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Prutha Parmar
Kokan Gyanpeeth's Rahul Dharkar College of Pharmacy and Research Institute, Karjat, Mumbai, Maharashtra, India

Swarali Bhoir
Kokan Gyanpeeth's Rahul Dharkar College of Pharmacy and Research Institute, Karjat, Mumbai, Maharashtra, India

Pravin P Naik
Kokan Gyanpeeth's Rahul Dharkar College of Pharmacy and Research Institute, Karjat, Mumbai, Karnataka, India

Sandeep Waghulde
Kokan Gyanpeeth's Rahul Dharkar College of Pharmacy and Research Institute, Karjat, Mumbai, Maharashtra, India

Nilesh Gorde
Kokan Gyanpeeth's Rahul Dharkar College of Pharmacy and Research Institute, Karjat, Mumbai, Maharashtra, India

MK Kale
Kokan Gyanpeeth's Rahul Dharkar College of Pharmacy and Research Institute, Karjat, Mumbai, Maharashtra, India

Correspondence
Prutha Parmar
Kokan Gyanpeeth's Rahul Dharkar College of Pharmacy and Research Institute, Karjat, Mumbai, Maharashtra, India

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Guggulsterone –Farnesoid X receptor interaction

Prutha Parmar, Swarali Bhoir, Pravin P Naik, Sandeep Waghulde, Nilesh Gorde and MK Kale

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Abstract
Guggulsterone is a plant sterol derived from gum resin of Commiphora wightii. The gum resin from guggul plants has been used for thousand years in Ayurveda to treat various disorders, including internal tumors, obesity, liver disorders, malignant sores and ulcers, urinary complaints, intestinal worms, leucoderma, sinuses, edema, and sudden paralytic seizures. Guggulsterone has been identified a bioactive components of this gum resin. This plant steroid has been reported to work as an antagonist of certain nuclear receptors, especially farnesoid X receptor, which regulates bile acids and cholesterol metabolism. Authors are interested to study Guggulsterone – Farnesoid X receptor interactions. Interactions were studied on Molecular Operating Environment software and the interactions of guggulsterone confirms its activity at Farnesoid X receptor.

Keywords: Guggul, Guggulsterone, Farnesoid X receptor, Receptor Binding etc.

Introduction
Oleogum resin, known as guggul or gum guggul, is extracted from *Commiphora mukul* (known as guggul tree) found in India, Bangladesh, and Pakistan. The use of guggul for a wide variety of ailments, including atherosclerosis, hypercholesterolemia, rheumatism, and obesity is described in the Ayurveda, the ancient Indian medical system. In fact, the there is a mention of the drug as early as from 3000 to 10,000 years ago in the Vedas, the holy scriptures of India for treating human ailments.

Guggul was first introduced in the medical world in 1966 [1]. The centuries-old Ayurvedic text, in which guggul was recom- mended for the treatment of a condition called "coating and obstruction of channel," resembling the description of atherosclerosis, inspired her studies on the effects of Guggul on rabbits. Guggul was approved formarketing in India as ahypolipidemic drug [1, 2] in 1986, with proven efficacy and safety.

In the middle 1990s, guggul was introduced into the Western medical literature [3]and, consequently, there was a widespread of the interests in using guggul as a remedy for treating or preventing hypercholesterolemia and related cardiovascular diseases in the Western world. Currently, guggul is available in the United States and other Western countries, as an over-the-counter dietary supplement. Apart from the numerous animal and human clinical trials conducted in India, limited studies involving Western populations have been carried out to analyze the various therapeutic effects of guggul. In 2003, one such clinical trial was conducted in the United States. However, unlike the previous preclinical and clinical data, the study found that gugulipid, the guggul extract, did not appear to have significant hypocholesterolemic effect in the Western subjects, whereas its anti-inflammatory effect was detected [4]. The study raised questions regarding the hypocholesterolemic efficacy of guggul, especially in Western populations [4, 5].

Guggul became one of those herbs holding huge prospects for the development of hypolipidemic and anti-atherogenic drugs. Substantial progress has since been made recently which has led to a better understanding of the molecular mechanisms responsible for the diverse pharmacological effects of guggul, especially its hypolipidemic activity. Guggulsterone, the bioactive constituent of guggul, has been identified as an antagonist at the

nuclear receptor farnesoid x receptor (FXR) [6, 7], a key transcriptional regulator for the Maintenance of cholesterol land bile acid homeostasis [8]. Subsequent studies also found that guggulsterone is a potent antagonist at them ineralocorticoid receptor (MR), glucocorticoid receptor (GR), and androgen receptor (AR), and antagonista pregnane receptor (PXR), progesterone receptor (PR), and estrogen receptor (ERα) [9]. Recent studies have also demonstrated that guggulsterone upregulates the expression of the bile salt export pump (BSEP), a rate-limiting efflux transporter for eliminating cholesterol metabolites bile acids from the liver. Such upregulation is possibly mediated through the activating protein 1 (AP-1) signaling pathway [10]. The FXR antagonism and enhanced BSEP expression have been proposed as possible causes for the hypolipidemic effect of guggulsterone [6, 10, 11]. In addition, guggulsterone has been found to be a potent inhibitor of the nuclear factor-κB (NF-κB) [12, 13, 14], a key factor in regulation of inflammatory responses. Such repression of NF-κBactivation may put forth a mechanism for the antiinflammatory effect of guggelsterone.

Guggulu has been used in Indian Traditional System of medicine, Ayurveda, for thousands of years in the treatment of arthritis, inflammation, gout, rheumatism, obesity, and disorders of lipids metabolism [11]. It has different names like guggula, guggul, guggal, gugar, and Indian bdellium [15].

Guggulu occurs as vermicular pieces of pale yellow or brown coloured mass with aromatic odour and bitter astringent taste; when fresh it is viscid and golden in colour. It should produce not more than 5 percent of total ash and 1 percent of acid-insoluble ash. It yields not less than 27 percent of alcohol-soluble matter and not less than 53 percent of water-soluble matter. The true samples of guggulu contain 1 percent of volatile oil [16] and between 1.0 and 1.5 percent of guggulsterones and [11] Guggulu Shodhana (shodhanvidhi). It has been mentioned in Ayurvedic literature that administration of raw guggulu may lead to skin rashes, irregular menstruation, diarrhoea, headache, mild nausea, and, with very high doses, liver toxicity [17]. In order to overcome undesired effects of raw guggulu, Ayurveda describes a number of purification processes (shodhanvidhi) using different fluids (dravyas), which not only take care of the adverse effects but also synergise with the therapeutic activity. According to Ayurvedic texts, guggulu must be purified before being incorporated into formulations [18]. During the process of shodhan, guggulu is treated with specific materials of biological origin, for example, herbal juices, cow urine, and cow milk. It is possible that some of the properties (chemical and biological) of shodhan materials are added to guggulu during the purification process. It is also possible that some of the toxic or harmful constituents of raw guggulu are neutralized, detoxified, or removed during this process.

