Plant Archives Vol. 19, Supplement 2, 2019 pp. 983-993 **e-ISSN:2581-6063 (online), ISSN:0972-5210**

NOVEL DRUG DELIVERY APPROACHES FOR GUGGUL

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Abstract

Guggul, an oleo gum resin released from *Commiphora weightii*, known for its immense applicability as hypolipidemic, anti-inflammatory, antioxidant, thyroid stimulatory agent, Platelet aggregation, fibrinolytic agent and the cytotoxic agent. Guggulsterones i.e. E & Z guggulsterones are the major constituents responsible for its pharmacological use. Traditionally, it's been used as antimalarial, antidysenteric, anticholesterolemic, antihypertensive, anti-rheumatic and indicated for many clinical conditions like dysmenorrhea, dyspepsia, impotence, leprosy, leucoderma, anemia etc. Nowadays, Guggul is available as the marketed formulation for curing numerous clinical conditions and is accessible in combination with various other ingredients. Though conventional dosage form shows the dominance as patient compliance and easy availability, yet it has found to pose the problems like dose fluctuation, peak-valley effect, non-adjustment of the administered drug, invasiveness etc. Guggul lacks its desired effect due to its low bioavailability and less water solubility. This makes it a partial or a deficient therapy for remedy of many signs and symptoms. Novel drug delivery system (NDDS), a new approach in the pharma sector has excluded many of drawbacks exhibited by conventional dosage forms. Some of the novel dosage forms of guggul has been formed like nanoparticles, nanovesicles, gugglusomes and proniosomal gel. But still, the novel formulations for guggul has its less outspread in the market. Guggul can be executed as a profitable drug using NDDS. There is a need to highlight the unidentified and unexplained facts about guggul so as to make it more efficacious and effective in terms of bioavailability and aqueous insolubility.

***Keywords*:** Guggul; guggulipids; herbal drugs; guggulsterones; Novel Drug Delivery Systems

Introduction

Commiphora weightii, commonly known as Indian bdellium tree, Guggul, Gugglu, Gugal belongs to family Burseraceae. Guggul word came from is *Gunjo vyadhegurdti rakshati* which means to relief from various diseases. It is a flowering plant consist of oleo gum resin released as exudates by tapping the branches and stems of *Commiphora weightii*. It is distributed from Northern India to Central Asia (Singh *et* al., 2015) and is found in arid areas of India, Bangladesh and Pakistan. Rajasthan, Gujarat, Assam, Madhya Pradesh, and Karnataka are the states where it is being grown up in a good amount (Kulloli and Kumar, 2013). Africa, Arabica is known as major regions yielding fragrant oleo gum resin (Poonia *et al*., 2014).

The generic name is derived from the Greek word, "Kommis" and "Phora" meaning gum bearer. It produces a yellowish resin in small ducts located throughout its bark and is allowed to flow out and harden. The suitable time period for tapping is from November to January and the resin is collected from May to June (Narasimhan and Patel, 2014) and the plant is a small, thorny shrub, unisexual, dioecious, bears oval-shaped fruits, pulpy in nature (Jasuja *et al*., 2012). Leaves are small, sessile, rhomboid-ovate, 1-3 leaflets, alternate, leathery, green on top and grayish below with irregular edges. Branches are spirally ascending, spinescent and young parts are glandular and pubescent. Flowers are small, ranges from pink to brown, polygamous in fascicles. Petals are 4-5 times as long as sepals, stamens are 8-10 bilobed (Poonia *et al*., 2014). Average 250-500g of drug-resin is collected from Guggul tree per year (Narasimhan and Patel, 2014).

Phytochemistry

The oleoresin consists of 0.37% essential oil, which mainly has myrcene, dimyrcene and polymyrcene. No. of different approaches such as solvent extraction, hydrolysis and column chromatography has been performed over a guggul resin. It has come up with a no. of compounds such as diterpene hydrocarbon, a diterpene alcohol, Z-guggulsterone, E-guggulsterone, Guggulsterone-1, Guggulsterone-2 and Guggulsterone-3, Cholesterol, Sesamin & Camphorene. Solvent extraction method identifies the two fractions: a 45% soluble & 55% insoluble fraction, using ethyl acetate as solvent. Guggulipid i.e. soluble fraction has been shown to have the bioactive compounds and insoluble part lacks the therapeutic effects. On further fractionation, soluble guggulipid leads to the formation of two small acid-base fractions (4% and 1% respectively) and a major neutral fraction (95%) which contains a maximum amount of bioactive compounds. Fractionation of neutral part results in isolation of non-ketonic 88% and small ketonic fraction 12%. Non-ketonic neutral part is found to be responsible for lowering lipid level and is due to the formation of two important steroids E and Z-guggulsterones from it. Acid fraction has anti-inflammatory activity and the base fraction is of no activity (Jain and Gupta, 2006, Deng, 2007, Tomer *et al.,* 2014, Kalshetti *et al*., 2014). Genus *Commiphora weightii* contains a big selection of phytochemicals answerable for numerous helpful medicine effects like:

Volatile oil and its terpenoidal constituents

Monoterpenoids: Essential oil obtained from the gum resin of *C. weightii* consists of myrcene [Fig. 1(A)], dimyrecene [Fig. 1(B)] and polymyrecene in major proportion. Other components such as d- limonene, eugenol, α-pinene, linalool, cineole, d-α-phellandrene, geraniol and some unknown compounds.

