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ORIGINAL ARTICLE

Antifungal activity of Myrrh gum resin against pathogenic *Candida* spp.

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Abstract

Introduction and Objective. Medicinal plants have a long and significant history of being used for their healing properties. One famous example is *Commiphora*, which is mostly found in the southern part of Arabia. The objective of this study was to evaluate the effectiveness of a water-based extract obtained from two different varieties of myrrh in suppressing the proliferation of *Candida* spp. at different concentrations.

Materials and Method. The inhibitory activity of the aqueous extract of two different varieties of myrrh, commonly used in traditional medicine, was assessed against five pathogenic yeasts using the diffusion technique. Mass spectrum was used to analyze myrrh's chemical composition for antimicrobial effects.

Results. The aqueous extract of both tested species of myrrh (*Commiphora myrrha* and *Commiphora molmol*) showed inhibitory effects on all tested isolates. During the chemical examination of myrrh, it was noted that the material included 12 components known for their antimicrobial properties. The essential oil derived from two varieties of myrrh showed the most significant effects on *Candida tropicalis* (ATCC 66029), *Candida guilliermondii* (ATCC 6260), *Candida laurentii* (ATCC 18803), *Candida neoformans* (ATCC 66031), and *Candida albicans* (ATCC 14053). Analysis of chemical composition of the myrrh revealed 19 known components, of which 12 compounds have been proven by research to suppress the growth of microorganisms.

Conclusions. *C. myrrha* and *C. molmol* aqueous extracts exhibit a promising antifungal effect against common *Candida* infections. The aqueous extracts present a variety of antimicrobial compounds; however, further research is necessary to elucidate the specific mechanisms of action of these compounds, and to evaluate their efficacy, toxicity and safety before considering their clinical application.

Key words

Myrrh, *Commiphora Myrrha*, antimicrobial properties, essential oils, fungal infection, *Candida* species, terpenoids

INTRODUCTION

Many healthy individuals suffer from cutaneous, oral, vaginal, and gastrointestinal *Candida albicans*. However, under conditions of dysbiosis and immune suppression, this commensal organism can transition into a pathogenic state leading to a spectrum of infections ranging from superficial to life- threatening. *C. albican's* ability to transition between yeast, pseudo-hyphal, and hyphal forms is crucial for its virulence [1]. Beyond *C. albicans*, other *Candida* species, such as *C. guilliermondii* and such emerging pathogens as *Papiliotrema laurentii,* pose significant challenges. Patients with cancer undergoing immunosuppressive therapies, or with underlying conditions such as gastrointestinal or cardiovascular surgery, are particularly at risk of severe *C. guilliermondii* infection, a common skin and mucosal commensal. The yeast-like environmental fungus, *P. laurentii,* evolved from *Cryptococcus laurentii,* with the first case of *P. laurentii* fungemia being reported in a preterm infant with low birth weight in the Middle East [2]. *P. laurentii* has also been associated with cutaneous infections [2]. Given the escalating problem of *Candida* infections and the development of antifungal drug resistance, there is an urgent need to explore the potential of myrrh as a source of novel antifungal agents [3].

Biofilm-related *Candida albicans* disorders pose a significant challenge due to the development of antifungal drug resistance. To address this challenge, researchers have explored innovative phytotherapeutic approaches utilizing medicinal plants and essential oils [4]. Myrrh, a resinous exudate derived from *Commiphora* species (members of the Bruseraceae family), has been employed in traditional medicine for centuries. Historical records indicate that the Sumerians and Egyptians recognized its therapeutic potential in treating cavities and intestinal parasites. Today, myrrh continues to be used for a wide range of conditions, including wounds, digestive issues and respiratory ailments. *Commiphora myrrh*a in particular has been traditionally used to treat wounds, oral ulcers, discomfort, fractures, stomach disorders, microbiological infections, and inflammation. Al-Madi et al., [5] have identified four antimicrobials' terpenes in *Commiphora molmol,* including mansumbinone, 3,4-seco-mansumbinoic acid and β-elemene; of these, the latter is antibacterial. It slightly enhances the efficacy of ciprofloxacin and tetracycline against *Salmonella* strains SL1344 and L10, and Norfloxacin against *Staphylococcus* [5]. The resin fights chest infection-causing pathogens by inhibiting inflammation and cytotoxicity. *C. myrrha* resin and extract have been shown to reduce inflammation and alleviate symptoms, such as chest discomfort and sore throat associated with chest infection [6]. Diffusion trials

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have demonstrated the inhibitory effects of myrrh against *C. albicans* [7]. It is well-established that *Commiphora* resin and Fiorano sesquiterpenoids exhibit antimicrobial and antifungal properties.