There are a large number of commercial polyherbal anti-inflammatory formulations which use guggulu as the chief ingredient [19]. However, no study has been done to investigate the process of Ayurvedic purification and its probable effect on therapeutic efficacy except for one report which states that gastric irritancy of guggulu is reduced with purification [20].

During the process of purification, foreign matter is removed from raw guggulu manually and is then broken into small pieces. The broken mass is wrapped in a piece of cloth (called potli) and hanged into an inert container (called dolayantra) containing one of the recommended media which are gomutra (cow urine), triphalakasaya (decoction of triphala), vasapatrakasaya (decoction of Adhatodavasica leaves), vasapatrasavrasa (aqueous extract of Adhatodavasica leaves), dugdha (milk), and water. The guggulu is kept immersed, while fluid is boiled till all the soluble matter of guggulu is dissolved in the purifying vehicle. The insoluble part of guggulu is taken out and thrown away. Further boiling is continued till guggulu solution forms a soft mass. It is then poured out over a smooth wooden board smeared with cow ghee or castor oil and dried in the sun. The dried mass is called purified guggulu (suddhguggulu) [18].

1.1 Phytoconstituents of Guggulu

Guggulu contains diterpenoids, triterpenoids, steroids, long-chain aliphatic tetrols, aliphatic esters, ferulates, lignans, carbohydrates, and a variety of inorganic ions besides minor amounts of sesamin and other unidentified constituents.

1.1.1 Volatile Oil and Its Terpenoidal Constituents

1.1.1.1 Monoterpenoids

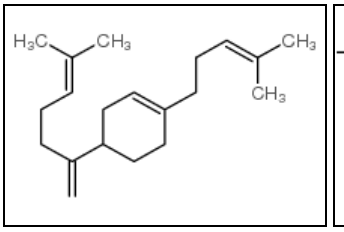
The gum resin of C. wightii yields about 0.4% of essential oil by steam distillation and its chief components are myrcene, dimyrcene, and polymyrcene [21]. Other components of the oil are eugenol, d-limonene, α-pinene, (±) linalool, cineole, α-terpineol, d-α-phellandrene, methylheptanone, bornyl acetate, (±) geraniol, and some other unidentified compounds [22].

1.1.1.2 Sesquiterpenoids

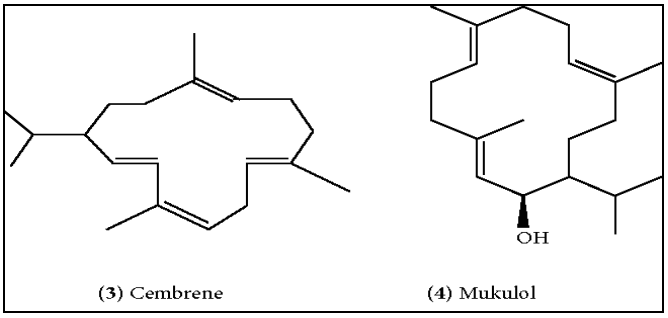
The gum resin of C. wightii has been reported to contain bicyclic sesquiterpene, cadinene [22].

1.1.1.3 Diterpenoids

Diterpenoid constituents from guggulu include α-camphorene (1) (Figure 1) [23], cembrene-A (2) (Figure 1), cembrene (3) (Figure 2) [23], and other cembrenoids. Cembrene-A is one of the most elementary tetraenes derived from geranylgeranyl pyrophosphate by C-1 to C-14 cyclization.



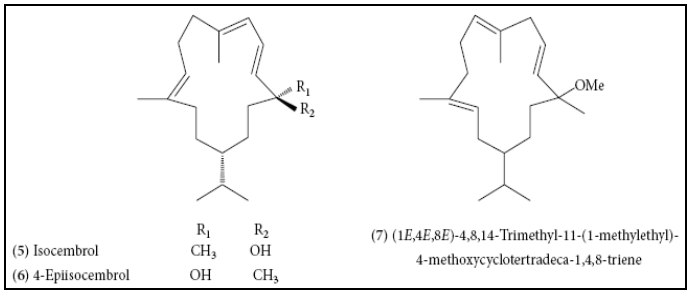
(1) **(2)**



(3) Cembrene **(4)** Mukulol

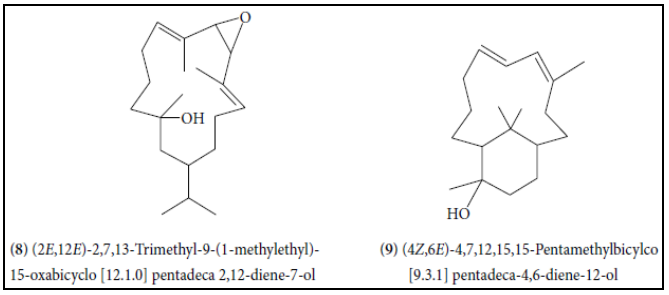
Mukulol (allylcembrol) (4) (Figure 2) is a new cembrane alcohol which was isolated from the aerial parts and also from the resin of guggulu [24, 25]. The allylcembrol structure was established by spectral analysis and mild dehydration which yielded cembrene. Other isolated cembrane type diterpenes include isocembrol (5) (Figure 3) and 4-epiisocembrol (6) (Figure 3). (1E, 4E, 8E) -4, 8, 14-Trimethyl-11-(1-methylethyl) 4-methoxycyclotertradeca-1, 4,

8-triene (7) (Figure 3), -(2E,12E)-2, 7, 13-trimethyl-9-(1-methylethyl)-15-oxabicyclo[12.1.0] pentadeca-2, 12-diene-7-ol (8) (Figure 4), and (4Z,6E)-4, 7, 12, 15, 15-pentamethylbicylco [9.3.1] pentadeca-4, 6-diene-12-ol (9) (Figure 4) were novel compounds obtained by bioassay-guided isolation from hexane-soluble portion of the methanol extract of guggulu [26].



