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Review on Frankincense Essential Oils: Chemical Composition and Biological activities

Sura M. Abbood[1]*,Sura Mohammed Kadhim[2], Aziz Yasir Hasan Al-Ethari[3], Zyad H AL-Qaisia[1], Mustafa Taha Mohammed[1]

[1] Department of Chemistry, College of Science, Mustansiriyah University, Baghdad, Iraq
[2] Ministry of Education, Rusafa-1, Iraq
[3] Department of Biology, College of Science, University of Kerbala
*Corresponding author: Sura Mohsin Abbood, Department of Chemistry, Mustansiriyah University, Baghdad, Iraq.
E-mail: sura_bio2006@yahoo.com
https://orcid.org/0000-0002-8671-4447

Abstract

Frankincense plant is one of the most widely used groups of medicinal herbs and has been extensively used due to the biological activities it possesses. Recently, a considerable literature has developed around the theme of frankincense and its different components, alongside with numerous researches published on its historical role in curing various chronic diseases. The present review has focused on the chemical ingredients of frankincense essential oil and pharmacological activities of these components. Essential oils (EOs) are known to have anti-inflammatory and antiviral effects in addition to what being suggested about having activity against virus of SARC-CoV-2. These activities, which attributed to different chemical ingredients such as phenolic monoterpenes could have a protection and/or relief of some illnesses. The current study provides reference for further research in attempt to become a relevant basis of development for new remedies to combat chronic disease and viral infection such as Coronavirus.

Key words: Frankincense essential oil, Antioxidant, Anti-inflammatory, Coronaviruses, Monoterpenes.

مراجعة للزيوت الأساسية في لبان الذكر: التركيب الكيميائي و الفعاليات البايولوجية

سرى محسن عبود[1]– سرى محمد كاظم[2]– عزيز ياسر حسن [3] – زياد القيسي[1]– مصطفى طه محمد[1]
[1] قسم الكيمياء، كلية العلوم، الجامعة المستنصرية، بغداد، العراق
[2] وزارة التربية، تربية الرصافة الأولى، بغداد، العراق
[3] قسم علوم الحياة، كلية العلوم، جامعة كربلاء، كربلاء، العراق

المستخلص:

يعتبر نبات اللبان الذكر من أكثر الأعشاب الطبية استخدامًا حيث تم استخدامه على نطاق واسع بسبب امتلاكه فعالية بيولوجية. تتناول هذه الدراسة المرجعية المكونات الكيميائية لزيت اللبان العطري والأنشطة الدوائية لهذه المكونات.

من المعروف أن الزيوت العطرية الأساسية لها تاثيرات مضادة للالتهابات ومضادة للفيروسات بالاضافة الى وجود . دراسات تقترح امتلاك الزيوت العطرية لبعض النباتات فعالية ضد فيروس كورونا. وتعزى هذه الفعالية الى مكونات كيميائية مختلفة مثل المركبات الفينولية التي تحمي الجسم من مختلف الامراض. تقدم الدراسة الحالية مرجعًا لمزيد من البحث في محاولة لتطويرعلاجات جديدة لمكافحة الأمراض المزمنة والعدوى الفيروسية مثل فيروس كورونا

الكلمات المفتاحية: الزيوت الأساسية في لبان الذكر، مضادات الاكسدة، مضادات الالتهاب، فيروس كورونا، التربينات الاحادية

Introduction

For many years, a number of studies have begun to examine the natural sources for bioactive extracts that can be used as alternative treatment or combined with synthetic drugs to produce safer and more effective medicines. There is historical knowledge of medicinal plants in folk medication to treat human various diseases. Frankincense plants (also named *olibanum*) have emerged as powerful candidate platforms for this task due to their pharmacological and physiological properties with low toxicity on normal cells.

