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Review

Can Myrrh Combat COVID-19?

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ABSTRACT

This paper reviews the therapeutic effects of *Commiphora myrrh* in different diseases. It is organized by sub-themed sections: nature and history of myrrh, its use in different cultures, its chemical action, and effect on virus or/and bacteria, benefits of its utilization for respiratory problems and oral diseases.
A literature research for the Myrrh or *C. myrrh* was performed using Cochrane Library databases and Medline. Forty two papers, including abstracts and full articles published from 2007 to 2020, in the area of interest were reviewed. It was found that Myrrh or *C. myrrh* is one of the medicinal plants believed to have therapeutic effects in various diseases. It has medicinal properties, such as immunomodulatory, anti-inflammatory, cytotoxic, antioxidant, antimicrobial, hepatoprotective, anti-tumor, anti-ulcer, and analgesic activities. Besides, Myrrh has also shown to have antiviral properties that help in preventing different types of viral diseases. It noticed in the State of Qatar, sales of herbs and Myrrh has escalade since the surgency of COVID-19 cases, so is there a belief in Myrrh's effectiveness to be used during COVID-19? Studying the effectiveness of Myrrh mouthwashes to combat COVID-19 can emerge as a promising avenue in the field of research.

1. INTRODUCTION

Medicinal plants are the primary sources of new drugs globally. There is a rapid growth in the utilization of such plants around the world due to the high demand for natural health products, herbal medications, and metabolites of medicinal plants [1]. They are natural resources which can be used to develop and synthesize new drugs. Medicinal plants are believed to have wide spectrum of biological activity and therapeutic effect on different types of diseases [2].
Medicinal plants have been in use throughout the world across generations. Researchers have observed that from one generation to another, medicinal plants have a crucial role globally, especially in the pharmacological industries for drug development [3]. As such, the studies on pharmacological and biological activities of essential oils in the medicinal plants have attracted special attention to gain deeper insights into their potential application from pharmacological and chemical investigation to their therapeutic use [3]. This review highlights the usage of *C. myrrh* in different diseases.

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The paper is organized on the sub-themes of: nature and history of myrrh, its use in different cultures, its chemical action, and effect on virus or/and bacterial, benefits of its utilization for respiratory problems and oral diseases. (Figure 1).

Figure 1: *Myrrh resin. Pictures extracted from reference 4.*

2. NATURE AND HISTORY OF *COMMIPHORA MYRRH*

Commiphora myrrh is a tree (Figure 2) belonging to the genus *Commiphora* and is one of the flowering plants in the Burseraceae family [4]. The family of *Burseraceae* consists of 150 different species that originate primarily from the arid tropical and subtropical areas [5]. The name "Myrrh" derived from the word "murr", which is an Arabic language means bitter. Traditionally, in Greek and Chinese literature it is also referred to as *Balsamodendron myrrha*, *C. myrrh* or *Commiphora molmol* [6].

The Commiphora myrrh tree is mainly found in India, East Africa, and Arabia. It produces an aromatic resin, referred to as "Myrrh". Myrrh is an exudate from the bark of the plant, which has therapeutic properties that supports its medicinal use [3, 4]. It is a brownish yellow in color, with aromatic balsamic odour and bitter taste. When combined or mixed with water, it forms an emulsion with different constituents, which include 2% to 8% volatile oil, 23 to 40% resin known as the myrrhin, 40% to 60% gum [7]. The essential oils found in myrrh are used for various purposes, which include cosmetics, perfumes, and secondary metabolites. These oils mainly consist of terpenoids and terpenes. Additionally, myrrh consists of pharmaceutical elements with sesquiterpene lactones that are used to treat some ailments [3].

3. USE OF MYRRH IN DIFFERENT CULTURES

Myrrh is one of the oldest medicinal plants used in different cultures as a source of medicine for treating different diseases. It has extensive references in Chinese and Roman culture. It is widely used as traditional medicines, especially in Rome, India, Babylon, China, and Greece [8]

Myrrh was first introduced and described in the literature of Chines medicine in 600 AD, where it was explained as the best herbal drug for good health [8]. Myrrh was used in Chinese culture as a traditional medicine for pain management. In the past centuries, Myrrh was the most famous Chinese medicine used together with resinous Frankincense to treat blood stagnation. It was used as a blood moving medicine because of its antioxidant and anti-inflammatory activities [9]. Additionally, it is documented that although China is not the leading producer of myrrh, it has the largest market globally, primarily for its use in Chinese traditional medicine [7].