	R_1	R_2
(5) Isocembrol	CH_3	OH
(6) 4-Epiisocembrol	OH	CH_3

(7) (1*E*,4*E*,8*E*)-4,8,14-Trimethyl-11-(1-methylethyl)-4-methoxycyclotertradeca-1,4,8-triene

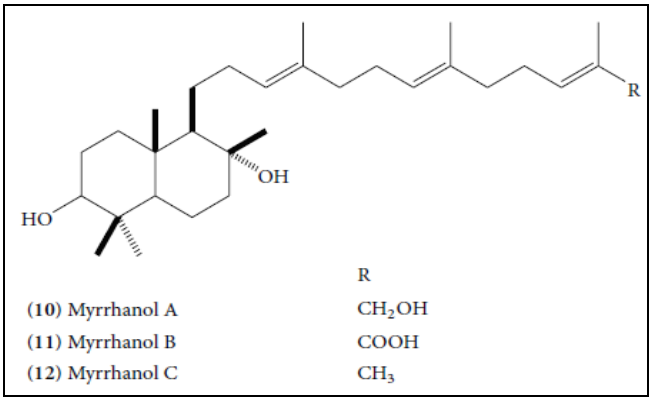


(8) (2*E*,12*E*)-2,7,13-Trimethyl-9-(1-methylethyl)-15-oxabicyclo [12.1.0] pentadeca 2,12-diene-7-ol

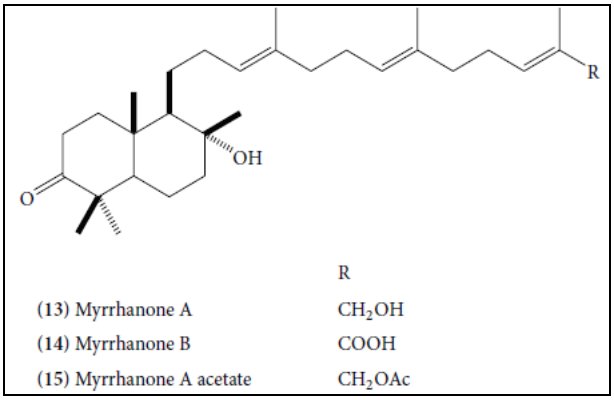
(9) (4*Z*,6*E*)-4,7,12,15,15-Pentamethylbicylco [9.3.1] pentadeca-4,6-diene-12-ol

1.1.1.4 Triterpenoids

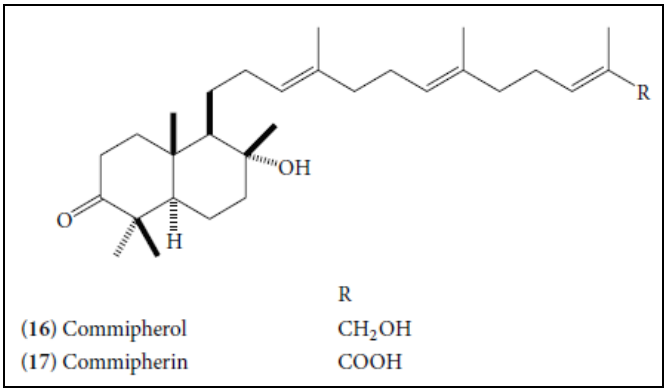
Polypodane-type triperpenes, myrrhanol A (10) (Figure 5), B (11) (Figure 5), and C (12) (Figure 5), myrrhanone A (13) (Figure 6), myrrhanone B (14) (Figure 6) [27, 28], myrrhanone A acetate (15) (Figure 6), commipherol (16) (Figure 7), commipherin (17) (Figure 7), and octanordammaranetriperpenoid, epimansumbinol, (18) (Figure 8), have been isolated from the gum resin [29]. The isolation of two more triterpenoidal components has been reported, which are identified as mansumbinone (19) (Figure 9) and mansumbinoic acid (20) (Figure 9) [30].



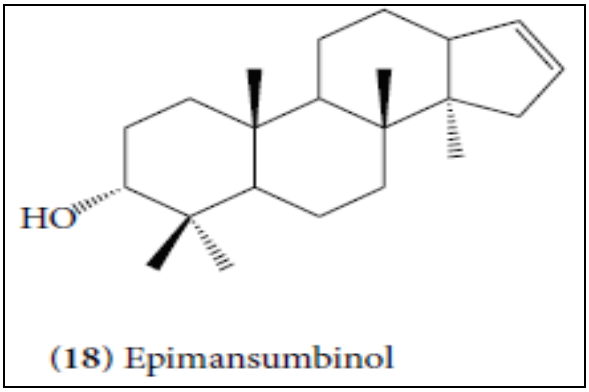
	R
(10) Myrrhanol A	CH_2OH
(11) Myrrhanol B	COOH
(12) Myrrhanol C	CH_3



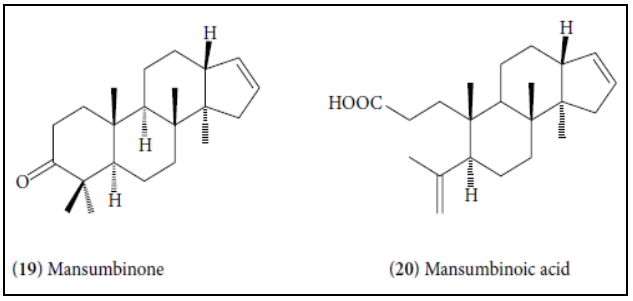
	R
(13) Myrrhanone A	CH_2OH
(14) Myrrhanone B	COOH
(15) Myrrhanone A acetate	CH_2OAc