Historically, frankincense had been used in religious and cultural ceremonies as well as in folk medicine by Ancient Egyptians, Mesopotamians, Greeks, Romans, Jews, Christians and Muslims. The word *of "frankincense*" derived from the old French term "*franc encens*" meaning pure and high-quality incense while the word of *olibanum has an* origin in the Arabic *al-lubān* and in the Latin *oleum libani* [Van Vuuren et al.,2010; El-Nagerbi et al., 2013]. This herbal plant was part of traditional Arabian medicine. Where Avicenna (Ibn Sina) for example mentioned this herbal plant in his a medical encyclopedia, Canon of Medicine, which set as standard medical textbook in Medieval Europe and the Islamic world up to the 18th century. Earlier, frankincense was used as medication to various illnesses such as diarrhea, stomachache, burns and bruises, infections, tuberculosis, eyesores. In Indian Ayurvedic and traditional Chinese medicine (TCM), frankincense was widely used as treatments for chronic diseases [Eferth and Oesch, 2020]. Frankincense is a natural oleo-gum resin produced through series incisions made in the genus Boswellia trees trunks in March or April then the exudate thick white liquid is harvested from the wound during summer and autumn as shown in figure 1. When the white fresh resin is dried, it will change to golden brown color [Csuk and Al-Harrasi, 2020; Paul, 2012]. The components of final product are approximately 30-60% resin, 30-55% polysaccharides and 5-10% essential and aromatic oil (mainly monoterpenes) [Siddiqui, 2011].

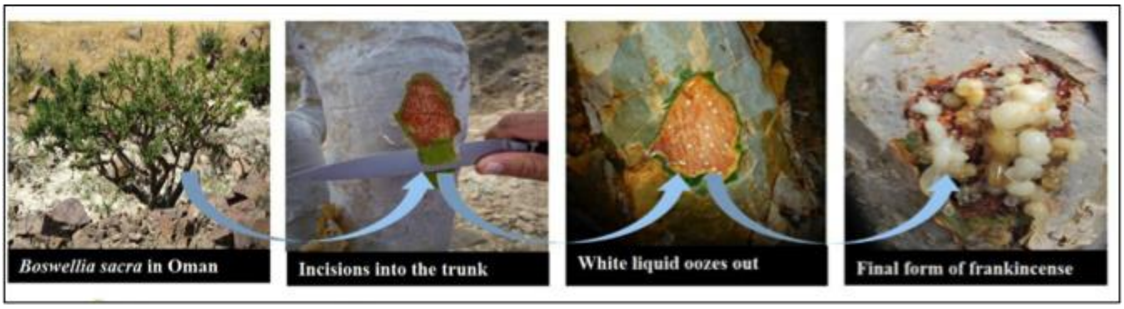

Figure 1: Shows the production of oleogum resin of frankincense from genus Boswellia sacra trees [Csuk and Al-Harrasi, 2020].

In terms of species, it has been reported that the genus Boswellia has nineteen species recognized around Arabian Peninsula, India, and the Horn of Africa. In which, five species include the Boswellia sacra, B. serrata, B. carterii, and B. papyrifera are the most popular ones [Al-Harrasi et al., 2018]. Each species remarkably differ from the other in terms of their chemical components and physical properties such as appearance and odor. The characteristics of resins are affected by the geographical changes of the same species (Figure2) [Csuk and Al-Harrasi, 2020].