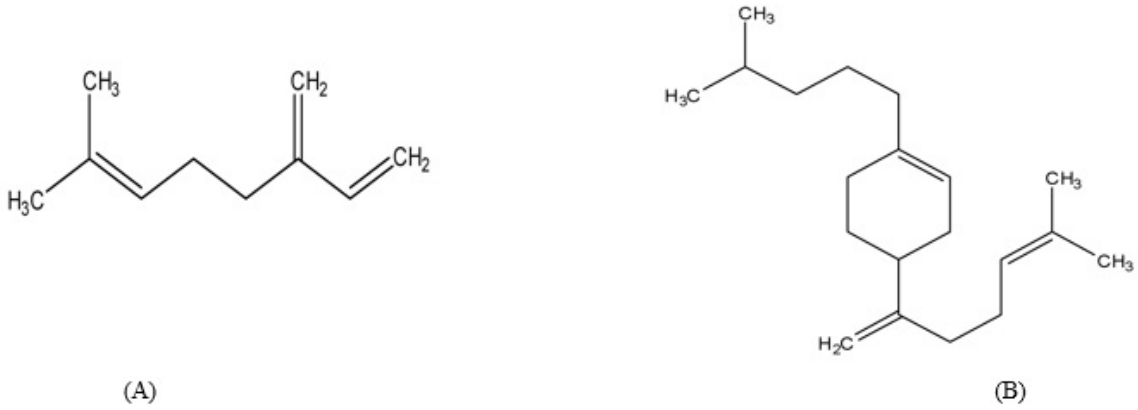

Fig. 1 : (A) Myrcene (B) Dimyrcene

Diterpenoids: Diterpenoid constituents include camphorene [Fig. 2(A)], cembrene-A [Fig. 2(B)], cembrene, and other cembrenoids. Cembrene-A is one of the most elementary tetraenes obtained from geranylgeranyl pyrophosphate by C-1 to C-14cyclization. Mukulol (allylcembrol) isolated from the aerial parts and from the resin Guggulu.

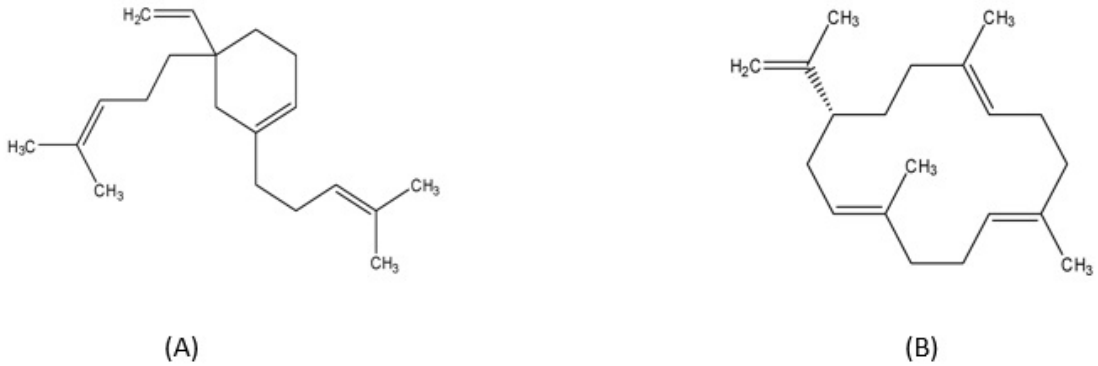

Fig. 2 : (A) camphorene (B) Cembrene A

Triterpenoids: myrrhanol A [Fig. 3(A)], B and C, myrrhanone A, myrrhanone B, myrrhanone A acetate, commipherol, commipherin, and octanordammaranetriperpenoid, epimansumbinol are polypodane type triterpenoids. Two more triterpenoidal components have been identified as mansumbinone [Fig. 3(B)] and mansumbinoic acid.

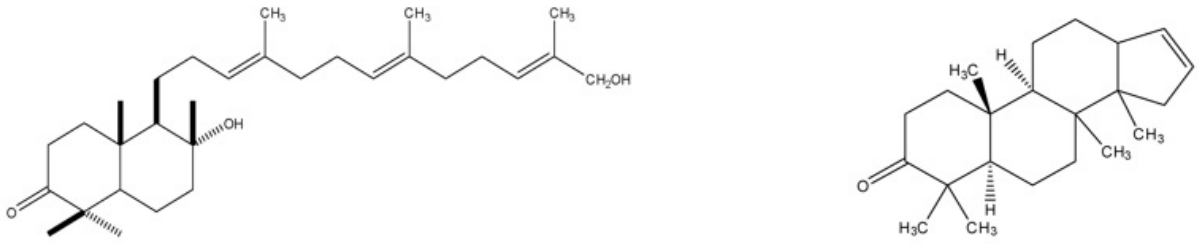

Fig. 3 : (A) Myrrhanol-A (B) Mansumbinone

Sesquiterpenes: Bicyclicsesquiterpene, cadinene [Fig. 4] is present in it.

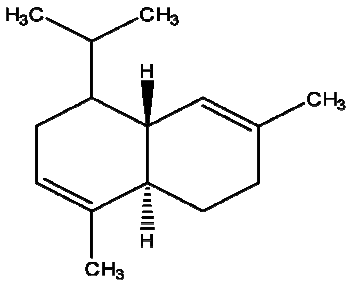

Fig. 4 : Cadinene

Steroids: *E*-guggulsterone [Fig. 5(A)], *Z*-guggulsterone [Fig. 5(B)], guggulsterol-1 [Fig. 5(C)], guggulsterol-II [Fig. 5(D)], guggulsterol-III [Fig. 5(E)], guggulsterol-IV, guggulsterol-V, and guggulsterol-VI are major steroidal constituents. Sigmasterol and Campesterol [Fig. 5(F)] are other phytosterols present commonly.

