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Review Article

A Review on Bioactive Phytoconstituents and Pharmacological Uses of *Commiphora mukul.*

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Abstract

Commiphora mukul possesses a vast ethno medical history and represents a photochemical reservoir of heuristic medical value. It is one of the key ingredient in various treatment procedures. *C. mukul* contains a wide variety of chemical constituents such as monoterpenoids, diterpenoids, triterpenoids, steroids, sesquiterpenoids and volatil oil. Aim of the review is based on comprehensive review of traditional uses, phytochemistry, pharmacological and toxicological data on genus *Commiphora,* the future research and development to be planned. The need to review this plant is in order to provide scientific proof for its application in traditional medicinal system. The active constituent of the guggulipid is guggulsterone. The extract of *C. mukul* is used to treat variety of disorders in human beings as dyslipidaemia, obesity, inflammation.

Keywords: Guggulsterone, *Commiphora mukul,* phytochemicals.

1. Introduction

The biological properties and pharmacological uses of many of the herbs are still unknown. Importance of plants and its traditional uses are always a concerning issues to resolve health care problems of world [(1)]. Inspite of great development of synthetic molecules, the major source of drug discovery still comes from natural herbal medicine [(2).] The synthetic medicines are having some lacunae owing to their side effects, but the inherent properties of herbal drugs have increased so as to fill the lacunae created by synthetic medicines. [(3)] The scientists are exploring the possibilities of utilizing pharmacologically active compounds from the medicinal herbs [(4)]. *C. mukul* is a small thorny plant (Fig:1), flowers are red, fruit is oval in shape and pulpy in nature.

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The plant is also known as guggul gum, guggal, guggulsterone, guggulu and gum guggul.

Fig. 1. Commiphora mukul plant.

The oleo gum resin of *C. mukul* is called guggulipid [(5)]. The resin produced by the stem of plant has been largely used in Ayurvedic medicine, mainly to treat arthritis, inflammation and also as antioxidant.[(6)] Ketoacids named cis- and trans-4,17 (20)–pregnadiene-3,16-

dione are also known as E and Z guggulsterones[7]. These ketoacids are extracted from the resin and have a safe profile as well as it is the effective remedy for osteoarthritis treatment [8]. This plant has been widely used in the indigenous medicine. It also stimulates phagocytosis by elevating blood leucocytes level as done by all oleo-resins. Guggulu is a complex mixture containing amino acids, aliphatic esters, carbohydrates, diterpenoids, steroids, triglycerides and these ingredients are used in several medicines[9]. The plant has been used as anti-inflammatory, antispasmodic, anti-suppurative, nervine tonic, thyroid stimulant, cardiovascular disorders, anthelmintic, depurative, pyorrhea, skin disorders, leprosy, muscle spasm, urinary disorders, hypertension, antiseptic, vulnerary, antiseptic, aphrodisiac stimulant, liver tonic and demulsant etc. [10, 11, 12, 13, 14, 15, 16, 17, 18]. *C. mukul* also has antibacterial, antifungal, anti-inflammatory and antiarthritic activity. Hypolipidaemic activity was reported in dogs and monkeys [19]. The plant extract showed significant antibacterial activity against human pathogenic strain [20, 21]. The antifungal and antibacterial activity was studied in a variety of pathogenic bacteria [22].

The plant worked as a effective remidy in some infectious diseases in traditional medicine [23]. The plant in it's hydroalcoholic extract acted as a cardioprotective. It prevented the heart from myocardial ischaemia, cardiac failure and the conditions are menifested by increase in heart rate, decreased arterial presssure and altered myocardial contractility [24]. The plant acts as antioxidant and reduces the stickiness of platelets. The ayurvedic herb *Inula racemosa*, in combination with *Commiphora mukul,* isused to attenuate the chest pain and angina pectoris [11,14]. The resin contains E and Z isomers of guggulsterone and related guggulsterols as guggulsterol-I, guggulsterol-II, guggulsterol-III, guggulsterol-IV, guggulsterol-V and guggulsterol-VI. Myrcene and dimyrcene are the two major constituents of oleo resin essential oil. The plant has the property to reduce the cholesterol and triglyceride level. So the plant was found to be of great use in atherosclerosis [25]. Guggulipid, a purified fraction of commiphora mukul has been developed as hypolipidaemic agent at CDRL, Lucknow [26]