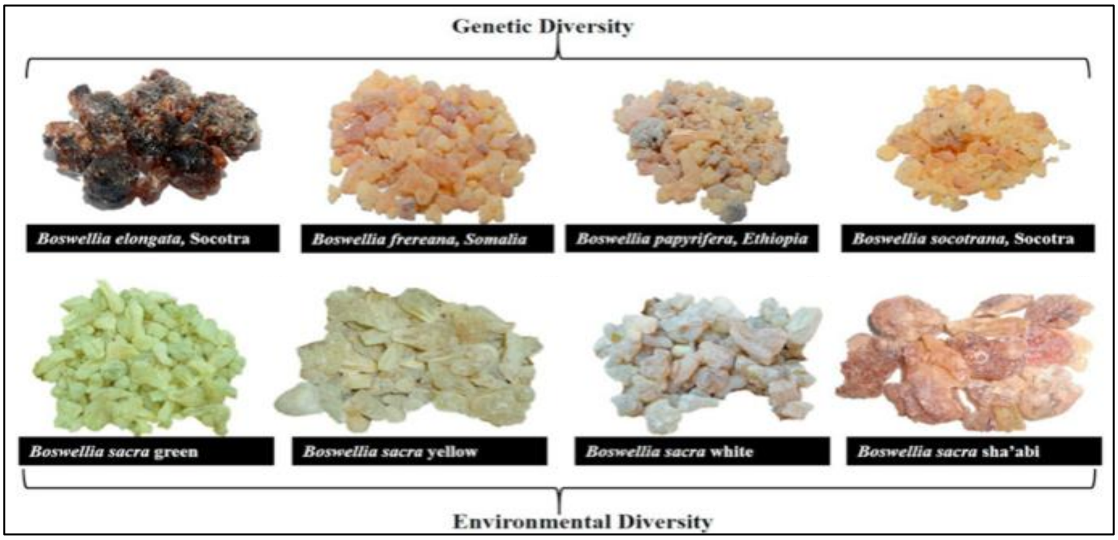

Figure 2: Displays the different types of frankincense oleogum resin because of genetic and geographical diversities [Csuk and Al-Harrasi, 2020].

Regarding to technique of extraction and isolation, a number of appropriate methods has been used to separate Bowellia species depending on the chemical composition of the resin: Gas chromatograph-toroidal ion trap mass spectrometer (GC-TMS), High-performance liquid chromatography (HPLC) based method focusing on triterpenic constituents [Paul, 2012; Büchele et al., 2003; Math et al., 2003], thin layer chromatography TLC based methods [Hairfield et al., 1984; Kowalska et al., 2006 ; Al-Harrasi et al., 2013], GC-MAS analysis of triterpenoids after derivatization [Mathe et al. , 2007; Culioli, et al., 2014], and of volatiles from the resins [Hamm et al., 2005], Fourier transform infrared (FT-IR) [Archer et al., 2000], and Raman spectroscopy [Edwards and Falk, 1997].

Recently, scientists have unraveled some of the frankincense medicinal secrets, demonstrating its superior properties include antioxidants, anti-inflammatory, anti-cancer and anti-depression [Akihisa et al, 2006; Gupta et al, 1998]. Therefore, current review highlighted the chemical component, biological activities and therapeutic uses of frankincense essential oil to provide reference for further research in attempt to become a relevant basis of development for new remedies to combat chronic disease and viral infection such as Coronavirus.

Main Chemical Ingredients of Frankincense

The main fractions of frankincense oleogum resin are volatile, semi-volatiles and non-volatile. Whereas, to date, there are contradicting reports established in the literature about the frankincense essential oils, volatiles and semi-volatiles. In terms of chemical constituents, phytochemical studies have revealed that there are more than 200 chemical compounds are identified in the oleogum resin of frankincense. As the main compounds separated from frankincense are pentacyclic triterpenoids [Grbić et al., 2018; Baser et al., 2003; Hamm et al., 2004; Gerbeth et al., 2013], tetracyclic triterpenoids [Büchele et al., 2003; Wang et al., 2011; Badria et al. 2007, Banno et al., 2006; Wang et al., 2011], saponins, al- kaloids, polyphenols, tannins, mucus, sugars, [Maupetit et al.,1984; Morikawa et al., 2017] and a variety of essential oils [Li et al. 2016; Frank et al., 2009]. Essential oil is a natural product produced by the herbs secondary metabolism and their components have been used for various purposes for example food additive, medicines, nutritional supplements and cosmetics [Zengin et al., 2014]. Therefore, several investigations focused on the chemical constituents of herpes essential oil.

In general essential oils ingredients are categorised into two different groups of chemical components; the hydrocarbons and the oxygenated compounds. Hydrocarbon components are exclusively comprised of terpenes including monoterpenes, sesquiterpenes, and diterpenes while oxygenated compounds are mainly made up of aldehydes, ketones, alcohols, phenols, esters and oxides [Zengin et al., 2014].