Phytochemical analysis of myrrh has revealed its complex composition, encompassing monoterpenoids, sesquiterpenoids, essential oils, diterpenoids, triterpenoids, and steroids. Myrrh's richness in these bioactive compounds attracts significant attention for its potential therapeutic effects. These compounds have demonstrated a variety of pharmacological properties, such as aromatherapy, anti-inflammatory, antioxidant, antimicrobial, neuroprotective, and analgesic effects [7]. Recent studies have even explored its potential treatment against COVID-19, diabetes, and cancers. Given its broad spectrum of activities, myrrh has garnered significant interest as a source of natural bioactive compounds for drug development.

The aqueous extract of myrrh is comprised of essential oils, 30–60% water soluble gum, 3–8% ether (myrrhol), and resin (myrrhin). The *Commiphora* species produces fragrant myrrh resin as an exudate from their stem bark, with the resin colour ranging from yellow to reddish-brown, and is characterized by a bitter taste and a pleasantly pungent balsamic aroma [7]. This *Commiphora myrrh* resin is rich in Heerabolene, elemol, acadinene, cuminaldehyde, eugenol and furanosesquiterpenes, such as furanodienone, furanodiene, curzerenone, and lindestrene [7, 8, 9]. The volatile oil component, predominantly consisting of mono- and sesquiterpenoids, has been extensively investigated in *Commiphora* species through gas chromatography which detects monoterpenoids. Many gas chromatography experiments have investigated the volatile oils *C. myrrha*, quadricincta, holtziana, guidottii, kataf, and sphaerocarpa of the *Commiphora* species. While monoterpenoids, including camphene, myrcene, limonene, α-pinene, and β-pinene, have been reported, the volatile oil profiles exhibit significant interspecific variation. The low oxidation sesquiterpenoids, including β -selinene, β-Elemene, α-humulene, α-copaene and germacrene B, are commonly encountered in *Commiphora* species' volatile oils. Notably, furanosesquiterpenoids represent a characteristic class of compounds within this genus.

The aim of the study was to separate and isolate the natural active components of myrrh in an aqueous extract from the plant, evaluate its antibiotic potential against some pathogenic yeasts, and subsequently, characterize its chemical composition.

MATERIALS AND METHODS

Myrrh samples. The oleo-gum resins samples of *Commiphora myrrha* and *Commiphora molmol* were obtained from local stores in Dammam city. Samples were stored at 4°C until further processing.

Fungal isolates. Five *Candida* strains were obtained from the School of Medicine, King Saud University, Riyadh city. The strains are *Candida albicans* (ATCC 14053), *Candida neoformans* (ATCC 66031), *Candida laurentii* (ATCC 18803), *Candida guilliermondii* (ATCC 6260), and *Candida tropicalis* (ATCC 66029). Isolates were sub-cultured on Sabouraud's dextrose agar (SDA) (Scharlau, Spain) and incubated at 37 °C for 24 hours prior to testing [4].

Preparation of the Myrrh aqueous extracts. The oleo-gum resins of *C. myrrha* and *C. molmol* were ground into a fine powder. Myrrh powder (1, 2, and 5g) was dissolved in 10 mL sterilized distilled water and allowed to soak at ambient temperature for 24 hours. The mixture was subsequently filtered through gauze [10].

Antimicrobial susceptibility testing. The antimicrobial activities of the aqueous extracts were evaluated using the well-diffusion agar method [10]. Briefly, 1 ml of the fungal suspension of each *Candida* was added individually to sterile plastic petri dishes containing 10 ml of SDA. After solidification, a hole of half a centimeter in diameter was made in the agar using a sterile corkborer, in which the myrrh aqueous extracts were placed. The plates were incubated for 48 hours at 37 °C. Zones of inhibition were measured in millimeters to assess antimicrobial efficacy.

Chemical composition analysis. The chemical composition of the myrrh aqueous extract was determined using gas chromatography-mass spectrometry (GC-MS). The acquired mass spectrum data were analyzed to identify the primary constituents and potential antimicrobial compounds within the extract [10].

Statistical analysis. Performed using a properly randomized technique and three replicates of each treatment. Obtained results were subjected to analysis using LSD in SPSS 16 to compare data at 0.05 probability, according to Norusis [11].