Bioactove components

Some of the bioactive compounds like dimyrcene [27], α-camphorene [28], oleic, linoleic, palmitic and stearic acids, sitosterol [29], E and Z guggulsterones [30], (8R)-3α,8-dihydroxy-polypoda-13E, 17E, 21 triene, 20S-acetyloxy-4-pregnene-3,16-dione, 4,17(20)-(trans)-pregnadiene-3,16-dione, 4,17(20)-(cis)-pregnadiene-3,16-dione, 16β-acetyloxy-pregn-4,17(20)-trans-dien-3-one, 3α-acetyloxy-5α-pregnan-16-one have been reported in the *C. mukul.*[31]

Epiexcelsin and 5'-demethoxy-epiexcelsin

The lignans, (+)-5'-demethoxyepiexcelsin (1), and a known lignan, (+)-epiexcelsin (2), were isolated from Litseaverticillata. Lignan 2 showed moderate anti-HIV activity with an IC (50) value of 16.4 microg/ml (42.7 microM), while the known lignan 2 was inactive up to a concentration of 20 microg/ml (48.3 microM).[32]

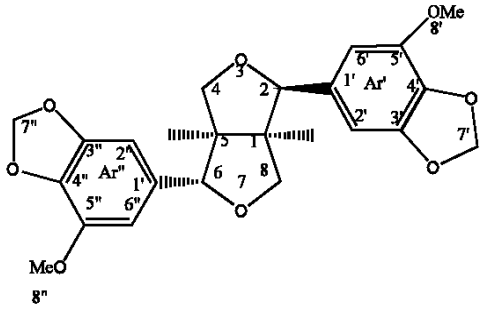

Fig.2. Epiexcelsin.

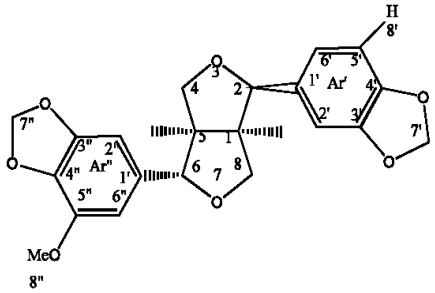

Fig.3.5'-demethoxy-epiexcelsin.

Guggulsterols

Guggulsterone-induced caspasedependant apoptosis. Guggulsterone-induced apoptosis was associated with induction of multidomainproapoptotic Bcl-2 family members Bax and Bak. Interestingly, the expression of

antiapoptotic proteins Bcl-2 and Bcl-xL was initially increased in guggulsterone-treated PC-3 cells but markedly declined following a 16- to 24-hour treatment with guggulsterone [33].Guggulsterone were found to be effective antioxidants against LDL oxidation [34]. Indeed several studies revealed the cardio and neuronal protective activity of guggulsterone in animal models [35].The antioxidant properties of guggulsterols could be explained by the fact that their hydroxyl groups are present at α-positions of double bonds, which is similar to antioxidant vitamins, and are soluble in lipids. The steroid structure also contains H, CH3 and O bond, which indicates that the drug, like other herbs may also quench free radicals such as hydroxyl and singlet oxygen owing to its antioxidant effect thus causing a decrease in lipid peroxides similar to the action of probucol[36].Guggulipid and guggulsterone have been demonstrated to reduce the riskof cardiac complications and improved cardiac function in experimental and clinical studies.[37,38,39,40,41]The protective action of guggulsterone is due to its antioxidant property because it inhibits the generation of oxygen free radicals [42].Guggulsterones were also reported to have protection against oxidative modifications of lipid and protein components of LDL and is induced by Cu^{2+}*in vitro* [43]. A standard alcoholic fraction from guggulipid containing E-guggulsterone was already studied and proved for its protection against free radical damage in the skin and scavenging of superoxide anions and hydroxyl radicals in non-enzymatic test systems [44]. Protective effect of gugulipid isolated from *Commmiphorawhighitii*was studiedagainst STZ-induced memory deficits model of dementia in rodents and the effect was found due to its antioxidant potential. [45] Thus, the antioxidant potential of *C. mukul* observed in the present study may be due to the guggulsterone component of the resin.

