Focus on Phytochemical Screening, Chemical Constituents, Pharmacological Effects and Medical Uses of *Gummi myrrha*

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Abstract: *Gummi myrrha* is the air-dried gum resin taken from the branches and stems of *Commiphora molmol* Engler (Burseraceae). The other names include myrrh, myrrhe, myrrha, Abyssinian myrrh, bal, barakande, bisabol myrrh, bola, guban myrrh, habaq-hagar-ad, heerbol, heerabol myrrh, mbebe, moyao, morr, myrr, Myrrhenbaum, molmol, turari, Somali myrrh [1-8]. Many *Commiphora* species are cultivated in tropical areas of Africa. *Commiphora molmol* occurs in Somalia, and it is cultivated in the Arabian Peninsula, North Africa, India, Ethiopia, Kenya, and Tanzania [1, 2, 7]. *Commiphora* species are shrubs with 3 m high. It has rounded tops, thick trunks, dark brown bark, and large, sharply pointed thorns on the stem.

Keywords: *Gummi myrrha*; *Commiphora molmol*; pharmacology; medicine; dose.

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1. Introduction

*Gummi myrrha* is the air-dried gum resin taken from the branches and stems of *Commiphora molmol* Engler (Burseraceae). Other names include myrrh, myrrhe, myrrha, Abyssinian myrrh, bal, barakande, bisabol myrrh, bola, guban myrrh, habaq-hagar-ad, heerbol, heerabol myrrh, mbebe, moyao, morr, myrr, Myrrhenbaum, molmol, turari, Somali myrrh [1-8]. Many *Commiphora* species are cultivated in tropical areas of Africa. *Commiphora molmol* occurs in Somalia, and it is cultivated in the Arabian Peninsula, North Africa, India, Ethiopia, Kenya, and Tanzania [1, 2, 7]. *Commiphora* species are shrubs with 3 m high. It has rounded tops, thick trunks, dark brown bark, and large, sharply pointed thorns on the stem. It has many

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asymmetrical stunted and spiny. The leaves are unequal and alternate. The flowers are small, yellow-red fascicled, and arranged in terminal panicles. The calyx is tubular, and teeth while the petals are found inserted on the edge of the disk. The stamens have 8-10 on disk alternately long and dilated below. The fruits are oval drupes (0.3 cm long). *Gummi myrrha* is taken from the schizogenous resin duct when stems are damaged or incised [1, 2, 6, 8]. *Commiphora leptophloeos* possesses polyphenols such as rutin, vitexin, and quercetin diglycosides. *Commiphora leptophloeos* has an important in-vitro and in-vivo antioxidant effect [9]. *Commiphora myrrha* water extract resin is used against many diseases in Saudi Arabian patients, such as many diseases related to abnormal cytochrome P450 expression where it modulates cytochrome P450-2C8, cytochrome P450-2C9, cytochrome P450-2C19, and cytochrome P450-3A4 gene expression [10]. Guggulipid is an ethyl acetate extract of resin known as guggul from *Commiphora wightii* or *Commiphora mukul*. It is used to treat arthritis, inflammation, obesity, cardiac protection, antiulcer, anti-epileptic, and disorders of lipid metabolism [11]. *Since ancient times, Commiphora myrrha has been used in traditional medicines against many health problems, including bone disorders. Commiphora myrrha* has anti-inflammatory activities by inhibiting the secretion of nitric oxide and suppressing the cyclooxygenase-2, interleukin-6, interleukin-1β, and inducible nitric oxide synthase expression [12].

2. Chemical constituents of *Gummi myrrha*

*Gummi myrrha* contains 6% essential oil [3]. The high-performance liquid chromatography revealed the appearance of furanosesquiterpenes constituent [13,14]. The phytochemical analyses of *Commiphora leptophloeos* leaf extract showed 6 flavonoids identified as orientin, isoorientin, vitexin and isovitexin, quercitrin, and isoquercitrin [15]. *Commiphora wightii* contains guggulsterones E and Z constituents which are responsible for plant pharmacological actions [16]. Commiphorane K, Commiphoranes L-N, sesquiterpenoids, commiphorane O, and sesquiterpenoid were isolated from Commiphora Resina. Commiphoranes L suppresses lipopolysaccharide-stimulated production of tumor necrosis factor-α in a dose-dependent manner [17]. 2 new compounds (Sesquiterpene 1 and Sesquiterpene 2) were isolated from myrrh by chromatography analysis [18]. Arabic *Commiphora myrrha* resin contains 2 furano-sesquiterpenoids (2-methoxyfuranodiene and 2-acetoxyfuranodiene) [19].