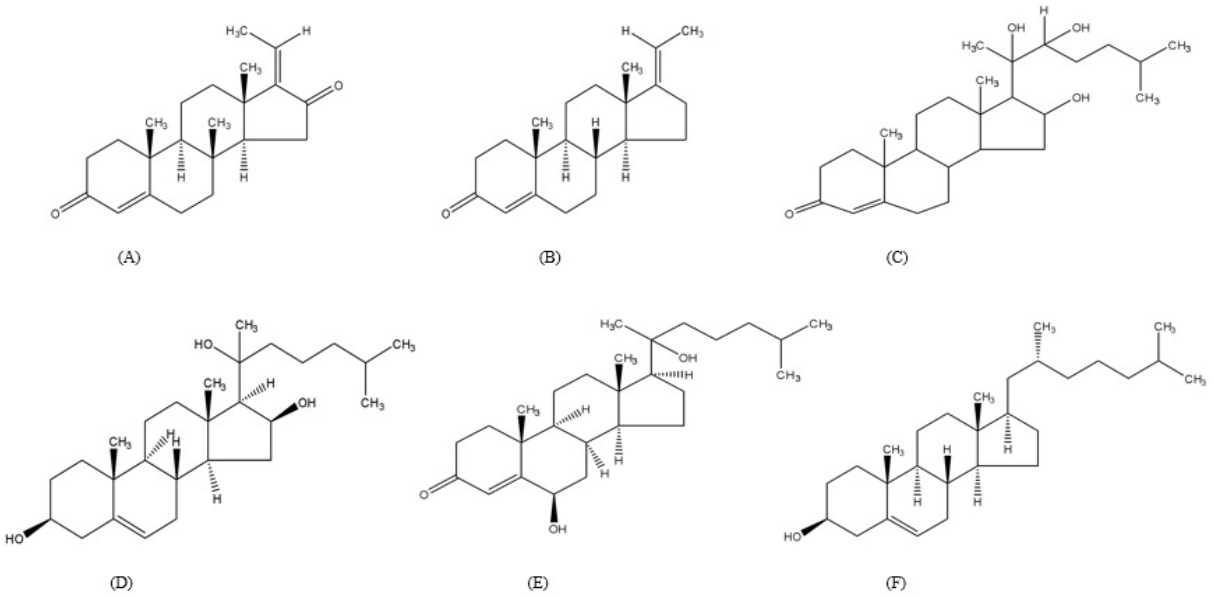

Fig.5 : (A) E- Guggulsterone (B) Z- Guggulsterone (C) Guggulsterol-1 (D) Guggulsterol (E) Guggulsterol-3 (F) Campesterol

Flavonoids: Flavonoidal components were separated on the column over silica gel using the ethanolic extract of the trunk of *C. weightii*. It provides new flavone compound Muscanone [Fig. 6. (B)] along with Naringenin[Fig. 6(A)]. Quercetin, quercetin-3-*O*-L-arabinose, quercetin-3-*O*-D-glucuronide, quercetin-3-*O*-D-galactoside, quercetin-3-*O*-L-rhamnoside, and pelargonidin-3, 5, di-*O*-glucoside are other flavonoid compound collected from flowers.

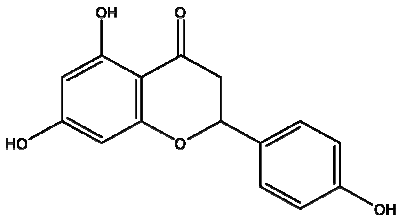

Fig. 6 : (A)Naringenin

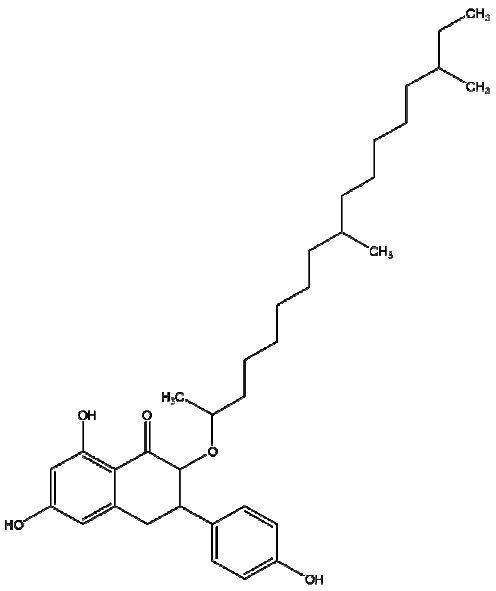

Fig. 6 : (B) Muscanone

Guggultetrols: are long-chain linear aliphatic tetrols with hydroxyl functions at C-1, C-2, C-3, and C-4 positions. A mixture of octadecan-1,2,3,4-tetrol, nonadecan-1,2,3,4-tetrol and eicosan-1,2,3,4-tetrol was isolated from saponified gum resin.

Lignans: Methanolic extract of guggul has come up with new lignin i.e.5, 5-tetrahydro-1, 3-furo[3,4-c]furan-1,4-diylbis[7-(methoxy)-1,3-benzodioxole].Sesamin [Fig. 7] and diayangambin are two lignin components reported from Guggul.

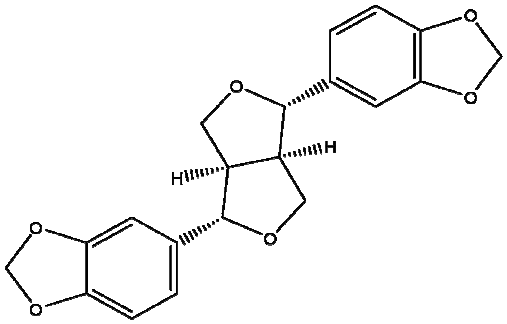

Fig. 7 : Sesamin

Sugars: L-arabinose[Fig. 8], D-galactose, L-fructose (traces), and 4-*O*-methyl-D-glucuronic acid are extracted from gum part of resin by hydrolysis.