The effects of guggulsterones on diabetic rats was observed by sharma *et al.* and they found that guggulsterone showed a differential effect with a significantly improved PPAR gamma epression and activity *in vivo* and in *vitro* respectively. The results suggested that guggulsterone has both hypolipidaemic and hypoglycaemic effects wich can treat type-II diabetes.[46] Guggulsterone is a potent inhibitor of NF-kB. COX-II and MMp-9.[47] It also inhibited paltalet aggregation [48]. Guggulsterone protects the heart against proterenol induced cardiac ischaemia [49]. The protective action of plant is due to it's antioxidant property as it inhibits generation of oxygen free radicals [14].

The E- and Z-guggulsterones, modulates the expression of proteins involved in carcinogenesis by binding to the nuclear receptar [50]. Guggulsterones by exhibiting control over molecular targets that regulates gene expression [51]. Guggulsterones antagonises the chenodeoxycholic acid activated by nuclear Farnesoid X receptar, which regulates the metabolism of cholesterol in liver.

The active components are E-guggulsterones and Z-guggulsterones and the non ketonic part of guggul was found to be responsible for hypolipidaemic action. Guggulsterones may be able to supress the carcinogenic growth in head and neck from smokeless tobacco by targeting smokeless tobacco induced PI3K/Akt pathway that plays a critical role in HNSCC development. Guggulsterones also appear to reduce circulating levels of pro-inflammatory cytokines and markers such as IL-1b, IL-2 and TNF-α [52].

Some researchers studied guggulsterones and isolated the Z- and E- guggulsterone and it's elated guggulsterols like guggulsterols I to VI (Fig.6,7,8,9,10,11). The compounds showed hypolipidaemic properties [53].

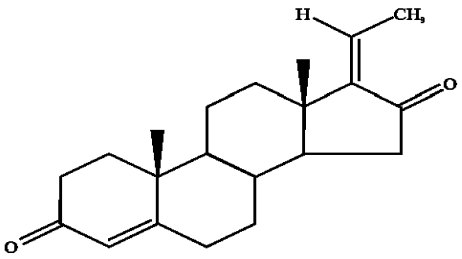

Fig.4. 4, 17(20)-(Trans)-pregnadiene-3.

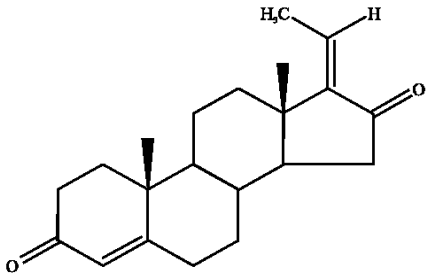

Fig. 5. 4, 17(20)-(cis)-pregnadiene-16-dione (guggulstrone, Z isomer), 16-dione (guggulsterone, E-isomer)

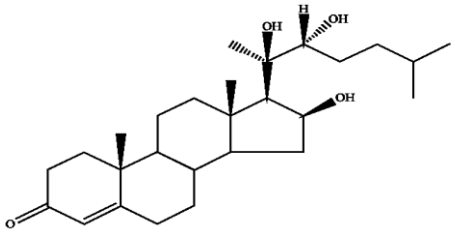

Fig. 6. Guggulsterol-I.

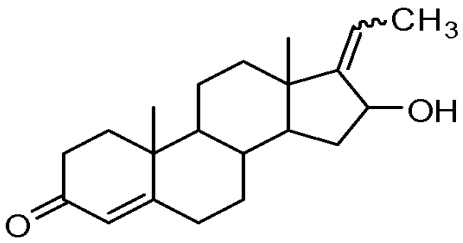

Fig. 7. Guggulsterol-II.

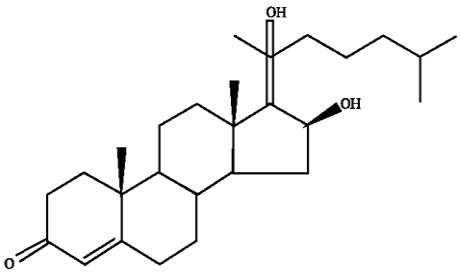

Fig. 8. Guggulsterol-III.

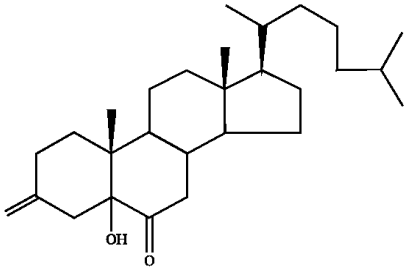

Fig. 9. Guggulsterol-IV.