RESULTS AND DISCUSSION

Antimicrobial effect of Myrrh aqueous extracts. Both *C. myrrha* and *C. molmol* aqueous extracts demonstrated inhibitory effects against all tested *Candida* species. The *C. molmol* extract exhibited a stronger antifungal activity, as indicated by larger inhibition zone diameters compared to *C. myrrha*. At 30% concentration of *C. molmol*, the inhibitory zone diameters for *C. albicans*, *C. neoformans*, *C. laurentii*, *C. guilliermondii*, and *C. tropicalis* were 2.45, 2.04, 2.26, 1.98, and 1.9 mm, respectively. However, the same concentration of *C. myrrha* aqueous extract used, resulted in a reduction in the zone of inhibition to 1.89, 1.62, 2.05, 1.78, and 1.74mm, respectively. These findings align with previous research by Akintobi et al. [12], who reported antimicrobial properties of both *Commiphora* species against *C. albicans*. The area of inhibition measured 1.76 and 2.01 cm^2 for doses of 250 and 1,000 mg/mL *C. myrrha*, respectively, while for *C. molmol*, the area of inhibition measured 1.53 and 1.76 cm^2, consecutively.

The observed inhibitory activity could be attributed to the virulence factors of the *Candida* species which contribute to their pathogenicity, including their ability to evade the immune system, adhere to surfaces, promote the growth of hyphae, form biofilms on medical devices and host tissue, and produce hydrolytic enzymes, such as proteases and haemolysin which damage tissues [13]. While *C. albicans* and *Candida parapsilosis* have become the dominant fungal infection in newborns, *C. glabrata* is the second most common species of candidiasis or vaginal candidiasis [13]. Non-albicans species are contributing to a concerning increase in infections which underscores the need for effective antifungal agents.

Table 1. Inhibition zone (mm) of Myrrh extracts at various concentration on some Candidiasis

Treatment	Conc. of myrrh %	Diameter of inhibition zone (mm)					
		Candida albicans (ATCC 14053)	*Candida neoformans* (ATCC 66031)	*Candida laurentii* (ATCC 18803)	*Candida guilliermondii* (ATCC 6260)	*Candida tropicalis* (ATCC 66029)	Mean*
control	0	0	0	0	0	0	±
	10	0±0	.73±0.05	1.24±0.16	1.01±0.05	0±0	0.60
C. myrrha	20	1.76±0.03	1.06±0.46	1.48±0.09	1.3±0.35	.38±0.33	1.20
	30	1.89±0.09	1.62±0.8	2.05±0.55	1.78±0,56	1.74±0,05	1.81
	10	0±0	.66±0.13	1.01±0.29	1.18±0.16	0.94±0.23	0.76
C. molmol	20	1.65±0.05	1.12±0.35	1.63±0.18	1.42±0.09	1.5±0.05	1.46
	30	2.45±0.05	2.04±0.33	2.26±0.2	1.98±0.05	1.9±0.09	2.13
Mean		1.29	1.20	1.60	1.45	1.08	

* Each value is a mean of 3 replicates (+SE)

Chemical composition of myrrh resin in aqueous extract. The aqueous extracts of myrrh contain substances that hinder the proliferation of the five types of *candida*. Chemical analysis to determine the nature of these compounds was conducted using the mass spectrum method (Fig. 1). The GC-MS study revealed the presence of 19 compounds, including 12 compounds with known antimicrobial properties in the aqueous extracts of both *Commiphora* species (Fig. 1, 2). All these chemicals are classified as fatty acids and their precursors, as well as phenolics and flavonoids (Tab. 2). The compounds are: β-Elemene, β-bisabolene, Dihydro butyl bezodoxepin, Tetradecanol, methyl palmitate, Tribenzo-1,2,3,4,5,6 anthracene, 9-Eicosene, 2-bromo-4-fluoro-N-(thiophen-2-ylmethyl) aniline, Octadecenoic acid methyl ester, dehydroabietic acid, and Docosene. These compounds, including terpene single molecules, exhibited potential antifungal activities [14] and have the capacity to inhibit many forms of yeast, which are known for their ability to examine the cell wall. This also results in the attenuation of the cellular biological processes by interfering with the cytoplasmic membrane's protein synthesis process, thus slowing and halting the process. This also impedes the active transport of ions and salts via the membrane [14]. The specific strategies used by microbes to survive the effects of microbial antibiotics are still unclear and subject to debate, Conversely, the chemical constituents of plants serve to safeguard them from internal microbial assaults. Nevertheless, some components within these substances possess inherent significance as natural chemical compounds that serve to protect the human body against microbial invasions [15].