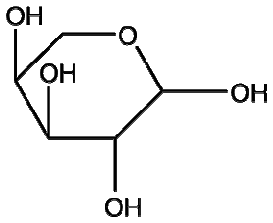

Fig. 8 : L-Arabinose

Traditional uses of Guggul

The list of ancient uses for guggul is kind of long. It has been used for numerous life-threatening diseases such as bone fracture, arthritis, cardiovascular diseases, and obesity (Tomer *et al*., 2014). Chemically, based on its active constituents, it has been tested to point out anticancerous, antimalarial, anthelmintic and antidysenteric properties (Sharma and Kumar, 2012). Besides this, it has its role in creating lacquer, incense sticks, varnishes and ointments (Rout *et al*., 2012). As we glance into the historical application, Santhal tribes used its bark for treating ulcers, it's bark and twig has been used up for curing pyorrhea, an organic compound for bronchial asthma and as mosquito repellent (Tomer *et al*., 2014). It has its great importance in alternative clinical conditions like dysmenorrhea, dyspepsia, endometriosis, hypercholesterolemia, hypertension, impotence, mania, rheumatism, sores, leprosy, leukoderma, anemia, occlusion etc. (Rout *et al*., 2012). It has conjointly been reported as antischistosomal, hepatoprotective, muscle relaxing, larvicidal, in diarrhea, cough and chest ailments (Kulloli and Kumar, 2012). Other traditional uses constitute its thyroid stimulant, antiseptic, astringent, carminative, diaphoretic, demulcent, emmenagogue, sedative, diuretic activity. It has been used extensively as combinations with other herbs and In India, "Yogarajguggulu", "Triphalaguggulu" for detoxifying, joint pain, obesity, arthritis, muscle aches, rheumatism and gout (Poonia *et al*., 2014, Tomer *et al*., 2014)

Pharmacological Activities

Research studies have proven its pharmacological properties and now several pieces of research are in continuation to find its other alternative uses for several diseases (Chaudhary, 2012). Recently, *Commiphora Mukul* evidenced to treat the osteoarthritis of the knee, hypolipoproteinemia. In combination with the herb *Inula racemosa*, is used up to cure chest pain and dyspnea of angina (Poonia *et al*., 2014). Plant sterols guggulsterones E and Z have been reported to exert effects on lipids (Chaudhary, 2012, Basavaraj *et al.,* 2016, Vaidya, 2006):

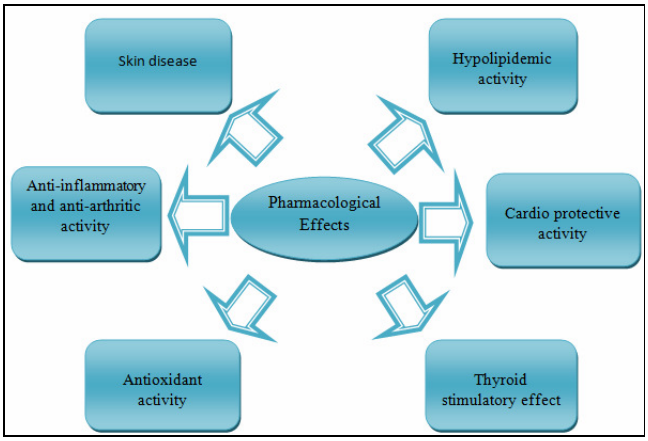

Fig. 9 : Depicts the various pharmacological activities of Guggul

Hypolipidemic activity

Satyavati *et al*. (1964-1966) conducted the first animal study to examine the result of guggul in lowering the serum cholesterol levels using hyperlipidemic rabbits. They demonstrated its hypolipidemic, anti-atherosclerotic nature, furthermore as established to cause weight loss. To grasp its mode of action for acting as hypolipidemic, Burnstein (1985) had investigated the effect of guggulsterone on lipid metabolism. Animals were found to own more important alteration in serum cholesterol, phospholipid, and triglycerides in conjunction with decreased free fatty acid levels in the body fluid, heart, and liver. Several mechanisms have been found to be included to regulate the high concentration of lipids (Jain and Gupta, 2006). Guggulipid blocked the biosynthesis of cholesterol by blocking the HMG-CoA that resulted in decreased in LDL (low-density lipoprotein) level and inflated HDL(high-density lipoprotein) level (Poonia *et al*., 2014), enhancement in cholesterol degradation and excretion. Farnesoid X receptor (FXR), which is a bile acid receptor, plays a role in cholesterol metabolism. Guggul compounds act as an antagonist to it (FXR) (Wu *et al*., 2017). High levels of lipid in systemic circulation can act as the causes of other diseases like atherosclerosis, coronary heart disease, and stroke. The natural resin of guggul has been used for the treatment of hyperlipidemia. Guggulsterone, a guggul constituent prevents the oxidative conversion of LDL (Wang *et al*., 2004). Reduction in lipid peroxides, xanthine oxidase has observed due to its protective and antioxidant nature (Derlin, 1997). Guggulipids, majorly have been found to lower VLDL (very low-density lipoprotein), LDL and triglycerides along with an increase in high density lipoprotein (HDL). HDL takes the cholesterol back to the liver, shows that guggul provides the protection against atherosclerosis (Singh *et al*., 1997).

Cardio protective activity

Platelet aggregation and fibrinolysis are the underlying elements for coronary heart disease. A purified combination of guggul has been mentioned to prevent the platelet aggregation with the aid of ADP, adrenaline, serotonin. Its activity is found to be equal to that of E and Z guggulsterones which resembles with clofibrate in inhibitory effects (Sarup *et al*., 2015; Mester *et al*., 1979). Poonia *et al.* (2014) suggested the cardio protective activity of gum guggul with *Inularacemo*sain remedy of ischemia and other metabolic changes (Deng, 2007). Guggul has shown the use in diminishing the stickiness of platelet, improving the coronary artery disease (Shishodiya and Aggarwal, 2004).