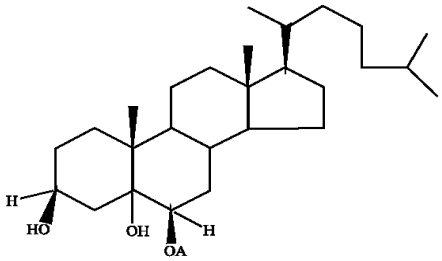

Fig.10. Guggulsterol–V

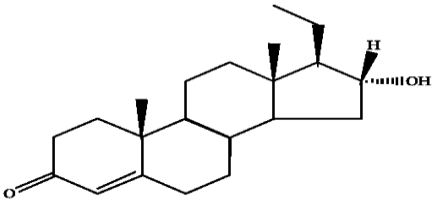

Fig. 11. Guggulsterol – VI (16-α-hydroxy-4-pregnen-3-one).

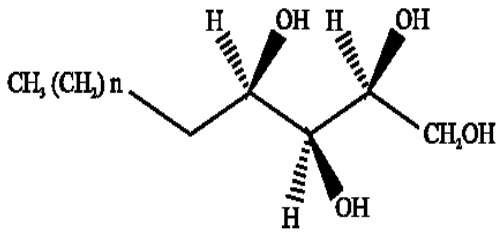

Fig. 12. Guggulsterol-18(D-xylo-octadecane-1,2,3,4-tetrol) n=2.

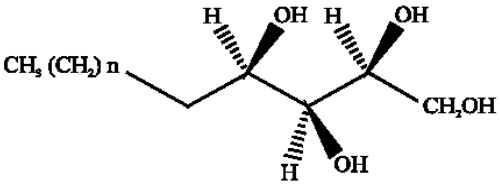

Fig. 13. Guggulsterol-20 (eicon-12,3,4-tetrol).

Naringenin

Neuroprotective effect of naringenin was studied against carbaryl toxicity in mouse neuroblastoma cell line; where it found to be effective neuroprotective by maintenance of mitochondrial membrane potential [(54)] Chronic treatment of diabetic rats with naringenin prevented abnormal changes in vascular reactivity in diabetic rats through nitric oxide [(55)]. Therapeutic potential of naringenin was

studied in retinopathy where it is proven to be effective for the protection of ocular ischemic diseases [56]. Naringenin (Fig.14) can prevent the accumulation of plasma lipids and lipoproteins very effectively. Naringenin also has hepatoprotective activity. The flavonoids displaying antihistaminic, anti-inflammatory, antiviral and antibacterial properties[57]

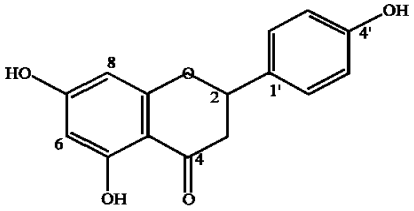

Fig. 14. Naringenin.

Cambranoids

Yu *et al*. (2009) observed that, cambrenoids did not show a noticeable effect on FXR, but lowered the cholate (1)-activated rate of human pancreatic IB phospholipase A2 (hPLA2), which controls gastrointestinal absorption of cholesterol and fat.

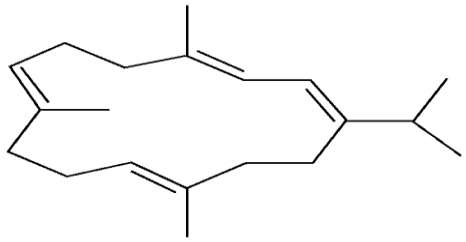

Fig. 15. Cambrenoids.

Myrrhanol-A

It is the triterpenoid of C. mukul gum resin and displayed a potent antiinflammatory effect on exudative pouch fluid, granuloma weight in adjuvant-induced air pouch granuloma of mice and angiogenesis. It was found that effects produced by Myrrhanol were more potent than convensional antiinflammatory drug hydrocortisone [57]. Oleo-gum resin of *C. mukul* in petrolium ether extract in a dose of 500mg/kg p.o. inhibited carrageenan-induced inflammation and cotton pellet granuloma, as well as significant antipyretic activity in mice [58]. Myrrhanol A, significantly reduced pain and stiffness in osteoarthritis.

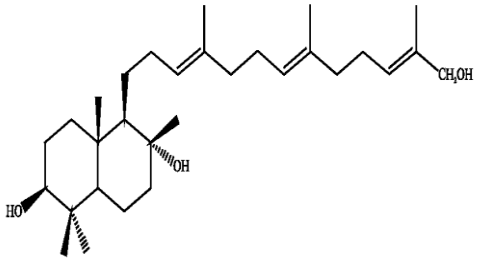

Fig. 16. Myrrhanol A.