3. Major chemical constituents of *Gummi myrrha*

*Gummi myrrha* contains: resins (25-40%), essential oil (3-8%) and a water-soluble gum (30-60%) [1, 20]. The *Gummi myrrha* contains 20% proteins and 65% carbohydrates (galactose, 4-O-methylglucuronic acid, and arabinose). The major constituents of the *Gummi myrrha* essential oil are furanosesquiterpenes [8] and the monoterpenes α-, β- and γ-bisabolene. A 2 new arabinofuranosidetridecanol (1,2-tridecanediol-1-O-α-L-5’-acetylaraibinofuranoside and 1,2-tridecanediol-1-O-α-L-arabinofuranoside) together with 1,2-tridecanediol were isolated from *Commiphora merkeri* [21]. Commiphoins A-C (3 new cadinane-type sesquiterpenes) were isolated from the *Commiphora myrrha*, and they all had significant anti-Alzheimer’s disease activities [22].
4. *Gummi myrrha* medicinal uses

*Gummi myrrha* is found in 2 forms (an ointment and oral uses). As an ointment, it is used for mild inflammations treatment. As an oral use, it is used to treat aphthous ulcers, pharyngitis, tonsillitis, common cold, and gingivitis [3, 23-25]. *Commiphora myrrha* essential oils possess a nematicidal effect [26]. *Commiphora myrrha* and its resin (myrrh) treat many inflammatory and metabolic disorders. Therefore *Gummi myrrha* controls osteoporosis in postmenopausal women [27]. *Commiphora molmol* is used in the treatment of early/mild common flu and especially in COVID-19 treatment. *Commiphora molmol* improves general patient well-being and pushes the human towards the therapeutic approaches [28]. *Commiphora molmol* showed higher cure rates than Praziquantel (standard treatment for immunocompetent and immunocompromised). It reached 100% good improvement of histopathological variations in the intestine and liver [29]. *Commiphora mukul* has pro-androgenic activity and performs an important effect on sperm parameters in diabetic rats, where it increases the total sperm count and decreases the proportion of sperm with abnormal morphology [30).

5. *Gummi myrrha* in traditional medicine

*Gummi myrrha* is used as an emmenagogue, expectorant, and antidote for toxins and to stop blood coagulation. It is treated menopausal symptoms, arthritic pain, diarrhea, fatigue, headache, jaundice, and indigestion. It is used for the treatment of burns and hemorrhoids in the form of an ointment [7, 8, 31, 32]. *Commiphora myrrha* has anti-viral, antipyretic, blood purifier, cardioprotective and expectorant activities [33]. *Commiphora mukul* is applied for the treatment of osteoarthritis in traditional Persian medicine. This disease is known to be the leading cause of pain and disability in the elderly [34]. *Commiphora mukul* ameliorates inflammatory factors (interleukin-1β and tumor necrosis factor-α) and antioxidative factors (catalase, glutathione, superoxide dismutase, malondialdehyde and nitrite). Also, *Commiphora mukul* prevented brain apoptosis by the inhibition of brain caspase-3 and Bax therefore, *Commiphora mukul* is useful to treat multiple sclerosis-related symptoms [35].

6. Pharmacology of *Gummi myrrha*

6.1. Experimental pharmacology.

6.1.1. Cardioprotective activity.

*Commiphora molmol* has a cardio-protective effect in the myocardial Infarction animal model by improving oxidative stress and myocytes. *Commiphora molmol* abolishes apoptotic and inflammatory activities in the myocardial Infarction animal model [36].

6.1.2. Analgesic and antipyretic activities.

The water suspension of *Gummi myrrha* had analgesic effects in mice by the hot-plate assay [37]. The intake of 50 mg/kg of a sesquiterpene, furanoeudesma-1,3-diene (taken from *Gummi myrrha* resin also had analgesic effects in mice as measured by the acetic acid writhing test [37]. The analgesic effect of *Prunus armeniaca* is similar in its effect to *Cupressus sempervirens* in its effect [38]. The intake of 400 mg/kg of ethanol extract of the resin declined
writings induced by acetic acid in mice by 25% [39]. The intake of 500 mg/kg of petroleum ether extract or ethanol extract of *Gummi myrrha* resin declined yeast-induced pyrexia in mice [40, 41].