Thyroid stimulatory effect

Thyroid performs a critical role in regulating the metabolic rate and further stimulation of the liver to metabolize LDL cholesterol (Jain and Gupta, 2006). Several studies have reported that guggulsterone particularly Z-guggulsterone revived the thyroid activity and increase the uptake of iodine by the thyroid, activities of thyroid peroxidase and protease (Poonia *et al*., 2014). However, some clinical studies have shown no alteration with the usage of guggul (Rout *et al*., 2012).

Anti-inflammatory and antiarthritic activity

Guggul has found to reduce the thickness of joint swelling indicates its useful role in treating arthritis (Poonia *et al*., 2014). *Commiphora Mukul* has been recently found to be effective against osteoarthritis of the knee (Chaudhary, 2012). Guggul along with ibuprofen has been utilized to make gugglusomes and which proved to reveal synergistic action. Studies had reported that guggul can be used as a carrier for developing sustain release drugs (Singh *et al*., 1997). In some studies, Myrrhanol A, a triterpene collected

from guggul displayed as an anti-inflammatory marker. Guggulsterone purpose activation of NF-kappa B and is playing a key function in inhibiting the inflammation (Shishodiya and Aggarwal, 2004).

Antioxidant activity

Guggul has decreased the risk of coronary artery disease as it has preventive action on oxidation of cholesterol and further hardening of arteries and reduced the platelet stickiness. Guggulsterone combination with Fe2+ and sodium ascorbate significantly stopped lipid peroxidation in liver microsomes, which is beneficial against atherogenesis (Wang *et al*., 2004).

Skin diseases

Guggulsterones have been found to be helpful for curing allergic dermatitis. Guggulipid with alcoholic fractions possessed two activities: anti sebum and antioxidant and it have been reported to control the sebum secretion with enhanced oil control. It led to improved skin color and provided the young appearance to the skin (Shishodiya and Aggarwal, 2004). Nodulocystic acne, one of the skin disease has been treated using guggulipid and it caused a significant reduction in lesions. Its therapeutic value is as equal as tetracycline (Thappa and Doger, 1994; Jaiswal *et al*., 2016). Instead of it, Guggul has shown other pharmacological activities which are enlisted in Table no 1.

Table 1: Other pharmacological activities of Guggul

Sr. No.	Pharmacological activity	Part/ Extract used	Dose	Model used	Mechanism of action / Effect	Reference
1.	Anti-atherosclerotic	Gum guggul	–	–	Antioxidant property of Guggulu prevents/slows down the oxidation of LDL and lipid-lowering property founds to prevent in-vitro LDL oxidation.	Singh *et al*., 1997, Singh *et al*., 2015, Jaiswal *et al*., 2016
2.	Antifertility	Oleoresin	2mg and 20mg/100g bodyweight	Female Rat	Reported data indicated the decrease in uterus, cervix, ovaries along with an increase in glycogen and sialic acid promised to have antifertility activity.	Thappa and Doger, 1994, Singh *et al*., 1997, Singh *et al*., 2015, Jaiswal *et al*., 2016
3.	Anticancer/cytotoxic	Ferulates , ethyl acetate extract	–	–	A significant role in in-vitro cytotoxicity by decreasing the cell viability in MCF-7 (breast) tumor cell, PC3 (prostate) tumor cell, parental and transfected P388 cells and found to prevent the abnormal cell growth, neoplasia, inflammation, and further cardiac diseases.	Poonia *et al*., 2014, Chaudhary, 2012
4.	Antihyperglyc-emic	Alcoholic extract	200mg/kg	Streptozotocin-induced diabetic rats	Biochemical parameters like GTT, glycogen content, glucose homeostatic enzyme, and insulin release in vivo expression revealed its hypoglycemic activity.	Singh *et al*., 1997
5.	Hepatoprotective	Ethanolic extract	–	Carbon tetrachloride-induced liver damage in mice	Diminished level of transaminases, alkaline phosphatase, bilirubin suggested its hepatoprotective property.	Poonia *et al*., 2014
6.	Neuroprotective	Guggulipid	–	Streptozotocin-induced neuronal damage or model of dementia	Guggulipid found to prevent oxidative stress in brains of diseased rats due to antioxidant and anticholinesterase activity; acting as anti-dementia drug and cognitive enhancer.	Poonia *et al*., 2014
7.	Antimicrobial	Volatile oil ethanolic extract methanolic extract.	5mg/mL (ethanol-c extract)	*Rhyzoperth-a Dominican Klebsiella pneumonia* gram positive and gram negative bacteria	Act as fumigant Best antibacterial Significant antibacterial	Thappa and Doger, 1994, Singh *et al*., 1997, Singh *et al*., 2015,

Prescribed formulations of Guggul

Nowadays, Guggul is available as the marketed formulation for curing numerous clinical conditions and is accessible in combination with various other ingredients some of which are enlisted in table no.2.