α-pinene

It is a bicyclic monoterpine and showed considerable antifungal activity [59]. However there is no clear idea about it's antimicrobial activity [60].

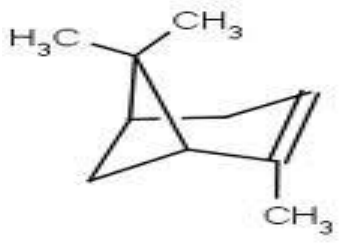

Fig. 17. α- pinene.

Eugenol

Eugenol (Fig. 18), by acting as a chain breaking antioxidant, inhibits the lipid peroxidation [61]. This action may play a very important role in cell proliferation and may be the most possible mechanism of action of eugenol as antimicrobial agent [62]. Eugenol causes apoptosis and is also involved in cytotoxic process [63]. Eugenol also inhibits the mutagenicity of B1 and N-methyl-N'nitrosoguanidine [64]

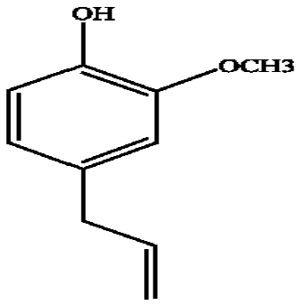

Fig. 18. Eugenol.

Ellagic acid

The ellagic acid has antimutagen, antioxidant and anticancer properties [65]. The research studies have shown the anticancer activity on breast, skin, oesophagus, colon, pancreas and breast. Ellagic acid prevents destruction of

P53 gene by cancer causing cell. Ellagic acid can bind with carcinogens and can make them inactive.Dietary ellagic acid causes a depletion in total hepatic mucosal cytochrome and increase in hepatic phase II enzyme activities. And thereby enhances the ability of target cells to detoxify the reactive intermediates [66]. Ellagic acid showed the protective effect against chemically induced cancer [66]. Oral administration of ellagic acid can prevent carbon tetrachloride induced toxicity and liver fibrosis [67]. The ellagic acid showed good antviral and antibacterial properties [67]. It bounds to sugar molecules in plants to convert in to ellagitanin, a potent antimicrobial agent. This molecules protects the plants from infections and parasites.

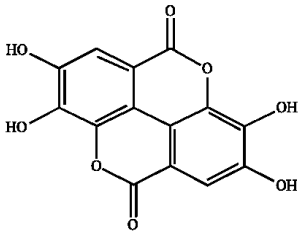

Fig. 19. Ellagic acid.

L-arabinose

L-Arabinose is a natural, poorly absorbed pentose that selectively inhibits intestinal sucrase activity. To investigate the effects of L-arabinose feeding on lipogenesis due to its inhibition of sucrase, rats were fed 0-30 g sucrose/100 g diets containing 0-1 g L-arabinose/100 g for 10 d. Lipogenic enzyme activities and triacylglycerol concentrations in the liver were significantly increased by dietary sucrose, and arabinose significantly prevented these increases. Arabinose feeding reduced the weights of epididymal adipose tissue. Moreover, plasma insulin and triacylglycerol concentrations were significantly reduced by dietary L-arabinose. These findings suggest that L-arabinose inhibits intestinal sucrase activity, thereby reducing sucrose utilization, and consequently decreasing lipogenesis[68]

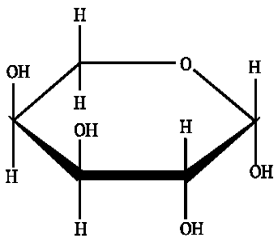

Fig. 20. L-arabinose.

Myrrhanols B, Myrrhanones A, Myrrhanones B

Myrrhanol A, a new triterpene isolated from guggul (Balsamodendron or Commiphora mukul Hook.)-gum resin, displays a potent anti-inflammatory effect on exudative pouch fluid, angiogenesis, and granuloma weights in adjuvant-induced air-pouch granuloma of mice.Its effects were more marked than those of hydrocortisone and the 50% aqueous methanolic extract of the crude drug. Absolute stereostructures of polypodane- and octanordammarane- type triterpenes with activities like inhibition of nitric acid production were studied by Matsuda *et al.* They observed several triterpines showed inhibitory effects on production of nitric acid and induction of inducible nitric oxide synthase.