The extract of Myrrh is believed to have anti-cancer activities; hence its consumption induces apoptosis in different types of cancer cell lines, such as that of breast, lung, prostate, and pancreas cancer cell lines [7]. More recent research investigating the chemical compounds and pharmacological properties of myrrh and frankincense support their application in Chinese culture to treat cancer.

Besides, the Chinese traditional medicine literature also shows that the myrrh resin is a crucial herbal remedy to vitalize blood circulations, especially in people with ailments associated with menstrual syndromes and stasis.

It is also believed by Chinese traditional practitioners that myrrh is safe and effective in treating painful inflammation, traumatic injuries, and specific masses. Based on the highest consumption of myrrh resin in China, the People's Republic of China thus remains the leading consumer of nutraceuticals and medicinal development of *Commiphora myrrh.* However, due to the bitterness and strong smell, it is assumed that overdose of myrrh may lead to vomiting, nausea and gastrointestinal tract injuries. As such, the Chinese practitioners advocate the use of myrrh resin in a capsular form or as a pill [11]. In general, traditional Chinese medicine suggest that myrrh has powerful pharmacological effects, which include synergistic analgesic, synergistic anti-inflammation, synergistic blood-activation, and synergistic antibacterial properties when used with frankincense [11].

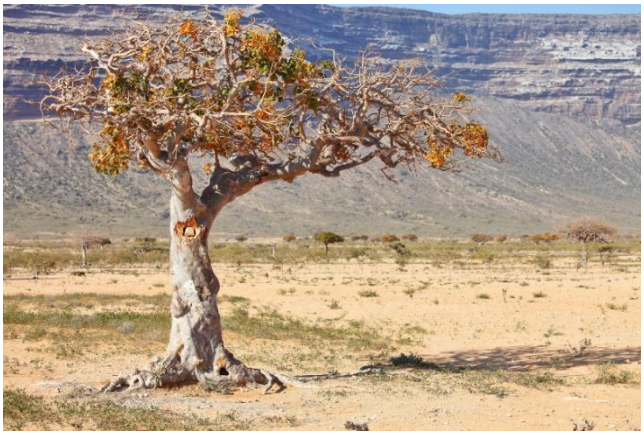

Figure 2: *Tree of Myrrh. Picture extracted from reference 4.*

Based on the traditions and culture in Egypt, *C. myrrh* is believed to be more effective in treating infectious diseases, including the *Trichomoniasis vaginalis* infection. It is believed that the use of myrrh extracts is safe in treating and preventing infections only in the reproductive organs of males [12]. The extracts are used as herbal remedies because of anti-inflammatory and antibacterial activities; hence are safe and effective in preventing the occurrence of *Trichomoniasis vaginalis* infections [13]. Also, myrrh is culturally believed to have antiparasitic activities in Egypt where people in Egypt assumed that myrrh is the most effective and safe antiparasitic agent to treat trematode infections [14]. It is believed that the molluscicidal effects of the herbal product of myrrh help in causing permanent loss to the musculature in trematodes.

Researchers explained that the use of traditional medicine remains a key aspect in Saudi Arabian culture in which many patients seek alternatives to use herbal remedies to treat their health conditions [15]. However, there are some cultural beliefs in Saudi Arabia that traditional medicine exposes people to different hazards. The authors also pointed out that the use of large amounts of herbal remedies from myrrh poses health hazards by causing infertility or recurrent miscarriages among pregnant women. It is evident that despite the cultural beliefs that traditional medicinal with a focus on herbal remedies and religious or spiritual healing to treat medical conditions, myrrh is not recommended for pregnant women because it is believed to be a uterine irritant and can affect female reproductive organs and cause miscarriages or infertility [15], still several compounds isolated from this myrrh resin are crucial in treating specific diseases [16].