Table 2: Various prescribed marketed formulations of Guggul

Sr. No.	Name of the formulation	Ingredients	Use
1.	Amrita guggul	Guduchi, Guggulu, Haritaki, Bibhitaki, Amalaki, Dantimula, Pippali, ShunthiTwak, Vidanga, Trivritmula.	Cures sixteen varieties if diseases such as leprosy, malingnant jaundice, urticaria, loss of appetite, catarrh in nose, enlargement of spleen, abdominal ailments.
2.	Abhaguggul	Babool, Haritaki, Bibhitaki, Amalaki, Maricha, Pippali, Shunthi, Shudhaguggulu.	Cures osteoporosis and low bone mineral density, increase bone strength.
3.	Abhayadi guggul	Haritaki, Amalaki, Munakka, Shatahwa, Bharangi, Shvetsariva, Krishna sariva, Vach, Haridra, Daruharidra, Majith, Shuddhaguggulu, Musli, Mulethi, Muramansi, Dalchini, Shukshamaila, Tejpatra, Nagkeshwar, Lvang, Vidanga, Durlabha, Trivrit, Traymana, Sunthi, Maricha, Pippali.	Cures mania, constipation, indigestion, Gout, produce watery stools
4.	Chandraprabha vati [24]	Chandraprabha, Karpura, VachaMusta, Bhunimb, Amruta, Daruka, Haridra, Ativisha, Darvi, Pippalimoola, Chitraka, Dhanyaka, Haritaki, Vibhitaki, Amalaki, Chavya, Vidanga, Gajapippali, Shunti, Maricha, Pippali, Makshika Dhatu Bhasma, Swarjika Kshara, Saindhava Lavana, Sauvarchala Lavana, Vida Lavana, Trivrit, Danti, Patra, Twak, Ela, Vamshalochana, Loha Bhasma , Sita, Shilajatu, Guggulu.	Used for Gonorrhoea, strangury calculi, urine retention, used as an aphrodisiac and as a tonic.
5.	Dashyang guggul	Sunthi, Maricha, Pippali, Haritaki, Bibhitaki, Amalaki, Musta, Vidanga, Shuddhaguggulu.	Cures obesity, nervous and rheumatic affections, used as alternative, tonic, and stimulant.
6.	Gokshurdi guggul	Gokshurapanchaag, Shuddhaguggulu, Sunthi, Maricha, Pippali, Haritaki, Bibhitaki, Amalaki, Mustaka	Used as demulscent, diuretic, alternative and tonic, used in Albuminaria, Phosphaturia, Dysuria, Caliculi, Gonorrhea, Rheumatism
7.	Kaishorguggul	Shuddhaguggulu, Haritaki, Bibhitaki, Amalaki, Maricha, Vidanga, Trivrit, mula, Dantimula, Guduchi, Sunthi, Pippali.	Cures ulcers, chronic otorrhoea, fistula, sciatica and rheumatism
8.	Kanchnarguggul	Kanchnar, Haritaki, Bibhitaki, Amalaki, Maricha, Pippali, Sunthi, Varun chaal, Tejpatra, Sukshmaila, Dalchini, Shuddhaguggulu.	Cures fistula, scrofula, leprosy, and ulcers. Used as alternative and tonic.
9.	Lakshaguggulu	Laksha ,Asthisamhrita, Arjun, Ashwagandha, Nagbala, Shuddhaguggulu.	Used as an ayurvedic treatment for osteoporosis and bone fracture.
10.	Lauh/Lohaguggul	Shuddhalauhbhasma, Shuddhaguggulu, Maricha, Pippali, Sunthi, Bibhitaki, Amalaki, Haritaki.	Used in sexual debility, chlorosis, scrofula, Anemia, heart affections and debility of old age.
11.	Mahayograjguggul	Sunthi, Pippalimula, Pippali, Chitrak, Chavya, Maricha, BhrishtaHingu, Ajmoda, Sarshap, Krishanjirak, Shwetjirak, Indrayav, Renuka, Gajpippali, Patha, Vidang, Kutaki, Bharangi, Vach, Ativisha, Murva, Tejpatra, Devdaru, Kustha, Rasna, Mustaka, Saindhav, Lavana,	Used in joint diseases, skin diseases, diabetes, gout, fistula, bloating, emaciation, asthma, cold, cough, anorexia, male and female infertility.

		Gokshur, Haritaki, Bibhitaki, Amalaki, Shuddhaguggulu, Vangabhasma, Rajatbhasma, Naga bhasma, Lohabhasma, Abhrakbhasma, Mandurabhasma, Rasa sindura.	
12.	MaharasnaKadha/ MaharasnadiKwath	Rasna, Dhanvayasa, Bala, Eranda-mula, Devadara, Shathi, Vaca, Vasaka, Nagara, Haritaki, Chavya, Musta, Punarnava, Guduchi, Vriddhadaru, Shatapushpa, Gokshura, Ashvagandha, Ativisha, Aragvadha, Shatavari, Krishna, Sahacara, Dhanyaka, Kantakari, Brihati, Prkshepadravya: Shunthi Churna, Pippali Churna. Ajamodadi Churna, Eranda Taila	Used in rheumatism, all kinds of nervous diseases, intestinal ailments, joint diseases.
13.	Navakaguggul	Pippali, Sunthi, Maricha, Haritaki, Bibhitaki, Amalaki, Musta, Chitrakmula, Vidang, Shuddhaguggulu.	Prescribed for obesity-related to PCOD, Hypothyroidism, diabetes. Also used for weight loss and to relieve rheumatoid arthritis.
14.	Navakarshikguggul	Bibhitaki, Haritaki, Amalaki, Pippali, Shuddhaguggulu	Cure fistula-in-ano, piles, dropsical swellings and abdominal tumours.
15.	Panchamritlauh/loha guggl	Shuddha parade, Shuddhagandhaka, Abhrakbhasma, Swarnmakshikbhasma, Rajatbhasma, Lauhbhasma, Shuddhaguggulu, Katutaila,	Used in treating neuromuscular disorders such as myalgia, neuralgia and myositis.
16.	Panchtiktghrit guggul	Nimbchaal, Guduchi, Adusapanchag, Patolpatra, Kantkarimula, ShuddhaGuggulu, Goghrita, Patha, Vidanga, Devdaru, Gajpippal, Swarjitkakshar, Yavakshara, Shunthi, Haridra, Shatahva, Chavya, Kushtha, Tejowati, Maricha, Indrayava, Jirak, Chitrakchaal, Kutaki, Shuddhabhallatak, Vach, Pipplamula, Manjishtha, Ativisha, Haritaki, Bbhitaki, Amalaki, Yavani.	Used in an abscess, gout, deep-seated ulcers, sinus, asthma, rhinitis, cold, cough and heart diseases.
17.	Pathyadi guggul	Bibhitaki, Amalaki, Haritaki, Guduchi, Vidanga, Guggulu, Danti, Pippali, Trivrit, Sunthi, Maricha.	Cures a headache, vascular headache, cluster headache, earache, toothache, night blindness, eye pain, vision disturbances.
18.	Punarnava guggul	Punarnavamula, Erandmula, Shunthi, Shuddhaguggulu, Trivritmula, Dantimula, Guduchi, Pippali, Maricha, Haritaki, Bibhitaki, Amalaki, Chitrakmula, Saindevlavana, Shuddha Bhallatak, Vidang, Swarnmakshik.	Rheumatoid arthritis, Hernia, Gout, Sciatica, frozen shoulder, backache, urinary bladder pain, spondylitis.
19.	Punarnavadi guggul	Punarnava, Devdaru, Haritaki, Guduchi, Gomutra, Shuddhaguggulu.	Used in abnormal fluid accumulation, act as a diuretic.
20.	Ras/Rasna guggul	Parad, Sharkara, Mahishakshguggulu, Ghrita.	In Sciatica and paraplegia
21.	Rasabhra guggul	Shuddhaparad, Lauhabhasma, Shuddhagandhaka, Abhrakbhasma, Guggulu, Svarasa, Pippali, Shunthi, Maricha, Haritaki, Bibhitaki, Amalaki, Dantimool, Indrayanmool, Vidanga, Nagkesar, Trivritmula.	Used in eczema, warts, herpes, enlargement of lymphatic glands, indigestion, leprosy, itches, psoriasis, and intestinal worms.
22.	Rasnadi guggul	Rasna, guduchi, Erandmula, devdaru, shunthi, gugglu.	Used in neurological disorders, joint pain, headache, earache, fistula, and sinus.
23.	Saptang/Saptangaguggulu	Shuddhaguggul, Haritaki, Bibhitaki, Amalaki, Shunthi, Pippali, Go ghrita	Used for sinus, enlargement of throat glands and leukoderma.
24.	Saptvinshatika guggulu	Pippali, Shunthi, Haritaki, Bibhitaki, Amalaki, Maricha, Mustaka, Vidanga, Guduchi, Chitrak,	For cold, cough, COPD, asthma, wheezing cough, inflammation, pain in the abdomen,