Various chemical components of Boswellia sp. essential oils are characterized according to some factors such as harvesting period, climates and the geographical source of this plant as well as storage and processing conditions [Mikhaeil et al., 2003]. It has been demonstrated that the chemical component of essential oil was utilized to distinguish between two main species of frankincense. According to Woolley et al. (2012), B.sacra is identified by elevating the content of α- pinene, which composed 68.0%, and lower percentage content of α-thujene that composed 0.6% [Woolley et al., 2012]. Alternatively, the B. carterii essential oil composition has contained a relatively minor quantity of α-pinene, which constituted 37.0%, and higher content of α-thujene, which comprised 7.9%. On the other hand, Hamm et al (2005) has established that the α-thujene is the main volatile components in a Boswellia serrate, which differentiates it from African *olibanum* [Hamm et al., 2005; Camarda et al., 2007]. Therefore, it is apparently difficult to distinguish between the different frankincense spices based on the oil chemical profile like a chemotaxonomic marker. As, the identification of these chemical compounds is subjected to influence of several factors.

In 1977, Obermann carried out an initial comprehensive study related to essential oil of frankincense from different origins using the technique of GC-MS [Obermann, 1977]. In reviewing the hydrodistillation frankincense extracts in recent literature, α-pinene, limonene, octyl acetate, α-thujene, and E-β-ocimene have been most frequently stated compounds to be the main volatile ingredients of the distillate of frankincense [Hussain et al., 2013; Di Stefano et al., 2020].

Traditionally, Soxhlet apparatus is used to extract frankincense heavy oil and the essential oil is isolated using vacuum distillation [Adeeb and Shaw, 2020; Hakkim et al., 2015]. This volatile fraction composes 5-15% of frankincense gum resin's weight based on its species [Al-Harrasi et al.,2018; Al-Harrasi et al.,2019]. Moreover, other evolved techniques can be used to extract frankincense essential oil for example microwave-assisted distillation that is more environmental friendly methods while three-phase partitioning technique is used to extract nonvolatile fractions such as boswellic acids BAs in addition to another method based on ethanol-modified supercritical fluid extraction [Turk et al.,2018; Niphadkar et al., 2017; Niphadkar et al., 2018]. Several chemical components of essential oil were recognized based on the chromatograms analysis by comparing their mass spectrum results with reference compounds saved in database or in literature [Al-Harrasi et al.,2008].

Biological Activity of Frankincense

According to several studies the essential oils of frankincense exhibit various biological activities that attributed to its chemical constituents. Anti-inflammatory, and antioxidants are among the bioactivities that have caught attention of many researchers.

Antioxidants Activity

There is a growing body of literature that recognises the anti-oxidative properties of Boswellia species essential oils. In 1998, Baratta et al. demonstrated that the α-tocopherol and butylated hydroxytoluene component of frankincense of B.thurifera essential oils have a substantial an antioxidant activity [Baratta et al.,1998]. However, Mothana et al. (2011) showed a weak free radical scavenging of essential oil of B. dioscorides, B. elongata, and B. socotrana with 22%, 21%, and 28%, respectively at 1mg/mL concentration [Mothana et al.,2011]. Thus, high antioxidant activity of B. socotrana essential oils could be attributed to its content of higher oxygenated monoterpenes concentration [Ali et al., 2008]. It has been reported that the essential oils of other plant such as Melissa of cinalis and M.

piperita that were rich in oxygenated monoterpenes had also showed higher free radical scavenging activity compared to Boswellia essential oils [Mimica-Dukic et al., 2004; Mimica-Dukic et al., 2003]. Other recent studies indicated that the antioxidant activity of essential oil of Royal upper, Hougari regular, Shabi frankincense, and Royal lower are related to high content of terpenes, which could behave as electron donors reacting with free radical to form stable product and terminate the reaction of free radical chain [Al-Harrasi et al.,2013; Prakash et al., 2014].

There are several studies revealed that frankincense essential oil possesses potent antioxidant effects. One of these studies showed that the potent antioxidant activity of frankincense essential oil could be ascribed to its high content of esters such as octyl acetate [Villa-Ruano et al., 2018] and to the presence of various types of phenolic constituents such as thymol and carvacrol ($C_{10}H_{14}O$) (Figure 3) [Brenes, and Roura, 2010; Zeng et al., 2015; Wojdylo et al., 2007]. It has been demonstrated that the compounds have phenolic groups within the structure afford protection against free radicals through neutralizing the free radicals and augmenting endogenous antioxidants [Sökmen et al. 2004; Sabah, 2021]. Accordingly, pharmacophore features of the thymol compounds that involve the presence of phenolic hydroxyl group within the structure has ascribed to its potent antioxidant activity by effectively scavenging free radicals. Similarly, carvacrol compounds have shown powerful antioxidant activity [Sökmen et al., 2004].