	R
(16) Commipherol	CH_2OH
(17) Commipherin	COOH

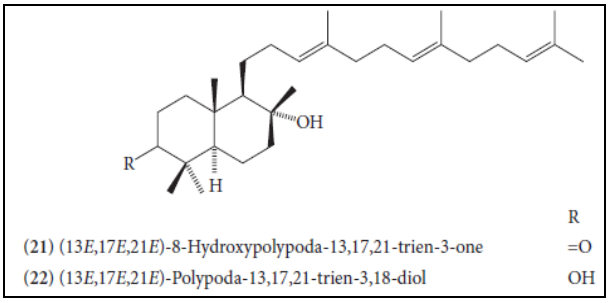


(18) Epimansumbinol



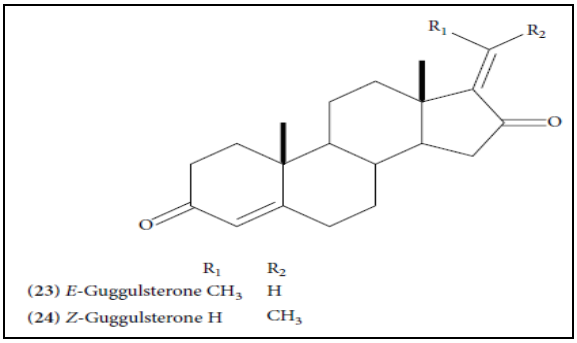
(19) Mansumbinone

(20) Mansumbinoic acid

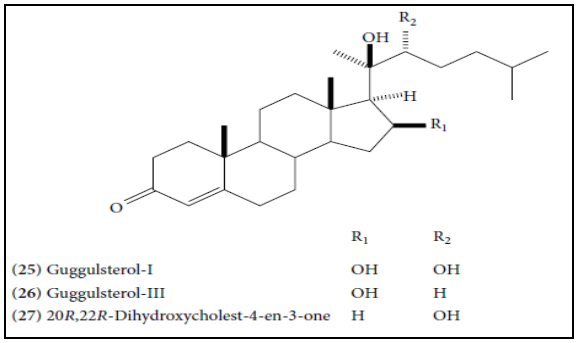


	R
(21) (13*E*,17*E*,21*E*)-8-Hydroxypolypoda-13,17,21-trien-3-one	=O
(22) (13*E*,17*E*,21*E*)-Polypoda-13,17,21-trien-3,18-diol	OH

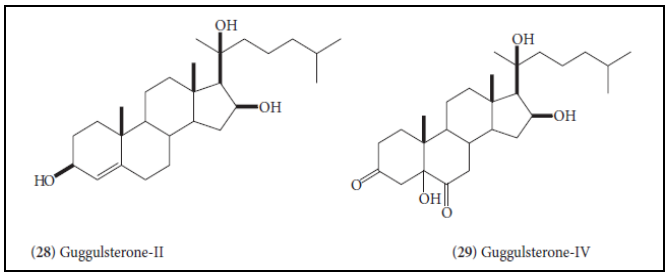
The absolute stereostructure of myrrhanol A was determinedto be (3*S*, 5*S*, 8*R*, 9*R*, 10*S*)-3, 8, 30-trihydroxypolypoda-13*E*, 17*E*, 21*E*-triene. Myrrhanol B is 30-oic acid ofmyrrhanol A with altered stereostructure at C-5 (5*R* incontrast to 5*S* in myrrhanol A). Myrrhanone A and B are3-keto analogue of myrrhanol A and B, respectively [31].A myrrhanone derivative, (13*E*, 17*E*, 21*E*)-8-hydroxypolypoda-13, 17, 21-trien-3-one (21) (Figure 10), and a myrrhanol derivative, (13*E*, 17*E*, 21*E*)-polypoda-13, 17, 21-trien-3, 18-diol (22) (Figure 10), have also been isolated [29].



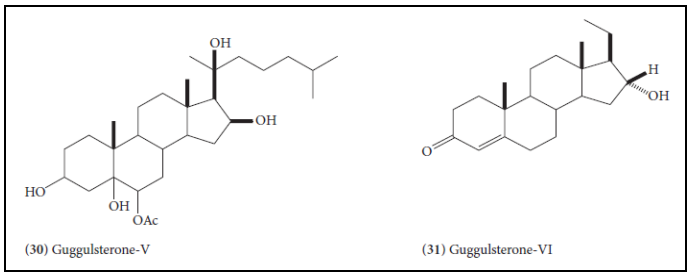
	R_1	R_2
(23) *E*-Guggulsterone	CH_3	H
(24) *Z*-Guggulsterone	H	CH_3



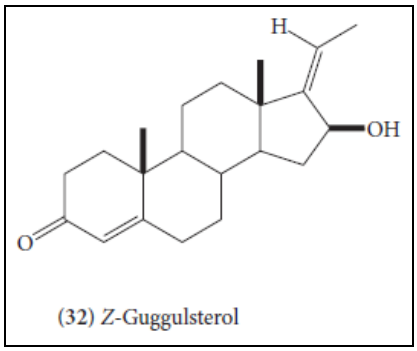
	R_1	R_2
(25) Guggulsterol-I	OH	OH
(26) Guggulsterol-III	OH	H
(27) 20*R*,22*R*-Dihydroxycholest-4-en-3-one	H	OH



(28) Guggulsterone-II (29) Guggulsterone-IV



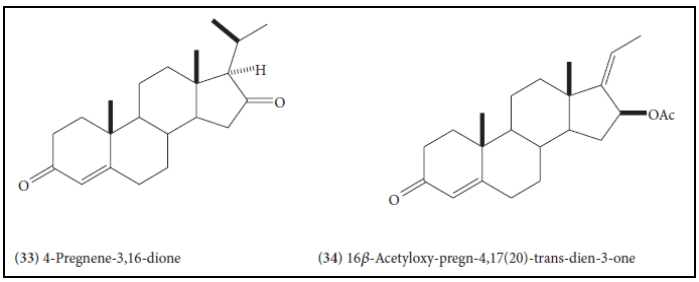
(30) Guggulsterone-V (31) Guggulsterone-VI



