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Review Article

Amazing Benefits of Myrrh

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ABSTRACT
Myrrh is the resin derived from the branches and stems of a tree, known as Commiphora myrrha. It is Native to East/Northeast Africa, Southwest Asia (particularly Ethiopia, Somalia, and Kenya) and Arabia, Myrrha is usually imported as gum. Myrrha is considered as herbal medicine, myrrh, an oleo-reddish-brown gum resin, has a valuable role. After making incisions in the stem of the plant, causing oleoresin to exude and dry, it is extracted from the medicinal plant *Commiphora myrrha*. Pharmacological research has indicated that myrrh has analgesic, anti-inflammatory, antiviral, antimicrobial, immunomodulatory, and hepatoprotective functions. The word Myrrh is derived from the Arabic "murr" meaning bitter, and its functions have been documented in the writings of Hippocrates since the time of ancient Rome. This material is marketed worldwide as a pharmaceutical plant, and customers purchase it because of its multiple benefits, having been licensed by the Food and Drug Admiration (FDA) for food use. In Arabia, Somali land, India, Ethiopia, Abyssinia, and to some degree in Northern Kenya, the tropical tree, *Commiphora myrrha*, grows. The use of myrrh in the treatment of pulmonary problems such as respiratory infections, in particular asthma, chronic cough, diphtheria, pharyngitis, tonsillitis, common cold, and bronchitis, and in gastrointestinal and genitourinary disorders has been identified by many Chinese, Unani, and Arabic physicians since 600 AD. The focus of this review is the immunoregulatory potential of the bioactive components of *Commiphora myrrha* and their efficacy in reducing inflammation risk.

Keywords: Commiphora myrrha, Myrrh, Immunomodulation, Anti-Inflammation, Cytokines Storm, Covid-19.

INTRODUCTION

Commiphora myrrha:

Commiphora myrrha (Nees) Engl., also known as Balsamdendron Myrrha and Commiphora molmol, is a small tree or large shrub with many irregulars, tangled stems and a trunk of considerable thickness that does not exceed more than 9 feet high (Shen et al., 2012, Shameem, 2018). The leaves are around half an inch long, and there are no flowers. The phloem includes schizogenous tubules that are filled with yellowish finegrained resinous fluid and lysigenous cavities. Commiphora myrrha is a plant species of the genus Commiphora, from the family Burseraceae, and its distribution is primarily in semi-arid and arid areas, including southern Arabia, northern Somalia (the biggest supplier), India, Sudan, northern Kenya, and Ethiopia, growing at an altitude of 1500-3000 feet in very hot and sunny areas (Abdallah et al., 2009, Shen et al., 2012, Shalaby and Hammouda, 2014, Shameem, 2018, Prompetchara et al., 2020).

After creating cuts in the branches of the Commiphora plant to allow the oleoresin to exude, exposed to air, and harden, myrrh can be harvested. The name Myrrh was created from the Arabic word (murr), meaning bitter (Shameem, 2018). Myrrh is mostly distinguished by its distinctive smell and, as shown in Fig. 1, hard reddish - brown-yellow surface (Shalaby and Hammouda, 2014). Also, it is distinguished by its unpleasant bitter and pungent flavour and balsamic fragrance, and when immersed in water, it produces an emulsion (Shen et al., 2012, Shameem, 2018). It is believed that myrrh was among the three presents that Magi has given to the infant Jesus (Nomicos, 2007). Its applications have been reported in the manuscripts of Hippocrates during ancient Rome times (Shen et al., 2012). It was reported that without a potion of myrrh to place on their injuries, Greek soldiers would not go to battles (Shameem, 2018).