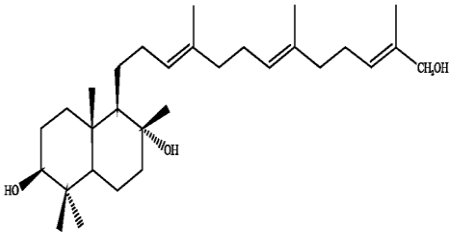

Fig. 21. Myrrhanones A.

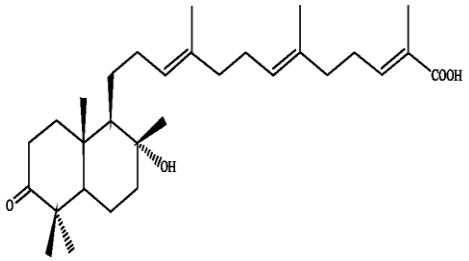

Fig. 22. Myrrhanones B.

Muscanone -

It is the antifungal flavanone isolated from C. mukul along with known naringenin. It showed good antifungal activity against the fungi *Candida albicance* at 250 µg/ml [69]

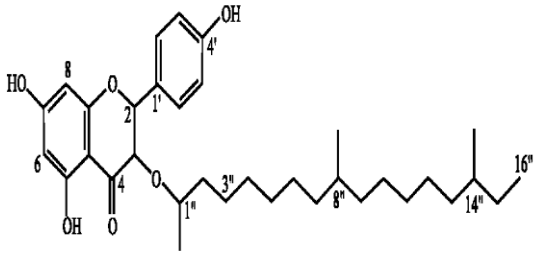

Fig. 23. Muscanone

Diayangambin

Immunomodulatory and anti-inflammatory effect of diayangambin both in vivo and in vitro was studied by De Leon *et al*. (2002). They found that diayangambin inhibited human mononuclear cell proliferation with an IC_{50} value of 1.5 (0.5-2.8) µM. The compound also reduced 40.8% prostaglandin E2 generation in stimulated RAW 264.7 macrophage cell line at 10 µM and *In vivo*, it showed the clear reduction of ear swelling at a dose of 40mg/kg orally to the mice previously treated with 2,4-dinitrofluorobenzene. The inhibited swelling was associated with reduction of leucocyte infiltration. Diayangambin showed good anti-inflammatory activity in rodents wherein the edema was induced by carragenan. It showed reduction in paw volume and prostaglandin E2 production. So, finally they concluded the use of diayangambin as immunomodulatory and anti-inflammatory [70]

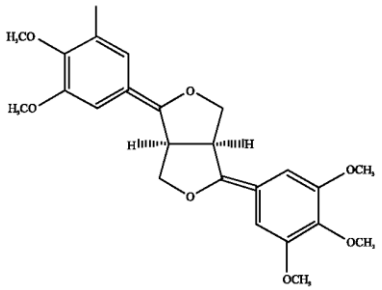

Fig. 24. Diayangambin.

Quercetin

The main flavonoids components of flowers of *C. mukul* were identified as quercetin (Fig.25), quercetin 3-O-β-D-galactoside (Fig. 27), quercetin 3-O-α-L-arabiniside (Fig. 26), quercetin-3-O-β-D- glucuronide[71], quercetin-3-O-α-L-rhamnoside (Fig. 28). The flavonoids pelargonodine-3, 5-di-O-glucoside is the anthocyanidin also isolated from Commiphora mukul flowers. It have been reported in some of the research studies that, in vitro, quercetin can inhibit various cytokines including TNF-β [72]. Anticarcinogenic phase II marker enzyme, Quinine reductase was effectively induced by quinine reductase. Only glycoside quercetin-4'-glucoside was able to induce QR activity in this assay [73].

The compound has a wide range of activities. It acts as good antioxidant *in vitro* and inhibit nitric acid pathway [74], inhibit LDL oxidation [75], anti-inflammatory most possibly due to it's influence on the production of leokotrienes, prostaglandins [75] and cytokines [76], through interaction with type II oestrogen binding site, showed good anticancer property [77], induction of apoptosis [78,79].

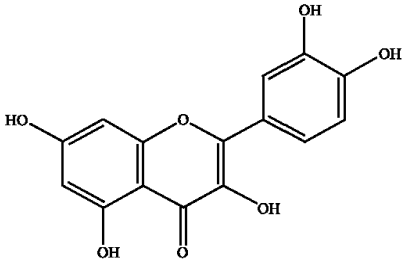

Fig. 25. Quercetin.