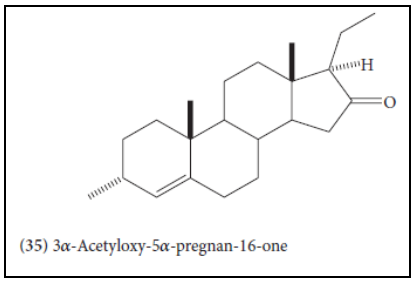
(32) *Z*-Guggulsterol

1.1.2 Steroids

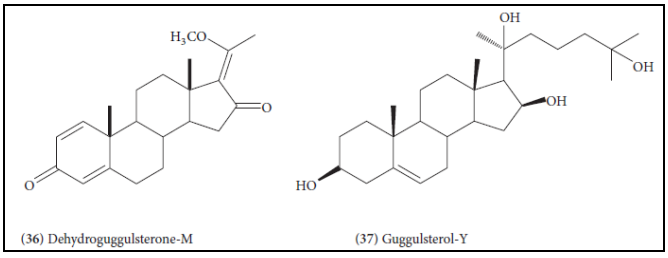
Isolation of several steroidal constituents hasbeen reported from the gum resin. The major constituentsinclude *E*-guggulsterone(23) (Figure 11), *Z*-guggulsterone(24) (Figure 11), guggulsterol-1 (25) (Figure 12), guggulsterol-II (26) (Figure 12), guggulsterol-III (27) (Figure 12) [32], guggulsterol-IV (28) (Figure 13), guggulsterol-V (29)(Figure 13) [33], and guggulsterol-VI (30) (Figure 13) [34] Other isolated steroids are 20α-hydroxy-4-pregnen-3-one(31) (Figure 13), 20β-hydroxy-4-pregnen-3-one, and 16β-hydroxy-4,17(20)-*Z*-pregnadien-3-one, which has beendesignated as *Z*-guggulsterol [34]. Progesterone and relatedsteroids, 4-pregnene-3,16-dione (32) (Figure 13), (20*R*)-20-acetoxy-4-pregnene-3,16-dione,16β-acetyloxypregn-4,17(20)-*trans*-diene-3-one (33) (Figure 14), 3α-acetyloxy-5α-pregnan-16-one (34) (Figure 14), and 20*R*,22*R*-dihydroxycholest-4-en-3-one (35) (Figure 14), have also been isolated [35]. Cholesterol has also been reported. Three new andrecently isolated steroids are guggulsterone-M, dihydroguggulsterone-M (36) (Figure 14), and guggulsterol-Y (37) (Figure 14) [17]. The steroidal constituents have been relatedwith hypolipidemic and anti-inflammatory activities of thedrug [32].



(33) 4-Pregnene-3,16-dione (34) 16β-Acetyloxy-pregn-4,17(20)-trans-dien-3-one



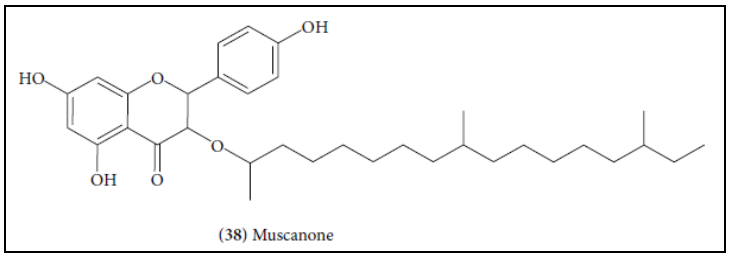
(35) 3α-Acetyloxy-5α-pregnan-16-one



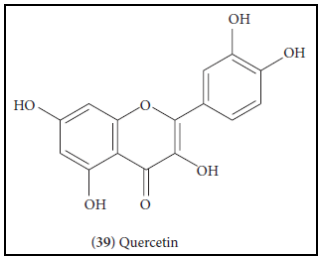
(36) Dehydroguggulsterone-M (37) Guggulsterol-Y

1.1.3 Flavonoids

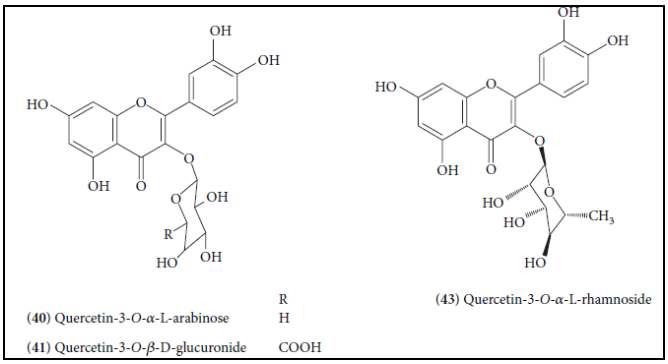
An ethanolic extract of trunk of *C. wightii* was separated on column packed with silica gel to give a new antifungal flavone named muscanone (38) (Figure 15) along with known naringenin. Muscanone was found to be active against *Candida albicans* in microbial sensitive assay [35]. The major flavonoid components of the flowers of *C. mukul* were identified as quercetin(39) (Figure 16), quercetin-3-*O*-*α*-L-arabinose (40) (Figure 17), quercetin-3-*O*-*β*-D-glucuronide (41) (Figure 17), quercetin-3-*O*-*β*-Dgalactoside (42) (Figure 17), quercetin-3-*O*-*α*-L-rhamnoside (43) (Figure 17), and pelargonidin-3, 5, di-*O*-glucoside (44) (Figure 17) [36].



(38) Muscanone

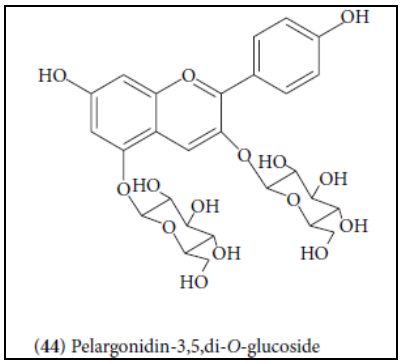


(39) Quercetin



(40) Quercetin-3-*O*-α-L-arabinose	R = H
(41) Quercetin-3-*O*-β-D-glucuronide	R = COOH