6.1.3. Anticoagulant activity.

The intake of 100 mg/kg bw of ethyl acetate extract of *Gummi myrrha* resin stopped platelet aggregation in mice. The water extract of *Gummi myrrha* resin was not active [38]. The intake of 100 mg/kg of ethyl acetate extract of *Gummi myrrha* resin had antithrombotic activity in mice [42]. *Commiphora mukul* declined anal irritation, bleeding, pain, and swelling sense; therefore, *Commiphora mukul* improved clinical signs and symptoms in patients with hemorrhoids [43].

6.1.4. Antidiabetic activity.

The intake of 10 ml/kg of water extract of *Gummi myrrha* resin/ day for 7 days declined blood glucose levels in diabetic rats [44]. The intake of 150-175 mg/kg of 2 furanosesquiterpenes (taken from *Gummi myrrha* resin) declined blood glucose levels in obese diabetic mice [45]. *Commiphora myrrha* resin (0.5-10 mg/ml) induced a concentration-dependent increase in insulin secretion where stimulation of insulin secretion in a concentration-dependent manner occurred after incubation of mice islets to *Commiphora myrrha* (0.1-10 mg/ml). *Commiphora myrrha* (2 mg/ml) caused rapid and reversible increases in insulin secretion from both mouse and human islets; therefore, *Commiphora myrrha* resin solution has a direct stimulatory effect on β-cells of Langerhans [46].

6.1.5. Anti-inflammatory activity.

The intake of 400 mg/kg of water extract of *Gummi myrrha* resin/ day for 18 days to rats with Freund's adjuvant-induced arthritis declined the inflammation progress [45]. The intake of 80 mg/kg of petroleum ether extract of *Gummi myrrha* resin stopped carrageenan-induced edema in rats [47]. The intake of 200-400 mg/kg of ethanol extract of *Gummi myrrha* resin declined xylene-induced ear inflammation in mice by 50% [48]. *Commiphora leptophloeos* declined the paw-edema and decreased myeloperoxidase effect at 200 and 400 mg/kg doses. *Commiphora leptophloeos* reduced the leukocytes migration, total protein concentration, myeloperoxidase, and malondialdehyde levels. *Commiphora leptophloeos* declined tumor necrosis factor-α level and increased interleukin-10 secretion [49]. *Commiphora molmol* exhibited an anti-inflammatory effect via the inhibition of the inflammatory mediator release. An intestinal barrier stabilizing effect was observed for myrrh from *Commiphora molmol*. Thus, *Commiphora molmol* is used in the treatment of an inflammatory bowel disease [50].

6.1.6. Cytoprotective activity.

The intake of 250 mg/kg of a water suspension of *Gummi myrrha* resin declined the formation of ulcers induced by ethanol, sodium chloride, and indomethacin in rats by increasing the secretion of gastric mucus [51]. *Commiphora kua* ameliorates transaminase enzymes, lactate dehydrogenase, alkaline phosphatase, and bilirubin, as well as, increases
antioxidant activity such as superoxide dismutase, catalase, and glutathione and induces important improvement of liver tissues; therefore, it possesses hepatoprotective effect [52].

6.1.7. Antimicrobial and antileishmanial activities.

Commiphora molmol with fluconazole against Candida albicans showed the best synergistic antibacterial activity [53]. On the other hand, Commiphora wightii possesses an antileishmanial effect [54]. Commiphora molmol manufactures silver nanoparticles with antiparasitic effects such as the anti-leishmanial effect in in-vitro and in-vivo studies [55]. Commiphora leptophloeos has an antifungal and antibiofilm effect. It is safe for human erythrocytes. Also, B-type oligomeric procyanidins, which were isolated from Commiphora leptophloeos exhibited an antifungal effect against Candida strains [49]. The furanodienone and curzerene constituent of Commiphora myrrha affect viral replication by acting on different steps of the virus life cycle [56]. Myrrh oil from Commiphora molmol has antibacterial activity and causes no bacterial resistance to occur. This is an exceptional example of an antibiotic that kills non-growing bacteria [57]. Myrrh essential oil has antibacterial and cytotoxic agents (on human liver cancer, human breast cancer, and colon cancer cell lines [58]. Commiphora myrrha showed antibacterial activity; therefore, it treated mixed cutaneous infections [59].