4. CHEMICAL ACTION OF MYRRH

Current research has demonstrated that the primary chemical action of myrrh includes anti-inflammatory, anticancer, and analgesic activities.

4.1. ANTI-INFLAMMATORY ACTION

Myrrh has active compounds that are known to have strong anti-inflammatory effects. This has been attributed to the essential steroid, guggulsterone (GS). The GS found in myrrh acts on acute pancreatitis by inhibiting the activation of c-Jun N-terminal kinase and extracellular-regulated protein kinase [17]. In addition, administration of myrrh resin, known as the Commiphora erythraea acts by restoring ROS control and viability of microglia BV-2 cells and reducing the production of nitric oxide and levels of pro-inflammatory cytokines, such as interleukin-6, interleukin-23, interleukin-17, tumor necrosis factor-B and interferon gamma, which are induced by lipopolysaccharides. Similarly, the use of myrrh resin facilitates the reduced expression of tumor necrosis factor-alpha and interleukin-1 beta in the brain and liver [18]. The 4-furanodien-6-one found in myrrh also acts by inhibiting a protein complex known as NF-κB that is involved in controlling transcription in DNA. This action, thus, leads to attenuation of neuro-inflammation, therefore providing anti-inflammatory activity [18]. Additionally, myrrh resin has been found to induce antibacterial activity by acting on specific pathways.

Researchers asserted that myrrh resin acts by inducing haem oxygenase activity, which stops the degradation of IKB alpha as a response to the activation of inflammatory receptors [19]. Such activation plays a crucial role in preventing the translocation of nuclear factor kappaB. It causes inhibition of gene expression under enzyme activity of cyclooxygenase-2 and nitric oxide synthase that inhibits p38 and c-jun N-terminal kinase [20]. In addition to anti-inflammatory effects on nuclear factor kappaB system, myrrh also has significant effects in inhibiting activator of transcription-1 and activator of transcription- 3 (STAT-1 and STAT-3), as well as a signal transducer, which leads to a reduction in the production of cytokines through janus kinase/STAT pathway [21]. It also decreases the down- regulation of suppressor of cytokine synthesis in response to the low production of interferon-gamma and interleukin-beta. This action acts as the auto-regulator of the JAK/STAT pathway through

transcriptional control of the activator of transcriptions, which also inhibits pathway activation [22].

4.2. ANTICANCER ACTION

The pharmacological studies have demonstrated the chemical action of myrrh in inducing anticancer activity. The essential compound in myrrh that exerts anticancer effects is elemene, which has been proven to be safe and effective for cancers, including glioblastoma. Elemene, mainly the beta-elemene, has been found to exert the anti-proliferation effect by activating thep38MAPK in glioblastoma [23]. Also, myrrh has the compound known as the furose-type sesquiterpene rel-1S, 2S-epoxy-4R-furanogermacr-10-3n-6-one, which contains a week cytotoxic activity against the cell line MCF-7 of breast cancer. Such a compound, together with bisabolene compound in myrrh acts effectively by reducing the growth of breast tumors, which indicates that myrrh can be used in pharmacology as a novel anti-breast cancer drug [24, 25]. On the other hand, the cyclobolinane triterpenoids found in myrrh acts by exerting moderate cytotoxic activity against the PC3 and DU145 of prostate cancer cell lines [7].

Triterpenoids and guggulsterone in myrrh act chemically on cyclin in tumor cells. The steroids act by inhibiting cyclin regulation, which, in turn, affects the growth and multiplication of tumor cells. They induce cell death or apoptosis through the down-regulation of the anti-apoptotic gene product. It inhibits the proliferation of cells and induces apoptosis of HepG2 cells, which, in turn, activates the intrinsic mitochondrion pathway [26, 27]. Besides, myrrh extracts act by interacting with the Bcl family of proteins, which facilitates the pro-apoptotic activity. Due to such interaction, myrrh induces pro-apoptotic protein expression while reducing the expression of Bcl proteins, mainly the Bcl-2 and Bcl-xl proteins [28]. When taken at low doses, myrrh works by activating the mitogen-activated protein kinase (MAPK) pathway of cancer cells and such action promotes the phosphorylation of N-terminal kinase and P38, which have a crucial role in both adaptive and innate immune systems [29].