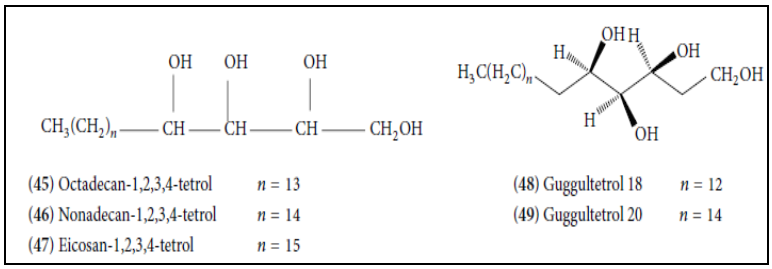
(43) Quercetin-3-*O*-α-L-rhamnoside



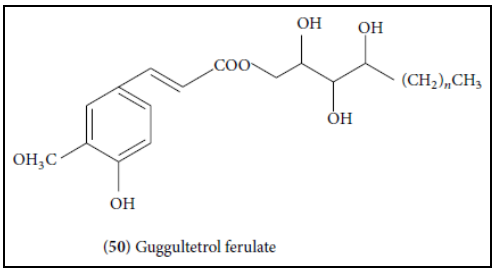
(44) Pelargonidin-3,5,di-*O*-glucoside

1.1.4 Guggultetrols

A crystalline material was isolated fromthe saponified gum resin which was characterized as a mixtureof octadecan-1, 2, 3, 4-tetrol (45) (Figure 18), nonadecan-1, 2, 3, 4-tetrol (46) (Figure 18), and eicosan-1, 2, 3, 4-tetrol (47) Figure 18) with minor amount of other components, possibly lower (C-16 and C-17) and higher (C-21 and C-22) homologoustetrols. These compounds constitute a new class of naturally occurring lipids, guggultetrols. They are long-chainlinear aliphatic tetrols with hydroxyl functions at C-1, C-2, C-3, and C-4 positions. Through derivatization and preparative GLC, guggultetrol-18 (48) (Figure 18) and guggultetrol-20(49) (Figure 18) were obtained in pure form [37]. A mixture of two ferulates (n = 16, 17) (50) (Figure 19) with an unusual skeleton was found to be responsible for thecytotoxic action of the drug. They have been isolated fromcytotoxic fraction of ethyl acetate extract of guggulu. It was identified as a mixture of esters based on homologous longchaintetrols and acid [38].



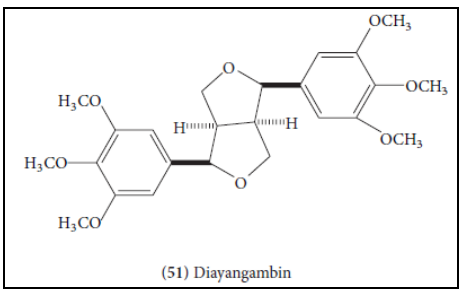
(45) Octadecan-1,2,3,4-tetrol	n = 13	(48) Guggultetrol 18	n = 12
(46) Nonadecan-1,2,3,4-tetrol	n = 14	(49) Guggultetrol 20	n = 14
(47) Eicosan-1,2,3,4-tetrol	n = 15		



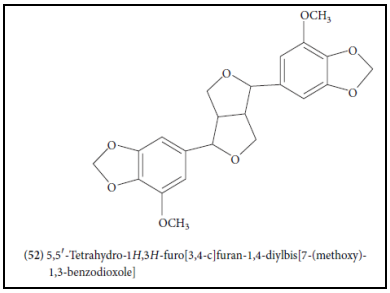
(50) Guggultetrol ferulate

1.1.5 Lignans

Two lignans, sesamin [18] and diayangambin (51) (Figure 20) [39], have been reported from guggulu. Also, 5,5□-tetrahydro-1*H*,3*H*-furo[3,4-c]furan-1,4-diylbis[7-(methoxy)-1,3-benzodioxole] (52) (Figure 20) has beenreported from methanolic extract of guggulu [27].



(51) Diayangambin



(52) 5,5′-Tetrahydro-1*H*,3*H*-furo[3,4-c]furan-1,4-diylbis[7-(methoxy)-1,3-benzodioxole]

1.1.6 Sugars
Complete hydrolysis of gum part of resin yielded L-arabinose, D-galactose, L-fructose (traces), and 4-*O*-methyl-D-glucuronic acid. Graded hydrolysis of the gum furnished an aldobiouronic acid [6-*O*-(4-*O*-methyl-*β*-D-glucopyranosyluronic acid)-D-galactose] [40]. Hydrolysis of methylated gum furnished 2,3,4,6-tetra-*O*-methyl-Dgalactose,2,3-di-*O*-methyl-L-arabinose, 2,3,4-tri-*O*-methyl-D-galactose, 2,4-di-*O*-methyl-D-galactose, and 2,3,4-tri-*O*methyl-D-glucuronic acid in the ratio of 1: 1: 1: 2: 1. The provisional structure showed the gumtobe a highly branchedpolysaccharide containing 1–6, 1–3, and 1–5 type of linkage [41].

1.1.7 Amino Acids
C. mukul was extracted with alcohol and the extract after removal of the solvent was partitioned between water and ether. The aqueous fraction was chromatographed and it showed the presence of various aminoacids. The amino acids detected were cystine, histidine, lysine, arginine, aspartic acid, serine, glutamic acid, threonine, alanine, proline, tyrosine, tryptophan, valine, leucine, andisoleucine [42].