6.2. Clinical pharmacology.

6.2.1. Anti-obesity activity.

Three months of treatment with Commiphora mukul declined serum cholesterol by 1.9% in the placebo and 3.3% in the intervention groups. Serum low-density lipoproteins declined by 4.9% and 4.8% in the placebo and intervention groups, respectively [60]. The increased fatty acid oxidation and lipolysis of Commiphora myrrha play an important role in decreasing lipids [61] Commiphora mukul treatment for 12 weeks declined low-density lipoprotein and cholesterol values by 18.78 mg/dL and 16.78 mg/dL, respectively, without any side effects [62]. Guggulsterone, the constituent in Commiphora wightii and Commiphora mukul, possess good cholesterol-lowering, appetite-regulating, and immunomodulatory effect [63]. The cholesterol-lowering and immunomodulatory effects of Commiphora myrrha play an important role in protecting from infectious diseases [64]. Commiphoranes A-E (5 new sesquiterpenoids, dinorditerpenoids, and heterodimers with carbon skeletons) were isolated from Resina Commiphora. These metabolites possess lipid regulatory activities [65]. Commiphora myrrha ameliorated a high-fat diet that caused higher body glucose, more body gain, high body fat, and ketone. These metabolites restored higher liver oxidative production, liver histopathology, and higher protein expression [66].

6.2.2. Antidiarrheal activity.

Commiphora leptophloeos leaf ethanol extract has an antidiarrheal effect due to inhibiting intestinal motility and antispasmodic effect through the antagonism of muscarinic receptors [67].
6.2.3. Wound healing activity.

Myrrh mouthwash has an improvement activity on wound healing during the early period after tooth extraction. Thus, Myrrh mouthwash improves postoperative surgical-site edema, tenderness, and socket size [68]. An improvement in the episiotomy wound healing was significantly greater in patients receiving Commiphora myrrha than those receiving frankincense or betadine on 2nd and 7th postpartum days in primiparous women [69].

7. Toxicology of Gummi myrrha

The oral intake of ethanol extract of Gummi myrrha resin in rats (1000 mg/kg), intramuscular injection (500 mg/kg), or intraperitoneal injection (250 mg/kg) daily for 2 weeks induced huddling, ruffled hair, depression, jaundice, hepato-nephropathy, hemorrhagic myositis and patchy peritonitis at the injection site. Also, there was an increase in serum alanine phosphatase, alanine aminotransferase, bilirubin, cholesterol, creatinine levels, and decreased total protein and albumin levels. With the decrease of the above-mentioned doses to their halves, the adverse effects were declined [70]. The oral lethal dose of the essential oil is 1.65 g/kg in rats [71]. There were no deaths reported in mice after intra-gastric injection of 3 g/kg of ethanol extract of Gummi myrrha resin [37].

Commiphora leptophloeos has no cytotoxicity, and acute toxicity did not result in any sign of toxicity and mortality or significant changes on the biochemical parameters [49]. The intra-gastric injection of 500 mg/kg of petroleum ether extract of Gummi myrrha resin declined carrageenan-induced edema and cotton pellet-induced granuloma in rats [23]. The intra-gastric intake of -5 g/kg of the resin/ day to Nubian goat kids caused grinding of teeth, salivation, soft feces, in-appetence, jaundice, dyspnoea, ataxia, and recumbency. There was an increase in serum alanine phosphatase activity and bilirubin, cholesterol, triglycerides, and creatinine levels while decreasing total protein and albumin levels. The oral dose of 0.25 g/kg/ day was not toxic [72].

The oral intake of Gummi myrrha resin for 24 hours (acute) and 90 days (chronic) toxicity studies in mice at doses of 0.5 g/kg, 1 g/kg, or 3 g/kg, and 100 mg/kg/ day, respectively showed no significant increase in mortality in an acute or chronic study. In the chronic study, there was an increase in body weight and increases in the weight of the testes, cauda epididymides, and seminal vesicles in treated animals compared with controls. Treated animals also showed an increase in red blood cells and hemoglobin levels. No spermato-toxic effects were observed in treated animals [73].

8. Pharmacokinetic and pharmacodynamics of Gummi myrrha

Commiphora mukul increased the bioavailability of Rosuvastatin calcium (a potent synthetic inhibitor used to treat dyslipidemia) in both single-dose and multiple-dose. It reduced the absorption rate of Rosuvastatin calcium but showed an increase in the maximum serum concentration of Rosuvastatin calcium. Commiphora mukul decreased the rate of absorption of Rosuvastatin calcium in the intestinal lumen. The hypolipidemic activity of Rosuvastatin calcium was augmented by Commiphora mukul extract in hyperlipidemic rats [74].
9. Adverse reactions of Gummi myrrha

The ointment of Gummi myrrha essential oil was non-irritating, non-sensitizing, and non-phototoxic to the human skin [47], although, in other studies, the ointment of the resin to the human skin caused contact dermatitis [75-77].