4.3. ANALGESIC ACTION

The myrrh has proven to be useful analgesics in ancient times due to significant compounds that act effectively as pain relievers [10]. The sesquiterpenes furanocudesma-1, 3-diene, and curzerene found in myrrh are essential compounds that act on the opioid receptors in the central nervous system by exerting analgesic activity [10]. In addition, the sesquiterpenes furanocudesma-1, 3-diene in myrrh, especially those extracted from *Commiphora mukul* has significant effects in relieving abdominal pain and alleviating health hyperalgesia. As a consequence, such extracts act by alleviating the pain in peripheral nerves from chronic compressive injuries that affect the sciatic nerves. Also, the extracts can be used as the alternative medication to treat nerve pains [30]. Additionally, the current study showed that compounds, such as lindestrene and sesquiterpenes furanocudesma-1, 3-diene found in myrrh have chemical action by acting on nerves and body joints to relieve pain. The compound acts by suppressing the production of prostaglandins and block the inward sodium currents, hence alleviating feelings of pain [22]. The high content of furanodiene compounds works by alleviating low pain and fever-dependent pain [5].

5. EFFECT OF MYRRH ON VIRUS AND BACTERIA

The impacts of myrrh on viruses and bacteria are well documented in previously conducted studies. The existing empirical evidence shows that myrrh extracts have viral effects in which the extracts from such plants have antibacterial and antiviral activity against different strains of viruses [16, 31]. A study investigated the anti-bactericidal, antifungal, and antiviral activity of essential oils from myrrh extracts supported the efficacy of the extracts in reducing the growth of different strains of bacteria and virus [31]. The study found that essential oils in myrrh provide antiviral activity against influenza virus type A (H1N1) and herpes simplex virus type 1 (HSV-1). The study found that myrrh acts by directly causing inactivation of free viral particles and interfere with the virion envelope structures, which are crucial for the virus to enter the host cells [31]. Also, the extracts act by inhibiting DNA polymerase in viral strains; therefore, preventing viral resistance to specificmedications. As such, myrrh can be used as antiviral medication in which new drugs can be developedwith the use of the extracts and ensure that they target DNA polymerase [31].

In terms of antibacterial effects of myrrh, a study showed that the essential oils in myrrh have antibacterial activity against different strains of bacteria, including *Staphylococcus aureus, Pseudomona aeruginosa,* and *Klebsiella pneumoniae* [16]. It demonstrated that the Oleo gum resin from *C. Myrrh* or *molmol* and essential oil cream from myrrh play a crucial role in reducing the resistance of bacteria. The study disclosed that the extracts have bactericidal activity and molluscicidal activity, which helps the bacterial from developing resistance to specific drugs. The extracts prevent multidrug resistance of bacteria; hence they are essential agents to use in multidrug pharmaceutical preparation of drugs [16]. Previously conducted studies showed similar information about the efficacy of myrrh resin in terms of antibacterial activity [31, 32, 33]. The studies showed that terpenoids found in myrrhextracts have antimicrobial, molluscicidal activity, anti-hyperglycemic, and cytotoxic activities, which make them essential therapeutic agents against Gram-positive and Gram-negative bacteria [32].

Further, the study revealed that due to biological and bactericidal activities of myrrh, the extracts or resin from *Commiphora myrrh* could be used as broad-spectrum drugs against multidrug-resistant bacteria, such as *Staphylococcus aureus, Pseudomona aeruginosa, and Klebsiella pneumoniae* [16].

6. USE OF MYRRH FOR RESPIRATORY INFECTIONS

Commiphora myrrh or myrrh has also been found to have clinical effects on chest infection and sore throat, mainly acting by suppressing the inflammation [16].