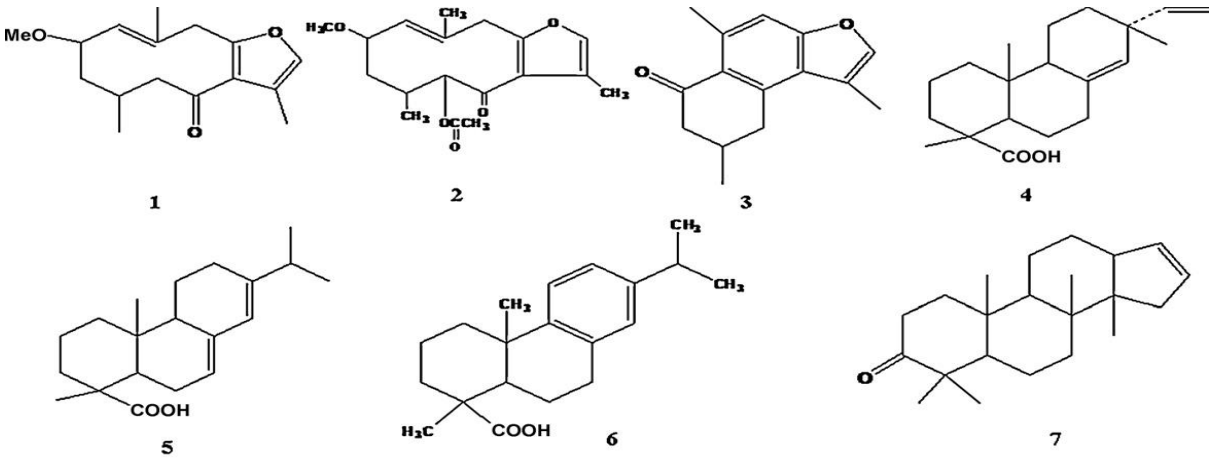
Myrrh has a range of applications and benefits, e.g. in anti-inflammatory and many infectious diseases treatment, and it is becoming a very popular and valuable alternative medicine (Shen et al., 2012, Shameem, 2018). Its extracts have been used to cure wounds, ulcers, and different diseases of the respiratory, gastrointestinal and urinary tract (Galehdari et al., 2016). Also, it was proven to be effective against HSV-1 infections and microbial activity, demonstrating its successful use in conventional treatments for aerosolized therapy for the treatment of bronchitis and sinus infections (Abdallah et al., 2009; Alamri, 2017). Generally, according to the World Health Organisation, around 80 per cent of

people worldwide chooses to use herbal remedies in their primary medical needs (Alamri, 2017).

Fig.1: Tree, leaves and oleo gum of Commiphora myrrha

Bioactive Components of Chommiphora:

Two bioactive constituents, 2-Methoxy-5acetoxy-fruranogermacr-1(10)-en-6-one and abietic acid, have been chemically characterized in Commiphora by several studies (Su et al., 2011, Su et al., 2015, Fatani et al., 2016). In addition, chemical analysis of the extract from Commiphora myrrha was conducted by Su et al. (2011). Their results showed the abundance of diterpenic acids, sesquiterpenes, and diterpenes. Moreover, seven main compounds were identified; 2-Methoxy-8,12-epoxygermacra-1 (10) 7,11-trine-6-one, 2-methoxy-5-acetoxy-furanogermacr-1 (10)-en-6-one, myrrhone, sandaracopimaric acid, abietic acid, dehydroabietic acid, and mansumbinone. Figure 2 shows the chemical structures of those constituents.



1. 2 - methoxy - 8, 12 - epoxygermacra-1 (10), 7, 11 – trine – 6 - one
2. 2 – methoxy – 5 - acetoxy - furanogermacr -1 (10) – en – 6 - one
3. myrrhone; 4. sandaracopimaric acid; 5. abietic acid; 6. dehydroabietic acid;
7. mansumbinone

Fig.2: The chemical structures of the seven main constituents found in the extracts of Commiphora myrrha (Su et al., 2011)

ANTI-INFLAMMATORY ACTIVITY OF MYRRH

Effect of Myrrh on Inflammatory Mediators:

Inflammatory agents that regulate inflammatory response are extracellular mediators and regulators, such as cytokines, growth factors, and eicosanoids. Myrrh has demonstrated anti-inflammatory characteristics in most research studies by suppressing pro-inflammatory signalling pathways and strengthening anti-inflammatory agents (Su et al., 2015; Anjum et al., 2017; Weber et al., 2020).

In the management of oral inflammatory response such as in periodontal diseases and gingivitis, and for inhibiting dental plaques, the anti-inflammatory features of myrrh have been utilized (Serfaty and Itic, 1988; Moran et al., 1992). laboratory experiments have shown that long term treatment with myrrh reduces the synthesis of IL-1β - stimulated IL-6 and interleukin-8 (IL8). Myrrh exposure decreased the inflammatory response of fibroblasts from the gingiva, hindering the reduction of osteoclast or

bone resorption by interleukins 6 and 8. There was no similar decrease in the inflammatory response following treatment of oral epithelium with myrrh (Tipton et al., 2003).

A research was carried out to examine the impact on rats with Adjuvant-induced Arthritis (AIA) and to investigate the mechanisms involved (Su et al., 2015). The findings showed that upregulation of TNF alpha, prostaglandin E2 (PGE2), interleukin-2 (IL-2), nitric oxide (NO) and malondialdehyde (MDA) expression in the blood and paw swelling of the animals declined substantially following the procedure. Another research tested the anti-inflammatory and analgesic properties of *Commiphora myrrha* ethanol extract (EE) on mice, and the findings suggested that it has anti-inflammatory efficacy and could help the conventional usage of this herb in the treatment of various inflammatory pain-related illnesses (Su et al., 2011). Furthermore, the research performed by Elbakry and his colleagues showed that treatment with myrrh might offer a degree of defence against *S. mansoni* infection and regulation of concentrations of certain Th1 and Th2 (Helper T cell) cytokines in S. mansoni – infected mice. (Elbakry and Abdelaziz, 2016)

