, for treating various human ailments [7]. An Indian medical researcher, G.V. Satyavati was the first who introduced guggul to the scientific world in 1966 [8]. Her studies on the effects of guggul were mainly based on rabbits and the malady resembled the description of atherosclerosis in Ayurved. Later in 1986, it was approved for marketing as a hypolipidemic drug in India with proven safety and efficacy [9-10].

However, in Western medical literature it was introduced only in mid 1990s making it a widely known remedy for treatment / prevention of hypercholesterole-mia and related cardiovascular diseases [11].

Tapping & Collection

The traditional tapping methods used for gum-resins by way of blazing, peeling or making deep cuts on the bole are not only unscientific and unproductive but also brutal and destructive. Due to wasteful and injurious tapping-techniques and over-exploitation, the natural population of this small tree of the semi-arid regions of India has depleted fast. There is an urgent need to develop a scientific and sustainable tapping method to increase the yield and ensure the survival of the tapped tree. Presently, an improved tapping-technique using 'Mitchie Golledge knife' coupled with ethephon (2-chloroethyl phosphonic acid), a plant growth regulator, can enhance guggul production by about 22 times and help in rapid healing of the wound. April and May are peak months for guggul tapping as established by localization of resins using epifluorescence microscopy [12]. A healthy guggul tree yields about 700-900 gm of resin [10,13].

The tapping and collection process itself leads to variable quality and also differs according to locality, season, size of the tree and surface of the wound exposed. Some pieces of resin have bits of bark and dirt adhering to them and this remains the case even after cleaning and grading. Once it has been collected, the main reasons for quality deterioration of the resin are its repeated handling in passing from the collector to the exporter, and the conditions in which it is stored at the various points in the marketing chain. At high ambient temperatures, loss of valuable volatile essential oil results in sticking and agglomeration into irregular masses. The good quality resin is slightly sticky on breaking, as it contains high oil content.

Impending Threat of Extinction

Over past many centuries, different communities around the world have developed their own systems to use medicinal plants. Some of these systems may be difficult to understand but all-out attempts have been on to cure the illness and sufferings and to make the life more comfortable. Ayurved or Indian system of medicine is one such attempt to improve and enhance the quality of life and has been in use since thousands of years to produce herbal medicines. Now-a-days, it is a very well-established fact that herbal medicines are more suitable to human body than the isolated chemical formulations. Unfortunately, many valuable plants are being lost at an alarmingly disturbing rate. With the rapid depletion of forests, impairing the availability of raw material from plants to developing and designing herbal formulations, the situation has reached a very critical phase/juncture. With the disappearance of about 50% of the tropical forests, the treasure-house/repository of plants and animal-diversity has already been destroyed. Many valuable medicinal plants are practically on the verge of extinction [14-15].

The guggul species too are under threat and have become an endangered species, mainly because of their over-exploitation for gum-resin and fire-wood, besides slower growth-rate of the plant, poor quality of seed-set and excessive tapping [16]. The collection and marketing of guggul is mostly done by the illiterates/tribals in India, being the primary source of their livelihood. There is always ample scope for adulteration and contamination in the whole process. Guggul gets often adulterated with the oleo gum-resin of *Boswellia serrata* and, sometimes with resin of pinus species. However, *Boswellia* gum can be identified by its whitish colour and powdery appearance. Pinus resin is stickier in nature and is generally in the form of paste at normal temperature. Heavy metals (such as mercury, arsenic and lead) contamination has also become a very critical problem. Market produce is stored under improper conditions for years which also cause contamination/adulteration by coming into contact with other materials, thereby adversely affecting the efficacy and sometimes even adding to the toxicity. Thus, the non-availability of adequate quality raw material free from adulterants at reasonable price has become a problem for industry, with the demand going up every year. Further, not so significant efforts have been made either by the Governments or the industry to seriously study the problem of supply and demand. We have to follow the GAPs (Good Agricultural Practices) to ensure the use of correct raw material and cover the entire life cycle including the harvesting, processing, transportation and storage.