2. Materials and Methods

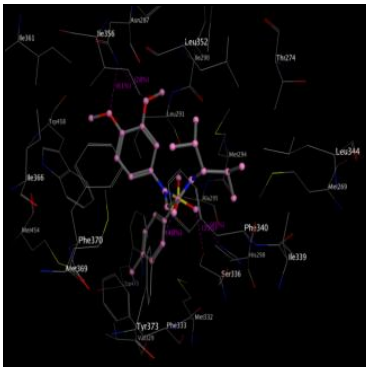


Fig 21: Farnesoid X receptor- Ligand

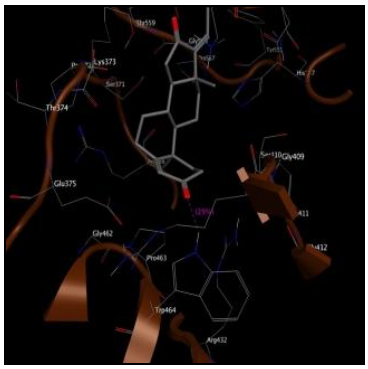


Fig 22: Farnesoid X receptor-Cholic Acid interactions

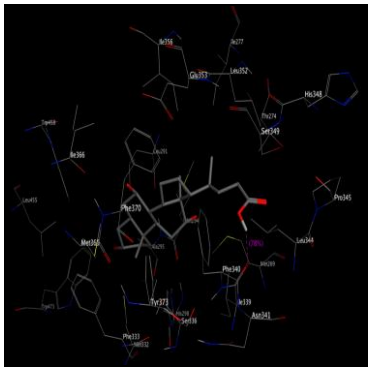
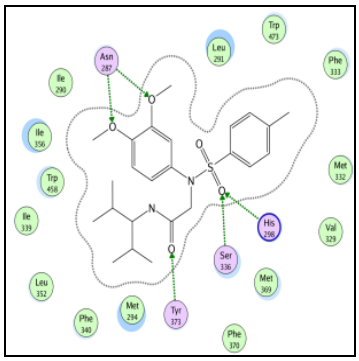
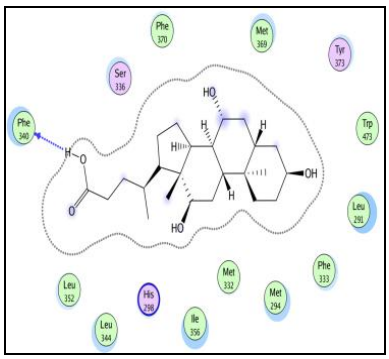
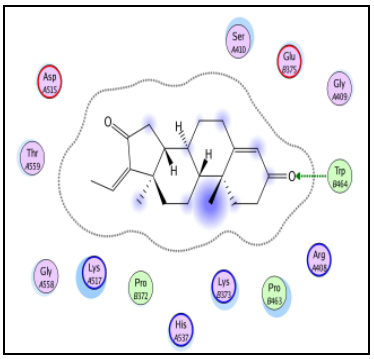


Fig 23: Farnesoid X receptor-Guggulosteroneinteractions







The computations for docking analysis were carried out on Intel Core-i 3 CPU @ 3.30 GHz workstation, 4 GB memory with windows XP- SP2 operating system and molecular operating environment (MOE 2009.10) as computational software. The co-crystallized protein structure of Farnesoid X Receptor was obtained from protein data bank with PDB code 5Q0J. MOE identifies favourable poses of flexible ligands in rigid binding sites of macromolecules, typically proteins. MOE offers different routines for conformational sampling, placement and scoring.

The co-crystallized protein structure of Farnesoid X Receptor was obtained from protein data bank with PDB code 5Q0J. The crystal structure was then protonated and then the energy was minimised using AMBER99 force filled. The active was generated using atom selector and labelled as 'Binding site'. All the design molecules were built, energy minimised and used as ligands for docking studies using the software. Docking was performed using placements like alpha PMI, alpha triangle and triangle matcher with London dG scoring. Different poses were scrutinised on the basis of suitable interaction and the best molecules were considered.

3. Result and Discussions
Gugglosterone is well-known for its different pharmacological activities. Authors were interested to study agonist and antagonistic Farnesoid X receptor interactions. Interactions were studied on Molecular Operating Environment software. Ligand has shown 61% & 28% dimethoxy receptor binding with Asn 287, Sulfonamide oxygen shown 35% & 45% receptor binding with Ser 336 and His 298, Amide oxygen shown 48% receptor binding with Tyr 373 residue. Cholic acid agonist has shown 78% hydrogen binding of acetate group with Phe 340 residue. At the same site when Gugglosterone was docked on FXR the cyclohex-2-enone oxygen shown 29% receptor binding with Trp 464 residue also 10, 13 dimethyl groups and few carbons are exposed to receptor residues. Since Gugglosterone indicates good receptor interaction it confirms that it behave as antagonist at FXR receptor.