Gao and colleagues examined the inhibition effect of myrrh on the human multiple myeloma cell line U266, and their findings indicated that phytochemicals of myrrh suppress proliferation of U266 cells (Gao et al., 2020). Shin and fellow researchers discovered whether myrrh modifies levels of histamine release and itch-associated interleukin (IL)-31 in stimulated human mast cells (HMC-1). The results showed that myrrh decreased the amount of IL-31 in HMC-1 cells successfully. Moreover, myrrh has the potential to inhibit extracellular signal-regulated kinase NF-1B, which refers to its activity in hindering of the release of IL-31 from HMC-1 cells (Shin et al., 2019). Also, myrrh has been found capable of inhibiting the release of histamine in those cells (Shin et al., 2019).

Furthermore, a research conducted by Galehdari et al. (2016) showed that in diabetic rats, the herb solution consisting of Aloe Vera, Henna, Adiantum capillus-veneris, and Myrrha was efficient in the healing process. The solution was observed to be extremely helpful in preventing the production of pro-inflammatory factors, particularly interleukins, IL6, IL1A and IL1B, and tumour necrosis factor (Galehdari et al., 2016).

Effect of Myrrh on Leukocytes:

The influence of myrrh on the activity white blood cells has been investigated by numerous experiments (Kim et al., 2012; Alkazzaz et al., 2018; AL-Mosawy and Hatroosh, 2019). Myrrh has been confirmed to have healing advantages on wounds by improving production and differentiation of neutrophils (Alsharif, 2020).

Compared with untreated animals, rats with skin wounds and gastric ulcers administered with myrrh demonstrated significant improvement in the neutrophil production and maturation phase during recovery (Haffor, 2010). In addition, myrrh-treated mice displayed reduced penetration of neutrophils into the peritoneal space and hepatic cells (Kim et al., 2012). Neutrophil gelatinase-associated lipocalin (NGAL) is a peptide molecule developed as a marker of the renal tubular injury by epithelial cells and activated neutrophils (AL-Mosawy and Hatroosh, 2019). Myrrh's influence on NGAL concentrations in rats injected with cadmium chloride was explored in recent research to trigger kidney failure (AL-Mosawy and Hatroosh, 2019). Management of chronic kidney disease in rats with myrrh has been found to substantially decrease NAGL concentrations in their blood relative to those in the comparison group (AL-Mosawy and Hatroosh, 2019). Mirazid®, a myrrh's industrial product marketed in pharmacies, has been confirmed to have contributed to a substantial rise in the number of neutrophils in treated mice relative to those in the normal control (Alkazzaz et al., 2018; Alsharif, 2020).

The effectiveness of myrrh-extracted medications in fascioliasis patients was observed in a study(Massoud et al., 2001). The results demonstrated that the medication enhanced the overall patient's condition and started to improve eosinophils levels (Massoud et al., 2001). An analysis of the health impacts of ether and ethanol extracts of myrrh in Wistar rats reported similar results (Omer and Al-Dogmi, 2018). Furthermore, Alkazzaz *et al.* (2018) confirmed that Schistosoma mansoni-infected mice had increased eosinophil levels. Mirazid® induced a substantial decrease in eosinophils in those animals (Alkazzaz et al., 2018). In addition, in a report by Haffor (2010), when administered with myrrh, animal models with a skin wound and gastric ulcer demonstrated a substantial rise in basophil numbers. In comparison, the basophil levels of Schistosoma mansoni-infected mice showed no significant improvements and the impact of myrrh on these mice was not noticed (Alkazzaz et al., 2018).

The goal of a recently published research was to assess the safety of feeding rats with different myrrh extract doses and to examine haematological effects (Omer and Al-Dogmi, 2018). Their findings demonstrated a substantial decrease in lymphocytes counts in rats treated with myrrh products (Omer and Al-Dogmi, 2018).

Additionally, in mice with hepatocellular carcinoma, a form of inflammation-related tumour, the researchers examined the impact of myrrh extract on lymphocytes levels (Xu et al., 2018). The anticancer activity of myrrh was abolished by lymphocyte reduction (Xu et al., 2018). Furthermore, by inducing lymphocyte differentiation, myrrh strengthened the cell-mediated immunity and could improve the development of T and B lymphocytes (Ashry et al., 2010).