The observed antifungal effects of the myrrh extracts are consistent with previous studies [12, 16], which attribute the antimicrobial activity to the presence of volatile oils, terpenes, phenols, flavonoids, and saponins. These compounds have been reported to damage fungal cell walls and mitochondria, leading to impaired energy production [17]. Murakami et al. [17] demonstrated the antifungal effects of *C. myrrha* essential oil against *C. albicans*, including a reduction in biofilm formation. Alshaikh and Perveen [16] performed Scanning Electron Microscopy analyses in which untreated cells (control) exhibited a normal budding profile and had a typical structure with smooth wall, while the cells treated with Thyme Essential Oil showed bumps and holes on the cell wall. Their study concluded that the killing of fungi by the active constituents is attributed to the fungicidal effects of the essential oil. Moreover, Braga and Ricci [18] found a similar observation by using atomic force microscopy (AFM) in which *C. albicans* cells showed major structural deformities at increasing thymol concentrations. A number of flattened cells with surface folds, cells with holes, and collapsed cells and ghosts, were also seen.

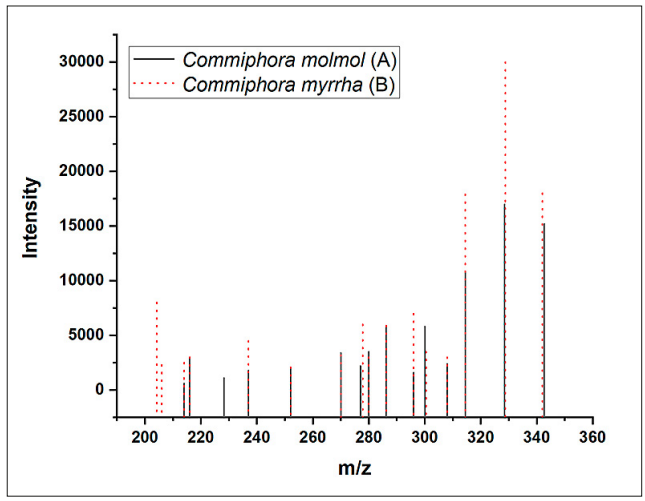

Figure. 1. Chromatograms differentiate the primary constituent of *C. myrrha* and *C. molmol* via mass spectrometry

The aqueous extracts of *Commiphora myrrha* and *Commiphora molol* significantly reduced the activity of the tested fungus. This might be due to fungal cell wall damage or even damage to internal organelles, such as mitochondria, which hampered their ability to gather energy for development [17]. Murakami et al. [17] noted that the essential oil derived from *C. myrrha* led to substantial decreases in the activity of mitochondrial dehydrogenase in *C. albicans*, hence affecting its potential to produce energy. Furthermore, a considerable reduction in biofilm production was noted – 62%.

There has been no prior research on the effect of *C. myrrha* essential oil on *C. albicans*. Furanoeudesma-1, 3-diene (17.65%), curzerene (12.97%), β-elemene (12.70%), and germacrene B, D, and A (12.15%, 9.13%, and 5.87%, respectively) are the primary components of *C. myrrha* essential oil. Antifungal effects of curzerene and β-elemene have been shown. Nonetheless, there has been little research on the effect of the compounds found in *C. myrrha* essential oil on *Candida albicans*. Additional research is required to explore this area [17].

Table 2. Analysis of the GC-MS chromatograph revealed the expected subcomponents of the SFE *C. myrrha* and *C. molmol* extract

No.	Compound predicted	*Commiphora myrrha* (B) M. wt.	*Commiphora molmol* (A) M. wt.	M. formula	Biological effect
1	Beta- Elemene Germacrene D	204.21	204.21	$C_{15}H_{24}$	A and antifungal [5], antiviral Activity [17]
2	β-bisabolene	204.21	204.21	$C_{15}H_{24}$	Anti-adipogenic and antibacterial activities [19]
3	Hydroquinone derivative Dihydro butyl bezodoxepin	-	206	$C_{13}H_{18}O_2$	Antimicrobial; antioxidant; antitumor; antiviral [8]
4	Tetradecanol Furanocudesma-1,3-diene	214	214	$C_{14}H_{30}O$	Antibacterial and anti-inflammatory (periodontitis) activity [8], antiviral cctivity [17], analgesic property [7]
5	Lindestrene	214	214	$C_{15}H_{18}O$	Analgesic property [7]
6	Curzerene Furanodiene	216	216	$C_{15}H_{20}O$	Analgesic property [7]
7	Myrrhone	228.27		$C_{15}H_{16}O_2$	Antiplasmodial [20]
8	2-(2-hydroxy-2-methyl-2-phenylethyl)-3-methyl	237	237	$C_{20}H_{20}O_4$	Analgesic activity [7]
9	Z,4Z-Furanodien-6-one	252=	252	$C_{15}H_{18}O_2$	Anti-inflammatory, anti-oxidant, wound-healing agent, anti-neoplastic [9]
10	Methyl palmitate	270	270	$C_{17}H_{34}O_2$	Antimicrobial [20]
11	Tribenzo-1,2,3,4,5,6 anthracene	277	277.80	$C_8H_6Br_2O$	Anticancer and antimicrobial [21]
12	9-Eicosene	280	280	$C_{20}H_{40}$	Antimicrobial [10]
13	2-bromo-4-fluoro-N-(thiophen-2-ylmethyl)aniline	286.17	286.17	$C_{11}H_9BrFNS$	Antimicrobial [22]
14	Octadecenoic acid methyl ester	296	296	$C_{19}H_{36}O_2$	Antimicrobial [23]
15	Dehydroabietic acid	300	300.47	$C_{20}H_{28}O_2$	Anticancer, antibacterial, antiviral, antiulcer, insecticidal, and herbicidal activities [24]
16	Docosene	308	308	$C_{22}H_{44}$	Antifungal [25]
17	Mansumbinone	314.40	314.4	$C_{22}H_{34}O$	Anti-inflammatory, anti-inflammatory, antioxidant, wound-healing agent, free radical scavenger, anti-neoplastic [9]
18	Tribenz [a,c,h] anthracene Or Tribenzo-1,2,3,4,5,6 anthracene	328.53	328.8	$C_{26}H_{16}$	Anticancer drug [21]
19	3,4- seco-mansumbinone acid	342.67	342		Anti-inflammatory, antioxidant, wound-healing agent, anti-neoplastic [17]. 18 (antibacterial [5]