4. References

1. Arya VP. Gugulipid. Drug Fut. 1988; 13:618-619.
2. Satyavati GV. Gum Guggul (*Commiphora mukul*)-The success story of an ancient insight leading to a modern discovery. Indian J Med Res. 1988 87:327-335.
3. Singh RB, Niaz MA, Ghosh S. Hypolipidemic and antioxidant effects of *Commiphora mukul* as an adjunct to dietary therapy in patients with hypercholesterolemia. Cardiovasc Drugs Ther, 1994; 8:659-664.
4. Szapary PO, Wolfe ML, Bloedon LT, Cucchiara AJ, DerMarderosian AH, Cirigliano MD *et al.* Guggulipid for the treatment of hypercholesterolemia: A randomized controlled trial. JAMA. 2003; 290:765-772.
5. Ulbricht C, Basch E, Szapary P, Hammerness P, Axentsev S, Boon H *et al.* Guggul for hyperlipidemia: A review by the Natural Standard Research Collaboration. Complement Ther Med. 2005; 13:279-290.
6. Urizar NL, Liverman AB, Dodds DT, Silva FV, Ordentlich P, Yan Y *et al.* A natural product that lowers cholesterol as an antagonist ligand for FXR. Science, 2002; 296:1703-1706.
7. Wu J, Xia C, Meier J, Li S, Hu X, Lala DS. The hypolipidemic natural product guggulsterone acts as an antagonist of the bile acid receptor *Cardiovascular Drug*. Mol Endo crinol, 2002; 16:1590-1597.
8. Ory DS. Nuclear receptor signaling in the control of cholesterol homeostasis: Have the orphans found a Home? Circ Res. 2004; 95:660-670.
9. Owsley E, Chiang JY. Guggulsterone antagonizes farnesoid X receptor induction of bile salt export pump but activates pregnane X receptor to inhibit cholesterol 7alpha-hydroxylase gene. Biochem Biophys Res Commun. 2003; 304:191-195.
10. Deng R, Yang D, Radke A, Yang J, Yan B. The hypolipidemic agent guggulsterone regulates the expression of human bile salt export pump: Dominance of transactivation over farsenoid Xreceptor-mediated antagonism. J Pharmacol ExpTher. 2007; 320:1153-1162.
11. Urizar NL, Moore DD. Gugulipid: A natural cholesterol-lowering agent. Annu Rev Nutr. 2003; 23:303-313.
12. Shishodia S, Aggarwal BB. Guggulsterone inhibits NF-kappaB and IkappaBalpha kinase activation, suppresses expression of anti-apoptotic gene products, and enhances apoptosis. J BiolChem. 2004; 279:47148-47158.
13. Ichikawa H, Aggarwal BB. Guggulsterone inhibits osteoclastogenesis induced by receptor activator of nuclear factor-kappaB ligand and by tumor cells by suppressing nuclear factor-kappaB activation. ClinCancer Res. 2006; 12:662-668.
14. Cheon JH, Kim JS, Kim JM, Kim N, Jung HC, Song IS. Plant sterol guggulsterone inhibits nuclear factor kappa-B signaling in intestinal epithelial cells by blocking Ikappa-B kinase and ameliorates acute murine colitis. Inflamm Bowel Dis. 2006; 12:1152-1161.
15. Indian Pharmacopoeia, the Controller of Publications, New Delhi, India, 1996.
16. The Ayurvedic Pharmacopoeia of India, Department of Indian Systems of Medicine and Homeopathy, 1st edition, Ministry of Health and Family Welfare, Government of India, New Delhi, India, 2001.
17. Masten SA, Gum Guggul and Some of Its Steroidal Constituents: Review of Toxicological Literature, US Department of Health and Human Services, National Toxicology Program (NTP), National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health, Durham, NC, USA, 2005, 2.
18. The Ayurvedic Pharmacopoeia of India (Formulations), 1st edition, Department of Indian Systems of Medicine and Homeopathy, Ministry of Health and Family Welfare, Government of India, New Delhi, India, 2007.
19. Karan M, Kumar V, Suneja V, Vasisht K. "Commercial herbal anti-inflammatory formulations-a survey," Pharmacos. 2009; 36:14-25.
20. Sangle VD, Nadkarni SD, Vahalia MK, Darp MS. "The study of effect of ayurvedic processing of Commiphora wightii on gastric irritancy index in experimental animals," Indian Drugs. 2004; 41(5): 268-271.
21. Bhati A, "Essential oil from the resin of *Commiphora mukul*, Hook. Ex. stocks," Journal of the Indian Chemical Society. 1950; 27:436-440.
22. Saxena VK, Sharma KN. "Constituents of the essential oil from *Commiphora mukul* gum resin," Journal of Medicinal and Aromatic Plant Sciences. 1998; 20:55-56.
23. Rücker G. "Monocyclic diterpenes from Indian gugul resin (*Commiphora mukul*)," Archiv der Pharmazie. 1972; 305(7):486-493.
24. Prasad RS, Dev S. "Chemistry of ayurvedic crude drugs-IV: guggulu (resin from *Commiphora mukul* -4 absolute stereochemistry of mukulol," Tetrahedron. 1976; 32(12):1437-1441.
25. Patil VD, Nayak UR, Dev S. "Chemistry of ayurvedic crude drugs—II. Guggulu (resin from *Commiphora mukul*)-2: diterpenoid constituents," Tetrahedron. 1973; 29(2):341-348.
26. Francis JA, Raja SN, Nair M. "Bioactive terpenoids and guggulusteroids from *Commiphora mukul* gum resin of potential anti-inflammatory interest," Chemistry and Biodiversity. 2004; 1(11):1842-1853.
27. Prasad RS, Dev S. "Chemistry of ayurvedic crude drugs-IV: guggulu (resin from *Commiphora mukul*-4 absolute stereochemistry of mukulol," Tetrahedron. 1976; 32(12):1437-1441.
28. Patil VD, Nayak UR, Dev S. "Chemistry of ayurvediccrude drugs—II. Guggulu (resin from *Commiphora mukul*)-2: diterpenoid constituents," Tetrahedron. 1973; 29(2):341-348.
29. Francis JA, Raja SN, Nair MG. "Bioactive terpenoidsand guggulusteroids from *Commiphora mukul* gum resin ofpotential anti-inflammatory interest," Chemistry and Biodiversity. 2004; 1(11):1842-1853.
30. Matsuda H, Morikawa T, Ando S *et al*., "Absolute stereostructures of polypodane-type triterpenes, myrrhanol an andmyrrhanone A, from guggul-gum resin (the resin of *Balsamodendron mukul*)," *Chemical and Pharmaceutical Bulletin.* 2004; 52(10):1200-1203.
31. Kimura I, Yoshikawa M, Kobayashi S *et al*., "New triterpenes, myrrhanol A and myrrhanone A, from guggul-gum resins, and their potent anti-inflammatory effect on adjuvant-induced airpouchgranuloma of mice," Bioorganic and Medicinal Chemistry Letters. 2011; 1198):985-989.
32. Patil VD, Nayak UR, Dev S. "Chemistry of *Ayurvedic* crude drugs I: *Guggulu* (resin from *Commiphora mukul*) 1: steroidal constituents," etrahedron. 1972; 28(8):2341-2352.
33. Purushothaman KK, Chandrasekharan S. "Guggulsterols from *Commiphora mukul* (*Burseraceae*)," Indian Journal of Chemistry Section B. 1976; 14:802-804.
34. Bajaj AG, Dev S. "Chemistry of ayurvedic crude drugs-V. Guggulu (resin from *Commiphora mukul*)-5 some new

steroidal components and, stereochemistry of guggulsterol-I at C-20 and C-22," *Tetrahedron*. 1982; 38(19):2949-2954.
35. Fatope MO, Al-Burtomani SKS, Ochei JO, Abdulnour AO, Al-Kindy SMZ, Takeda Y. "Muscanone: a3-O-(1, 8, 14-trimethylhexadecanyl) naringenin from *Commiphora wightii*," Phytochemistry. 2003; 62:1251-1255.
36. Kakrani HK. "Flavonoids from the flowers of *Commiphora mukul*," Fitoterapia. 1981; 52(5):221-223.
37. Kumar V, Dev S. "Chemistry of ayurvedic crude drugs-VII guggulu (resin from *Commiphora mukul*)-6: absolute stereochemistry of guggultetrols," Tetrahedron. 1987; 43(24):5933-5948.
38. Su SL, Tang JA, Duan YP *et al*., "Isolation and biological activities of neomyrrhaol and other terpenes from the resin of *Commiphora myrrha*," Planta Medica. 2009; 7594):351-355.
39. Matsuda H, Morikawa T, Ando S *et al*., "Absolute stereostructures of polypodane- and octanordammarane-type triterpenes with nitric oxide production inhibitory activity from guggulgumresins," Bioorganic and Medicinal Chemistry. 2004; 12(11):3037-3046.
40. Bose S, Gupta KC. "Structure of *Commiphora mukul* gumI: nature of sugars present and the structure of aldobiouronic acid," Indian Journal of Chemistry Section A. 1966; 2:57-60.
41. Ali MA, Hasan M. "Chemical investigation of *Commiphora mukul* Engl. (*Burseraceae*)," Pakistan Journal of Scientific and Industrial Research. 1967; 10:21-23.
42. Satyavati GV. "Guggulipid: a promising hypolipidemic agent from gumguggul (*Commiphora wightii*)," Economic and Medicinal Plant Research. 1991; 5:48-82.
43. Sarup P, Bala S, Kamboj S. Pharmacology and Phytochemistry of Oleo-Gum Resin of *Commiphora wightii* (Guggulu), Scientifica. 2017; 2015:2-5.