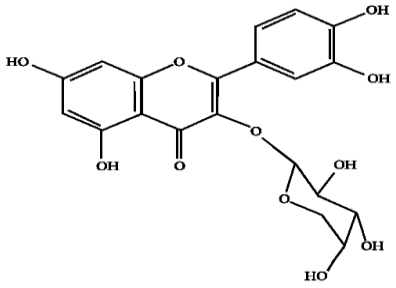

Fig. 26. Quercetin 3-O-α-L-arabiniside.

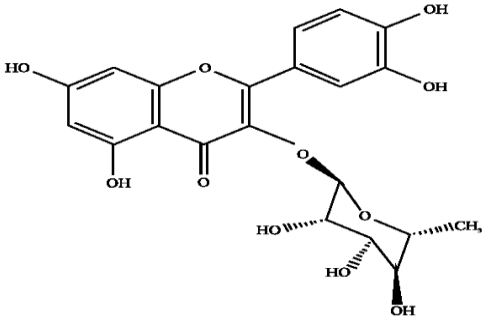

Fig. 27. Quercetin 3-O-β-D-galactoside.

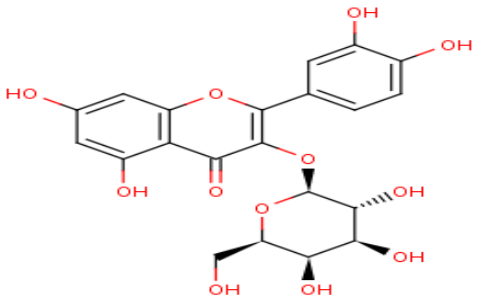

Fig. 28. Quercetin-3-O-α-L-rhamnoside

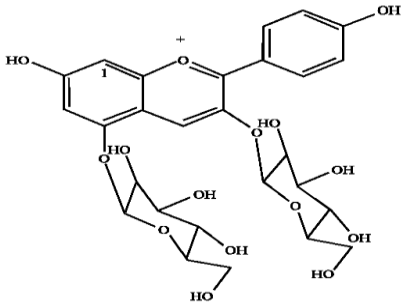

Fig. 29. Quercetin-3-O-β-D- glucuronide

Methyl Chavicol

The compound is also known as estragole[80].

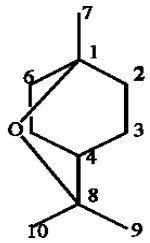

Fig. 30. Methyl chavicol.

1,8 cineole

A triterpenoid 1,8-cineole was studied for it's antinociceptive and anti-inflammatory effect, the results obtained suggested that, the compound has anti-inflammatory activity against some types of experimental inflammation in rats like cotton pellet induced granuloma and carrageenan induced paw edema [81]. Cineole also inhibits acetic acid induced increase in peritoneal capillary permeability and nociception induced by intraplantarformaline and intraperitoneal injection of acetic acid [81].

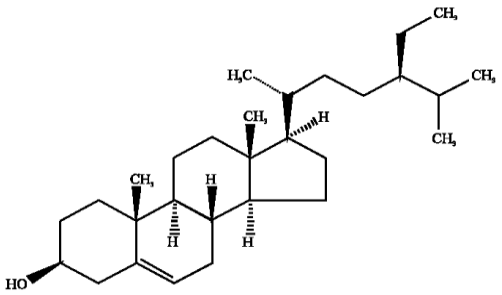

Fig. 31. 1, 8 Cineole.

β -sitosterol

β -sitisterol has structural similarity with cholesterol. So it is reasonable that β -sitisterol can inhibit cholesterol absorption in the body [82] and thus can inhibit the plasma cholesterol levels [83]. It is also known to improve liver function tests [84]. It can exert good anticancer activity in prostate and colon cancer [85]. Compound has in vivo topical anti-inflammatory activity in acute but not chronic use [86].