		Shati, Sukhamaila, Pippalimula, Hapusha, Devdaru, Tumbru, Puashkarmula, Chavya, Vishala, Haridra, Daruharidra, Vidlavana, Sauvarchallavana, Yavakshara, Saindhavlavana, Gajpippali, Shuddhaguggulu.	heart parts, urinary disorders, skin disorders.
25.	Trayodashang guggul	Babool twak, Ashwagandha, Hapusha, guduchi, shatavari, gokshur, vridhadaru, rasna, shathava, shati, yavani, shunthi, shodh guggulu, ghrita.	Cure asthma, cystitis, enlarged prostate gland, internal neuralgic affections.
26.	Triphala guggul	Haritaki, Bibhitaki, Amalaki, Pippali, Shuddha guggulu.	Used in fistula in ano, abdominal tumor, distension, edema, swelling, inflammatory conditions, Hemorrhoids
27.	Vatari guggul	Erand taila, Shuddha gandhak, Shuddha guggul, Amalaki, Haritaki, Bibhitaki.	Used in acute rheumatism, lameness, abdominal pain, abdominal dropsy.

Limitations of conventional dosage forms

Conventional dosage forms are being used commonly and are easily available e.g. compressed solid dosage forms such as tablets, pills etc., and other categories like topical and parenteral. Though parenteral preparations are promising to provide 100% bioavailability, it has the drawback that no control or adjustment of drug release and withdrawal, if required. Similarly, a typical peak-valley effect is observed in a solid dosage form which may result in a fluctuation in drug plasma concentration (Tiwari *et al*., 2012). In some cases, it becomes difficult to maintain the steady-state concentration for short therapeutic index drugs. In addition to it, patient compliance is one of limitation if patient miss to take the medicine particularly short half-life drugs which need frequent administration. Overall, Conventional dosage forms are posing problems like dose fluctuation, large dose requirement, patient in compliance further leading to less efficacy, toxicity, and adverse drug reactions, making the modern drug therapy unsuitable (Dikmen *et al*., 2011).

Superiority of Novel drug delivery system (NDDS)

Developing a new drug entity takes a long time and is expensive too. Rise in the field of research and development cost, numerous varying policies of investment firms, failure of testing at end of clinical trials makes the introduction of the new drug in the market troublesome. Novel drug delivery approach leads to the solution of most of the unwanted effects of conventional dosage forms. (Dua *et al*., 2018) Beside it, individualization of drug therapy, rational drug use, therapeutic drug monitoring, dose titration etc. are the other attractive approaches for making the pharmacotherapy safer and effective. (Mehta *et al*., 2019) Design of NDDS has created effective and safer use of existing drugs through newer technologies, better drugs with a long half-life, reduced side effects, site-specific action, controlled drug release at a predefined rate, patient compliance and many other useful advancements (Bhagwat and Vaidhya, 2013; Farokhzad and Langer, 2009). Nanosomes. Liposomes. Niosomes, nanoparticles, microspheres, micro emulsion, and micelles are some of the drug carriers used in NDDS.

Bioavailability problems of guggul lipids

A wide range of therapeutic activities has been reported for guggulipids. But it lacks its desired pharmacological action due to low bioavailability and water insolubility. New advancements such as niosomes, guggulusomes, proniosomes, nanoparticles, Nano vesicles etc. have come up to enhance the therapeutic concentration as well as to remove the undesired pharmacological effect. Niosomes has been reported to have vesicular instability such as fusion, aggregation, sedimentation and leakage associated with it which lead to the development of proniosomes. Proniosomal gel formulation revealed the faster release as well as the slow sustained release of the drug (Goyal *et al*., 2011). Guggulipid nanoparticles indicated higher medication content than trade emulgel (CEG) in receptor site and satisfactory stability profile (Yoshioka *et al*., 1994).