Induction of Nitric Oxide Synthase as an Anti-inflammatory Mechanism of Action for Myrrh:

The inflammatory response is a systemic response that aims to reduce detrimental agent toxic effects and speed up recovery (Kontush and Chapman, 2006). The stimulation of phagocytic cells participating in immune responses, creating an oxidative burst of reactive oxygen, chlorine, and nitrogen species, is a crucial part of the inflammatory process (Kontush and Chapman, 2006). In response to pathogens taking part in immune response, macrophages play a prominent role (Rao et al., 2005). They trigger the synthesis of cytokines, oxygen and nitrogen species, and eicosanoids when stimulated (Rao et al., 2005). Microbial lipopolysaccharide(LPS) is ideally capable of inducing the expression of genes that encode pro-inflammatory factors in macrophages (Rao et al., 2005). This activation leads to cytokine production and enzyme synthesis, such as inducible nitric oxide synthase (iNOS) (Rao et al., 2005).. In inflammatory immune responses, the NO radical is considered to make a significant contribution (Rao et al., 2005).

Numerous terpenoid substances were reported to prevent the release of nitric oxide in LPS-activated mouse peritoneal macrophages with regard to the mechanism of action of the anti-inflammatory activity of myrrh resins (Matsuda et al., 2004). The impact of the bioactive compounds of myrrh on iNOS activation was investigated. INOS has been identified following 20 hours of LPS addition (Matsuda et al., 2004). INOS activity in LPS-activated macrophages was observed to be concentration-dependently inhibited by the bioactive compounds of myrrh (Matsuda et al., 2004). These findings indicate that the bioactive components of myrrh inhibit NO formation in LPS-activated macrophages by inhibiting iNOS activation (Matsuda et al., 2004).

myrrh's impact on peritoneal macrophages is not well described. The inhibitory influence and mechanism of action of myrrh on inflammatory processes were studied by Kim *et al*. (2012). LPS-induced generation of inflammatory agents such as nitric oxide, prostaglandin E2, and tumour necrosis factor-alpha in peritoneal macrophages was reduced by myrrh. Moreover, LPS-induced stimulation of c-jun NH2-terminal kinase (JNK) was suppressed by myrrh (Kim et al., 2012).

Research was focused on the influence of *Commiphora molmol* resin on oxidative damage, inflammatory response, and haematological changes in hyperammonemic ammonium chloride (NH4Cl-)-induced rats, with a concentration on glutamate-nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) and nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) mechanisms (Mahmoud et al., 2017). The findings showed that in hyperammonemic rats, the resin dramatically reduced plasma level of ammonia, liver function indicators, and TNF-alpha. C. Molmol inhibited nitric oxide and lipid peroxidation and boosted antioxidant defences. C. Molmol considerably upregulated Nrf2 and reduced the production of glutamine and nitric oxide synthase. Those results proved that C. Molmol modulates liver damage, oxidative stress, inflammatory processes, and hematological disturbances caused by ammonia.

THERAPEUTIC DOSAGE OF MYRRH

Myrrh has been shown to have a dose-dependent function, and a dosage of 1 to 15 grams is reported to be adequate (Shameem, 2018).

Myrrh was administered for three days at a dosage of 10 mg/kg of body weight/day and achieved a 91.7 percent cure rate. Retreatment of patients who did not respond for six days with a 10 mg/kg body weight/day dose yielded a 76.5 percent cure rate, bringing the total cure rate to 98.09 percent. The medication has been well-tolerated, though there were slight and temporary adverse effects (Sheir et al., 2001).

METHOD OF USE

Myrrh may be powder-crushed and diluted in warm water. Then it could be orally consumed or used for skin and hair rinsing. The solution may also be gargled by mouth or inhaled in a fumigation machine. To increase the benefit without damage, it is also advisable to use myrrh with other medications and herbs. Myrrh, for instance, can be consumed in combination with paromomycin for the treatment of infection with parasitic cryptosporidiosis (Shameem, 2018).

CONCLUSION

This review described myrrh and discussed its anti-inflammatory properties. Myrrh is considered one of the earliest medicines used for the treatment of inflammatory diseases. Published research has shown that because of its numerous

phytochemical constituents, it possess dose-dependent anti-inflammatory, analgesic, cytotoxic, anti-septic, antibacterial and antiviral properties. *Commiphora* helps decrease inflammation and controls inflammatory mediators via many effective approaches, increases white blood cells counts without harm and helps to sustain white blood cells proliferation and activation during healing, meaning that during the effective healing process, myrrh triggers late steps in both proliferation and differentiation pathways for white blood cells. The potential effect of myrrh on the cell activities of white blood cells has been documented in several studies. However, the exact mechanisms underlying the influence of myrrh or its bioactive components on leukocyte function have not been extensively described. In order to determine the anti-inflammatory characteristics of myrrh, it is important to perform more in-depth analyses. Furthermore, research questions to recognize the function of bioactive components of myrrh on COVID-19 cytokine's storms to detect the action in the inflammatory response and co-immunomodulatory efficiency still need to be solved.

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