The review found that *C. myrrh* extracts and essential oils are used to develop expectorants, which are the essential medication for respiratory diseases, such as chest infections and associated ailments [6]. Similarly, a study supported the effects of aromatic gum resin in myrrh on chest infections [35]. The resin acts by exerting anti-inflammatory and cytotoxic activity against bacterial or fungal infection, causing chest ailments. It is also shared that resin or extracts in *C. myrrh* have anti-inflammatory and analgesic action, supporting the use of myrrh as an essential traditional or herbal remedy for different chest infections [22].

The existing body of evidence demonstrates that the volatile compounds, which include essential oils that are rich in furanosesquiterpenoids have antiseptic and antifungal properties, which are essential in treating mild inflammation that can lead to sore throat and related ailments in the pharyngeal and oral mucosa [36]. Also, myrrh has antiseptic properties that help in treating sore throat. Studies explained that myrrh is used together with peppermint and menthol to treat sore throat [37]. The authors shared that the myrrh gum can be used as a mouthwash, and since it has expectorant activities, it can act by reducing inflammation in the throat, hence preventing sore throat and related infections. It is evident that combining the myrrh extracts with peppermint oil and menthol, which, when administered as a mouthwash, it promotes mucosal circulation in the bronchial tract and throat [37]. Thus, in swollen tissues that occur due to sore throat, the extracts exert anti-oxidant, antibacterial, and anti-inflammatory effects, which help to treat sore throat, and in turn, prevent the onset of tonsillitis because it helps in triggering regeneration of healthy tissues and cells [37].

7. EFFECT OF MYRRH ON NASAL CONGESTION

Administration of myrrh or extracts from *Commiphora myrrh* helps in reducing nasal congestion in common cold and flu infections. Myrrh resin can be used as an immunostimulant during cold and flu season where it acts by strengthening the immune system and acts as an expectorant to treat nasal congestion [38]. Few drops on myrrh oil can be added to hot water and inhaled in the form of steam have been used traditionally. The analgesic effects of myrrh also help to reduce headache associated with nasal congestion [39].

8. EFFECT OF MYRRH IN THE ORAL CAVITY

It is found that myrrh suspension in low quantities is effective and produces clinical benefits as a mouthwash, especially when treating intra-oral mucosal wounds [40].

Additionally, a pilot clinical study that examined the effects of using *C. myrrh* as mouthwash supported the anti-plaque and anti-inflammatory activities [41]. The study was a randomized controlled trial that was conducted among healthy subjects in which gingivitis was allowed to develop, and the participants were assigned *C. myrrh* mouthwash. The trial revealed that the use of *C. myrrh* extracts as the mouthwash has significant effects in treating gums by reducing gingival inflammation [40].

In comparison to other mouthwash agents, such as Miswak, it has been found the myrrh extracts are more effective in terms of anti-inflammatory and anti-plaque activity to prevent gingivitis. This is evident in a study comparative clinical trial which compared the efficacy of using Miswak and myrrh mouthwashes against chlorhexidine in reducing chronic gingivitis [42]. The study revealed that myrrh is more effective in reducing gingivitis inflammation compared with Miswak and chlorhexidine, in which the subjects who participated in the study showed clinical improvement with myrrh mouthwash [43].

9. CAN MYRRH COMBAT COVID-19?

Myrrh or *C. myrrh* is one of the medicinal plants believed to have therapeutic effects in various diseases. It is believed that *C. myrrh* has medicinal properties, such as immunomodulatory, anti-inflammatory, cytotoxic, antioxidant, antimicrobial, hepatoprotective, anti-tumor, anti-ulcer, and analgesic activities. As a consequence, myrrh can be used to treat different types of diseases because of their therapeutic activities. Besides, myrrh antiviral activities that helps in preventing different types of diseases. As such, there is a possibility that myrrh or *C. myrrh* could be effective in treating the current cases of COVID-19.

It noticed in the State of Qatar, sales of herbs and Myrrh has escalade since the surgency of COVID-19 cases [44], and the price of Myrrh has soared equivalently. Whether this trend can attribute to the traditional beliefs in indigenous remedies or the existent preventive or therapeutic effects of Myrrh needs to be investigated. Studying the effectiveness of Myrrh mouthwashes to combat COVID-19 can emerge as a promising avenue in the field of research.

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