Novel drug delivery approach for guggul

A drug can be toxic or less efficacious depending on its therapeutic window. Concentration above than maximum safe concentration shows the toxic effect and below the minimum effective concentration may be of less therapeutic importance. An optimum conc. of the drug is required for the constant steady level in blood plasma. Novel drug delivery systems have increased the efficiency, further release, and effect. It helped the slowly acting drugs to show the significant effect for the treatment of a particular disease (Bhagwat and Vaidhya, 2013; Farokhzad and Langer, 2009). Nanoparticles, nanovesicles, liposomes, niosomes, proniosomes, micelles etc. are the newly developed nanotechnologies for targeting the receptor site and has solved the problem of low bioavailability and aqueous insolubility (Mehta *et al*., 2019).

Available novel drug delivery systems for guggul

Gugglusomes : Gugglusomes are the newer kind of vesicles in which guggul is used as a carrier. These are commercially used for transdermal as well as topical delivery of other anti-inflammatory drugs. These gugglusomes have been reported to show their acceptable results without any irritation. Dave *et al*. (2014) prepared the gugglusomes loaded with aceclofenac for its better transdermal absorption. These also formed to be non-irritant and devoid of any edema formation. Dave *et al*. (2017) have revealed its use in the improved topical administration of phenylbutazone. It has been found to show synergistic effect with phenylbutazone for protection from inflammation. It resulted into sustain release and better entrapment of drug. This enlighted the concept of gugglusomes for systemic as well as topical delivery of drugs omitting the side effects produced by conventional dosage forms.

Nanoparticles : Nanoparticles were introduced as novel approach for transporting the drugs across blood-brain barrier inside the CNS. These have profound importance in the field of drugs like antineoplastics, antipsychotics, CNS active drugs etc. Particularly, solid lipid nanoparticles were developed so as to avoid the problems exhibited by polymeric nanoparticles such as cytotoxicity and industrial scale up. Solid lipid nanoparticles are characterized as lipid-based nanoparticles. They show good physical stability, protection to labile drugs from degradation, provides site-specific and controlled release of a drug. They can be employed in any dosage form like for topical, oral, parenteral and rectal. Gaur *et al*. (2013) formulated the solid lipid nanoparticles (SLNs) for the topical delivery of diclofenac sodium loaded nanoparticles using guggul lipid as the carrier. It revealed its excellent permeation profile across the membrane. It has found to have controlled release and compatibility with skin. Sarkar *et al*. (2017) formulated silver nanoparticles of guggul extract and evaluated its antibacterial activity against three different gram negative and one gram positive bacteria i.e. *Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis* and *Staphylococcus aureus.* They found the optimum salt concentration of silver nitrate i.e. 3mM for preparing silver nanoparticles of guggul.

Nano vesicles : Nano vesicles are a sort of liposomes created because of low water solvency of some drugs. Gaur et al. (2014) arranged guggul vesicles of Aceclofenac utilizing cholesterol and dicetyl phosphate. It gave a data about the permeation through the skin and its stability.

Proniosomal gel : Proniosomes are pro vesicular carriers designed to conquer the shortcomings of niosomes and liposomes. Device of proniosomes has overcome the physical stability issues (aggregation, fusion, leakage, sedimentation) and chemical instability such as hydrolysis by water, provided ease of sterilization and improved bioavailability (Jha *et al*., 2011; Jadhav *et al*., 2016*;* Hu and Rhodes, 1999; Mishra *et al*., 2011 and Shukla and Tiwari, 2011). Topical application of anti-inflammatory agent can render systemic side effects and improve its therapeutic response (Mehta *et al*., 2016; Kumar *et al*., 2011). Goyal *et al*. (2011) formulated topical proniosomal gel to examine its anti-inflammatory activity and compared with commercial anti-inflammatory agents. They predicted that it is not good as commercial formulation but has immense potential for developing herbal anti-inflammatory products.

Future Targets

To eliminate the systemic side effects of Guggul associated with the lipidic nature such as low bioavailability and aqueous insolubility, another approach i.e. Novel Drug Delivery System (NDDS) has been introduced. Guggul has shown desirable effects when designed in the form of newer formulations. Proniosomal gel, solid lipid nanoparticles, silver nanoparticles, gugglusomes are some of the delivery systems holding the available data for their application. Some of the literature has evidenced the existence of nanovesicles as the new delivery approach. A proniosomal gel is a topical formulation, basically, a provesicluar system which on hydration gets converted to niosomes which release the drug at the faster rate than the free drug. Solid lipid nanoparticles are the lipid-based nanoparticles particularly for topical delivery, showed desirable permeation across the skin with the release at the controlled rate. Gugglusomes are a kind of vesicles employed as the transdermal film and topical preparation, have shown to sustain the release of the drug and efficient drug entrapment. Researches are going on to bypass the drawbacks associated with available conventional formulations, as not much of study has been performed in relevance to new approaches like liposomes, phytosomes, niosomes, dendrites, microspheres etc. This advanced technology can prove to be as useful marker due to its numerous pharmacological effects.

Conclusion

Collectively, it can be summed up that device of novel drug delivery system for guggul with better therapeutic results will be crucial for future development as a better remedy. It is evident that utilizing guggul in this newer approach will provide the controlled release of drug, uniform distribution, better expected results and without any systemic side effects. Though, it is a kind of tedious and costly process to design and examine the new formulation, the profitable uses of guggul can't be avoided. So, further studies should be performed regarding the novel delivery system and trials should be conducted to get a valuable products out of it.

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