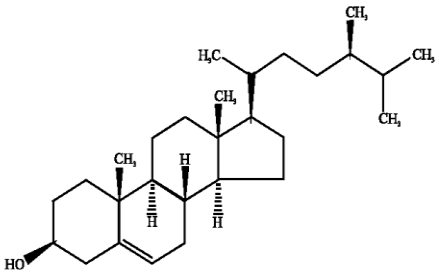

Fig. 32. β –sitisterol

Sigmasterol and campesterol

Sigmasterol and campesterol are the two most commonly found phytosterols with (C29) and (C28) respectively [87]. These are used in a variety of food products [88] due to their cholesterol lowering effect and hence can provide the protection against various cardiovascular diseases [89]. Acts as anticancer in mice [90] and acts as HIV reverse transcriptase inhibitor.

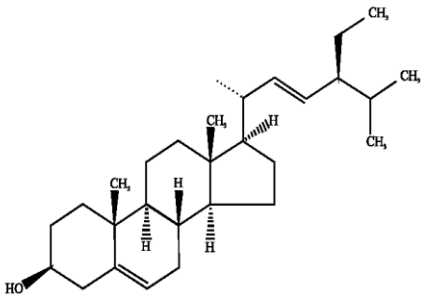

Fig.33. Sigmasterol.

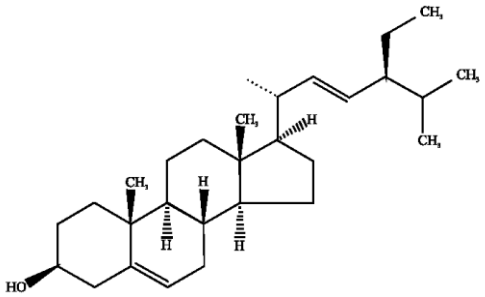

Fig. 34. Campesterol.

(±)-linalool and α-terpinaol

The compounds exhibited strong antimicrobial activity against cariogenic and periodontopathic bacteria. The concentration of these compounds should be kept below 0.4mg/ml [91].

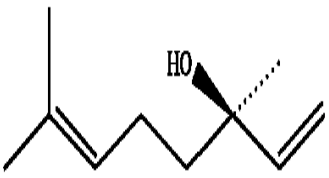

Fig. 35.(±)-linalool.

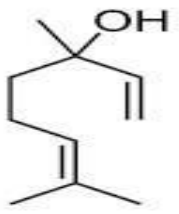

Fig. 36. α-terpinol.

Mansumbinoic acid and mansumbinone

The compounds exhibited significant anti-inflammatory activity. Mansumbinoic acid reduced the joint swelling [92]. The compound was also studied for antibacterial property and it was observed that mansumbinone and 3,4-seco-mansumbinoic acid showed antimicrobial property against the number of staphylococcus strains like SA1199B, XU212, ATCC25923, RN4220, EMRSA15. 3,4-seco-mansumbinoic acid showed highest MIC against *staphylococcus aureus* SA1199B ($4mL^{-1}$) [93].

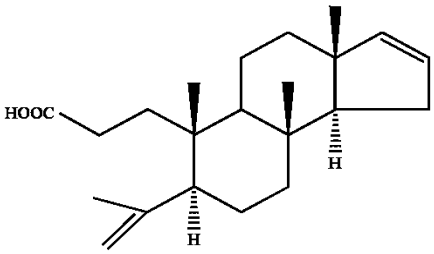

Fig.37. Mansumbinoic acid..

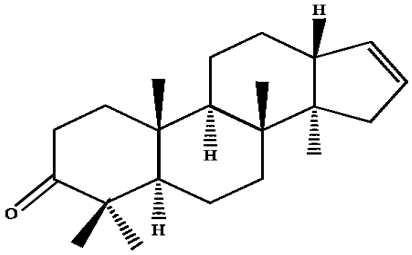

Fig.38. Mansumbinone.

Conclusion

Commiphora mukul have been studied in various laboratories for its pharmacological properties. The bioactive moieties can be categorized as both beneficial and poisonous. The effects may depend on the amount eaten and the context of intake.

The plant can be regarded as of huge medicinal value as it is an active source of number of bioactive compounds such as guggulsterone, eugenol, ellagic acid, quercetin, campesterol and campesterol. Guggulsterones may be c to prevent neck and head from chewing tobacco. Eugenol may play a very vital role in cell proliferation more specifically in tumors. Ellagic acid possess anti-mutagen, antioxidant, anticancer properties. Research studies have showed its

anticancer activities in breast cancer, oesophageal, skin, colon, prostate and pancreatic cancers. Quercetin acts as antioxidant in vitro to inhibit LDL oxidation, inhibition of nitric acid pathway and also have anti-inflammatory property. Plants being the gift of nature still possess unexplored potential.

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