10. Contraindications of Gummi myrrha

Gummi myrrha is used as an emmenagogue, although its safety during pregnancy has not been established. Therefore, Gummi myrrha should be used during pregnancy under a professional doctor [78].

11. Warnings of Gummi myrrha

The Gummi myrrha resin tincture may cause a transient burning sensation and irritation of the palate [3].

11. Precautions of Gummi myrrha

11.1. Drug interactions.

There is no drug interaction that has been reported, but oral intake of Gummi myrrha may interfere with antidiabetic drugs due to the resin declining the blood glucose level. Patients taking anticoagulant drugs should check their healthcare provider before use of the resin.

11.2. Carcinogenesis, mutagenesis, impairment of fertility.

Water extract of Gummi myrrha resin (40 mg/plate) without any mutagenic activity in Salmonella/microsome test using Salmonella typhimurium strains [79]. The intra-peritoneal injection of water extract of Gummi myrrha resin (10-40 times the normal therapeutic dose) did not have mutagenic effects [80]. The water extract of the resin (40 mg/plate) inhibited aflatoxin B1-induced mutagenesis in Salmonella typhimurium strains [80]. Commiphora mukul has been shown to have an antitumor effect in non-small cell lung cancer [81]. The antitumor effect of Gummi myrrha plays an important role in colon cancer protection [82]. Commiphora wightii has anti-cancer and anti-metastatic effects in both murine and human breast cancer cell lines. Thus, Commiphora wightii treats breast cancer growth and metastasis [83]. The intragastric injection of 125-500 mg/kg of Gummi myrrha resin did not have clastogenic effects but was cytotoxic in normal mice. In the mice bearing tumors, the resin had antitumor activity and was reported to be as effective as the antitumor agent cyclophosphamide [84].

11.3. Pregnancy: non-teratogenic effects.

Gummi myrrha should be used during pregnancy under a professional doctor [77].

11.4. Nursing mothers.

The Gummi myrrha should not be used by nursing mothers without consulting a healthcare practitioner.
11.5. Paediatric use.

The *Gummi myrrha* should not be administered to children without consulting a healthcare practitioner.

11.6. Other precautions.

There is no information on *Gummi myrrha* general precautions or precautions concerning drug and laboratory test interactions; or teratogenic effects in pregnancy.

12. Dose of *Gummi myrrha*

There are many forms of *Gummi myrrha* such as; capsules, powdered resin, myrrh tincture, and ointment form for topical use [24]. *Gummi myrrha* should be stored in a tightly sealed container away from heat and light. Myrrh tincture (1:5 g/ml, 90% ethanol), undiluted tincture applied to the affected area 2 or 3 times/ day; mouth rinse solution (5-10 drops of the tincture) in a glass of water [24]; mouthwash solution (30-60 drops of the tincture) in a glass of warm water [23]; *Gummi myrrha* ointment applied to the affected areas on the gums or the mucous membranes of the mouth with a brush or cotton swab, 2 or 3 times/ day [23]; *Gummi myrrha* dental powder (10% powdered gum resin) [24].

13. Conclusions

*Gummi myrrha* is the air-dried gum resin taken from the branches and stems of *Commiphora molmol* Engler (Burseraceae). The other names include myrrh, myrrhe, myrrha. *Gummi myrrha* contains resins (25-40%), essential oil (3-8%), and a water-soluble gum (30-60%). *Gummi myrrha* is used to treat aphthous ulcers, pharyngitis, tonsillitis, common cold, and gingivitis. It treats menopausal symptoms, arthritic pain, diarrhea, fatigue, headache, jaundice, and indigestion. The pharmacology activity of *Gummi myrrha* includes experimental and clinical pharmacology. Experimental pharmacology includes cardio-protective, analgesic, antipyretic, anticoagulant, anti-diabetic, anti-inflammatory, cytoprotective, antimicrobial, and antileishmanial activities. Clinical pharmacology includes anti-obesity, antidiarrheal, and wound healing activities. The ointment of *Gummi myrrha* essential oil was non-irritating, non-sensitizing, and non-phototoxic to the human skin. The dose of myrrh tincture=1:5 g/ml, *Gummi myrrha* tincture applied to the affected area 2 or 3 times/ day.

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**Conflict of interest**

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