Figure3: Shows the phenolic constituents thymol and carvacrol ($C_{10}H_{14}O$) in essential oil of frankincense.

The other constituents that have been identified in essential oil of frankincense in low proportion were cymene and 1,8-ceneole. It has been detected that cymene compounds have antioxidant properties in vivo and could represent a neuroprotective agent in the brain [de-Oliveira et al., 2015] while the compound of 1,8-ceneole stimulates cognitive function and memory [Moss et al., 2012].

Anti-inflammatory Activity

Inflammation is a complex pathophysiological action that regulated via a cascade of various inflammatory mediators, for example prostaglandin (PG) nitric oxide (NO), pro inflammatory cytokines; IL- 1β, IL- 2, IL- 6, or tumour necrosis factor- α (TNF- α) [Chen et al., 2018; Fujiwara and Kobayashi, 2005]. Frankincense essential oils and their active components reveal significant anti-inflammatory effects and activeness against immune disorder. α-pinene, 1-octanol, linalool, limonene, octyl acetate, α-thujene and (E)-β-ocimene are the main constituents of frankincense essential oils. These active compounds show considerable analgesic and local anti- inflammatory effects. The proposed mechanism is related to the inhibition of COX-2 overexpression and nociceptive stimulus-induced inflammatory infiltrates [Li et al., 2016]. It has been stated that the essential oil of frankincense significantly reduces the concentration of vital biomarkers of inflammation namely interferon γ-induced protein10 (IP- 104) and intracellular cell adhesion molecule 1 (ICAM- 15) [Han et al., 2017]. Recent studies have suggested IP-104 as an indicator to predict the severity of acute respiratory infection [Haney et al., 2017].

Further study found that the treatment with α-pinene attenuated the activation of both MAPKs and NF-κB pathways [Kim et al., 2015]. Additionally, α-pinene compounds considerably decreased the pro-inflammatory cytokines expression [Choi et al., 2010]. As this active component exhibited anti-inflammatory properties by inhibiting of TNF-α, IL-1β, nitric oxide, and mitogen activated protein kinases [Gayathri et al., 2007]. Other research revealed that α-pinene is beneficial to treat upper and lower respiratory airway diseases via attenuating NF-κB translocation in THP-1 cells [Zhou et al., 2004]. It has been demonstrated that the anti-inflammatory actions of frankincense essential oil are mediated by downregulation of COX-2, inhibition of NF-κB transactivation and decreasing the TNF- α as well as IL-6 production [Zhang et al. 2020].

Another bioactive component of frankincense essential oil that possesses potent anti-inflammatory effect is thymol. It has been reported that the treatment of rotenone rats model with thymol attenuating liberation and activation of the inflammatory mediators involving pro -inflammatory cytokines of IL- 1β, IL- 6, and TNF- α, enzymes; COX-2 and iNOS which in turn lead to substantial decrease the inflammation in brain tissues [Barone and Feuerstein, 1999; Javed et al., 2019].Various studies have shown that carvacrol, active ingredients of frankincense essential oil exhibit anti-inflammatory activities, which mediated by reducing the inflammatory mediators production such as IL-1β [Crofford et al. 1994].

Overall, there is clear evidence shows that frankincense essential oil and its bioactive constituent exert the anti-inflammatory activity. Therefore the essential oil of frankincense is prospective candidate for innovative therapy conceptions. The following section will discuss the role of the frankincense volatile part in the whole anti-inflammatory action and its activity against COVID-19.

COVID-19 and Frankincense Essential Oil

The main chemical ingredients of essential oils including monoterpenoids, sesquiterpenoids, and phenylpropanoids are responsible for their pharmacological activities including anti-inflammatory, anti-bacterial, anti-oxidant, and anticancer activity. A number of vitro studies and clinical trials have shown that the essential oils of several herbs have potent antiviral activities against a variety of viruses for example herpes simplex virus type 1, influenza virus, Junin virus, and SARS coronaviruses [Nadjib, 2020].