Composition of Guggul

The oleo gum-resin comprises 0.6 % essential oils, 29.3 % gum, 61 % resin, 6.1 % moisture and 3.2 % insoluble material. The resins have a fragrant aroma because of the presence of essential oils and they account for their commercial importance. The essential oil of gum-resin is one of the most commonly used oils in aromatherapy, paints and varnishes. Pure oleo gum-resin collected in the optimum season hardens slowly, retaining its golden color and transparency. It varies in colour from transparent golden brown to dark brown or dark greenish-brown depending upon the season, mode of collection and impurities found therein.

The gum resin contains Z and E isomers of guggulsterone and its related guggulsterols: guggulsterol-I, guggulsterol-II, guggulsterol-III, guggulsterol-IV, guggulsterol-V and guggulsterol-VI. Major components of essential oil from gum resin are myrcene and dimyrcene [17-18].

Extraction & Applications of Guggul

The extraction of resin, with moderately non-polar organic solvent, yields gugulipid. However, the extraction yield depends very much on the quality of the raw material. The gugulipid after pH gradients fractionation results into a major neutral fraction possessing the bioactive components of the resin. The neutral fraction on further fractionation leads to the isolation of ketonic preparation containing two isomers E- & Z- guggulsterone (cis- and trans-4,17 (20)-pregnadiene-3,16-dione). A standardized extract of the guggulsterones offered by Sabinsa Corporation has the trade-mark name Gugulipid. Survey of literature reveals that the isomeric forms of guggulsterone in their pure state are effective in controlling high blood cholesterol and lipids [19-26]. With the identification of guggulsterone in gugulipid as bioactive constituent, its contents in gugulipid are used as a standard for quality-control [10]. Guggulsterone and gugulipid have been demonstrated to reduce risk of cardiac events and improve cardiac function in experimental and clinical studies [27-31]. Guggulsterone also inhibits platelet aggregation and provides protection from myocardial ischemia in rats [32-34]. The protective action of guggulsterone is due to antioxidant property because it inhibits the generation of oxygen free radicals.

Very recently Ojha *et al.* (2008) have reported the effect of *Commiphora mukul* extract on cardiac dysfunction and ventricular function in isoproterenol-induced myocardial infarction [35]. They have found that hydroalcoholic extract of *C. mukul* significantly improved the cardiac functions and prevented myocardial ischemic impairment manifested in the form of increased heart rate, decreased arterial pressure, increased left ventricular and diastolic pressure, and altered myocardial contractility indices.

Guggulsterone is also an effective antagonist of the bile acid receptor, Farnesoid X receptor (FXR), both in vitro and in vivo, and a ligand dependent transcription factor that regulates the expression of CYP 7A I gene are involved in maintaining cholesterol/bile acid homoeostasis through bile salt export pump. The FXR antagonism by guggulsterone has been proposed as a mechanism for its hypolipidemic effect [36-41]. With proven hypolipidemic efficacy in rats, guggulsterone was also used as a positive control to assess the hypolipidemic activity of other chemical compounds as well [42-43].

Ayurvedic Formulations of Guggul

Guggul is quite well-known as a yog-vahi rasyan which improves the action of other herbal medicines that are used in its combination. About 21 drugs in combination of guggul are used for curing several serious diseases e.g., Mahayogaraja guggulu & Amratadi guggulu for gout & rheumatism, Yogaraja guggulu for nervous system disorders, Kaishor guggulu for skin diseases, Gokshuradi guggulu for all kinds of urinary troubles including stones, Triphala guggulu for hemorrhoids (piles), Lakchhadri guggulu & Abha guggulu for joining fractured bones and as pain-killer, Simhanad guggulu, Shunthi guggulu, Kanchanar guggulu, guggulu thiktaka and Chandraprabha vati etc. are used for various ailments [44-46]. These formulations are Shashtriya formulations and used as such. Firms consuming guggul for preparation of Shashtriya Ayurvedic medicines are Dabur India Limited, Sri Baidyanath Ayurvedic Bhawan Limited, The Himalayan Drug Company, Zandu Pharmaceutical Works, Charak Pharmaceuticals, Vicco Laboratories, Diviya and others. Most of the Ayurvedic formulations are in the form of crude extracts which are a mixture of several ingredients and the active principles when isolated individually fail to give desired activity. This implies that the activity of the extract is the synergistic effect of its various components [15].