In fact, no herbal remedies or other therapies have been approved to prevent or treat COVID-19 yet. However, recent study proposes that the major constituents of L. nobilis essential oil have exhibited strong antiviral activity against SARS.CoV-1 infection. The biochemical mechanism underling the action of these constituents involves inhibiting the replication of virus [Loizzo et al. 2008]. Nonetheless, silico study has suggested that the geranium and lemon essential oil compositions (linalool, citronellol, geraniol, limonene, and neryl acetate) can inhibit the expression ACE2 receptor, which serves as a gate for COVID-19 cell entry and thus can prevent the viral infection [Kumar et al., 2020; Albukhaty et al., 2020]. A study suggested that carvacrol and its isomer thymol that extracted from oregano have ability to prevent HIV-1 virus cell entry [Mediouni et al., 2020].

Recently, the anti-viral effect of essential oil against coronavirus infectious has been examined using a group of aromatic herbs. The anti-coronavirus activity of *Ammoides verticillata* essential oil has been assessed by molecular docking technique, which observed that some of its bioactive components such as carvacrol has the potential to inhibits ACE2 receptor [Abdelli et al., 2021]. Another study reported that the carvacrol bioactive compound interacts with the main protease protein (M^{pro}) and thus inhibits the replication of SARS- CoV-2 [Kumar et al., 2020]. Hence, these findings postulate that this bioactive compound could be selected as a potential therapy for COVID-19 infection. Furthermore, it has also been establish that some phenolic monoterpenoid such as carvacrol and thymol that potentially inhibit a spike (S) glycoprotein binding to the host cells [Kulkarni et al. 2020].

Frankincense plays a vital role in the treatment of anti-inflammatory chronic illnesses including asthma, osteoarthritis and bowel inflammatory illness. The pharmacological activities of frankincense extracts and their mechanism of action are established by several studies as a mentioned above.

As previously mentioned, the bioactive component of frankincense essential oil mediates anti- inflammatory effects by reducing the mediators of inflammation (IL-1ß, IL-6, TNF- α, IFN-γ, and PGE2), suppressing the concentration of (IP-104) a biomarker of severity of acute respiratory infection, inhibiting the MAPK/NF-κB signaling pathway activation which eventually could reduce the inflammatory response [Choi et al., 2010; Gayathri et al., 2007; Zhou et al., 2004; Zhang et al. 2020; Barone and Feuerstein, 1999; Javed et al., 2019]. Although there is insufficient evidence regarding the effect of use the anti-inflammatory therapies in COVID -19 patients, frankincense essential oil and its active components such as phenolic monoterpenoid (carvacrol and thymol) could represent a futuristic approach for treating COVID-19-related inflammatory complications [Ali et al., 2020]. Despite these promising data, one question that needs to be asked, however, is whether carvacrol and its isomer thymol extracted from frankincense essential oil have the same effect in term of inhibition of ACE2 expression and M^{pro}. Therefore further research should be undertaken to investigate the bioactive component of frankincense essential oil against COVID-19.

Conclusion

The present review summarized and debated recent studies on the importance of the volatile fraction of frankincensee (FEO) for a cure of several potential diseases in folk medicines, focusing on its bioactive components and pharmacological effects. Essential oil of frankincense is rich in active ingredients including phenolic compounds and terpenoids that have a vital role in the prevention and treatment of various diseases. These components exhibit a variety of pharmacological properties such as potent antioxidant, antimicrobial, anti-inflammatory, anticancer, and partial anti-depressant effects. Therefore, essential oil of frankincense might be a potential effective candidate therapy for different medical conditions. In addition, the review clearly illustrates that the phenolic monoterpenoid such as carvacrol and thymol of other essential oils suggested to have possible activity against SARC-CoV-2 via inhibited ACE2 expression and M^{pro}. To date, no sufficient evidence is found regarding the effect of these two active compounds that had been extracted from frankincense essential oil. Thus, it is necessary to investigate these compounds extracted from frankincense essential oil and how they exert their antiviral activity against COVID-19. However, utilize of carvacrol in cases affected by COVID-19 remains in terms of efficacy and safety indecisive. Thus it is not recommended to use carvacrol in any forms for COVID-19.

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