Traditional Uses of Guggul

Traditional (Indian) uses of *Commiphora mukul* Engl./ *Commiphora wightii* (Arnott.) Bhand. include as an anti-inflammatory, antispasmodic, carminative, hypoglycemic, diuretic, expectorant, anti-suppurative, thyroid-stimulant, anthelmintic, depurative, vulnerary, antiseptic, demulcent, aphrodisiac stimulant, liver tonic etc.

Gum guggul has also been used to treat hypercholesterolemia, hypertension, impotence, bronchitis, gingivitis, hay-fever, hysteria, inflammation, laryngitis, pharyngitis, pyorrhoea, rheumatism, sores, sore-throat, tonsillitis, tumors, wounds, bone-fractures, gout, scrofula, facial paralysis, leprosy, epilepsy, hemorrhoids and treatment of obesity etc. [47-55]. It is also used as incense, to make lacquers, varnishes, and ointments, as a fixative in perfumes, and in medicines.

Modern Applications of Guggul

Modern therapeutic uses of guggul (*Commiphora mukul* Engl./*Commiphora wightii* (Arnott.) Bhand.) cover nervous diseases, leprosy, muscle spasms, pyorrhoea, scrofula, skin disorders, spongy gums, hypertension, ulcerative pharyngitis, urinary disorders and cardiovascular diseases. It is also an anti-oxidant agent and reduces the stickiness of platelets. The Ayurvedic herb Inula racemosa, in combination with *Commiphora mukul*, is used to reduce chest pain and dysponea of angina [4, 56-62]. A web-page advertising sale of Gugulon states that it helps lower cholesterol, decrease high blood pressure, strengthen the structural system as also the immune system, to benefit the heart, and eliminate toxins.

Dosages & Side Effects

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 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 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.

Some side-effects have been associated with the crude gum guggul. These include skin rashes, irregular menstruation, diarrhoea, headache, mild nausea, and with very high doses, liver toxicity. Caution is recommended when using guggul in people with liver disease, inflammatory bowels, or diarrhoea. It should not be used during pregnancy and it can cause diarrhoea, hiccups, apprehension, and restlessness. Gum guggul interacts with several drugs.

Future Research Strategy——Suggestions

Traditional system of medicine continues to be widely practised for many reasons. Population-rise, inadequate supply of modern drugs, prohibitive cost of treatment, side-effects of several allopathic drugs and ever-increasing resistance to current drugs for infectious diseases have led to growing emphasis on the use of plant materials as a source of medicines for a wide variety of human ailments. However, a sustained supply of the source-materials often becomes difficult due to the factors like environmental variations, cultural practices, diverse geographical distribution, labour-cost, selection of the superior plant-stock and some exploitative practices by pharmaceutical industry. A fully integrated approach for the cultivation, conservation and preservation of important plant-species through plant molecular biology, plant-tissue culture, research on the rationale and methodology of Ayurvedic medical practices, isolation of active constituents and their development into new therapeutics, standardization and validation of known herbal medicines and other related aspects need to be continuously focussed upon.

Ever since the first therapeutic effect of guggul on animal model in 1966, numerous pre-clinical and clinical trials have been carried out. Differences in experimental designing, quality of methodology, sample-size, subject-population and statistical analysis result in certain inconsistencies in the therapeutic responses. As for the hypolipidemic activity, inconsistencies in individual responses to guggul treatment have also been observed during clinical trials especially in the subjects of different ethnic background, dietary-habits, obesity-status and severity of hyperlipidemia. Additional studies are urgently needed to determine the contributing effects of these variables on the efficacy of guggul or guggulsterone in the treatment of hypercholesterolemia.

Even though, the cumulative data from in vitro, pre-clinical and clinical studies sufficiently support the therapeutic claims of guggul described in ancient Ayurveda, both larger clinical and longer therapeutical studies are required to be conducted for further strengthening and consolidating such claims. Presently, no data on bioavailability, metabolism and pharmacokinetics of guggulsterone in animal models or humans are available. The knowledge of these basic parameters is extremely essential for proper evaluation and appreciation of clinical findings on guggul or guggulsterone. In such a scenario, comprehensive studies for accurate determination of the cumulative effects of these variables on the efficacy of guggul or guggulsterone in the field of therapeutics are eminently necessary.

No wonder, if, in near future, Guggul turns out to be the possible panacea for most of the serious chronic ailments presently afflicting the human race.

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