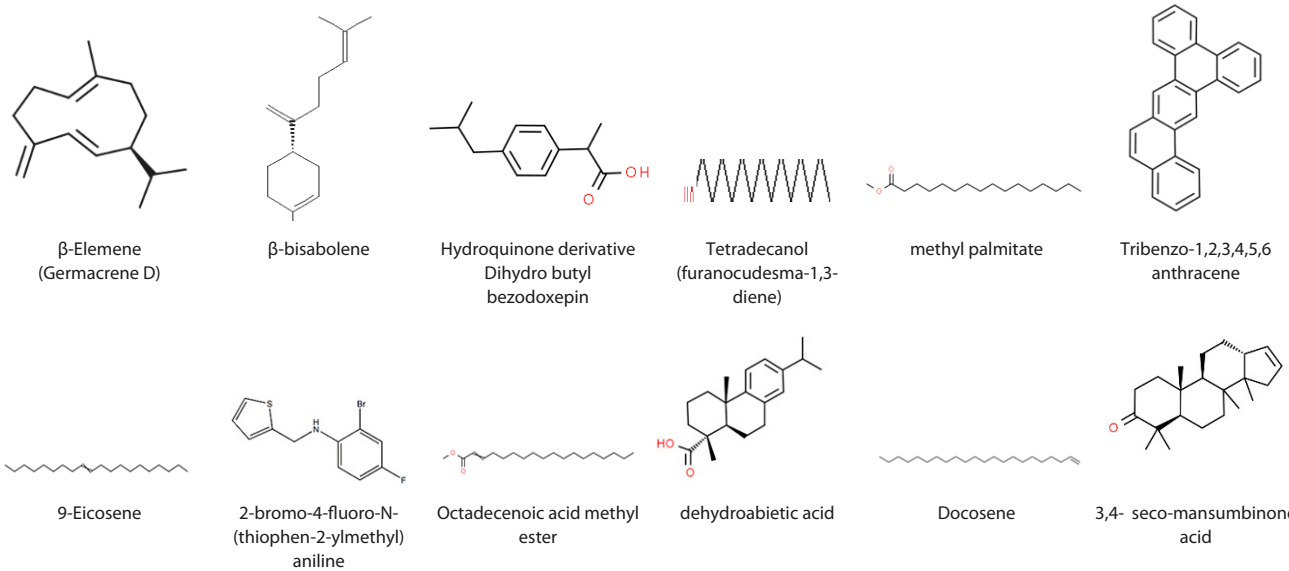

Figure 2. Chemical constructions of biologically-active compounds extracted from *Commiphora myrrha* and *C. molmol* oleo-gum resins

CONCLUSION

Myrrh resin is a valuable botanical resource in traditional medicine. *Commiphora* species exhibit anti-inflammatory, antioxidant, antimicrobial, neuroprotective, and analgesic effects. It can even treat respiratory infections, such as COVID-19. These pharmacological effects are caused by terpenoids (monoterpenoids, sesquiterpenoids, volatile/essential oils), diterpenoids, triterpenoids, and steroids. Myrrh essential oil is used in aromatherapy, scents and cosmetics.

The rich phytochemical components of pharmaceuticals, due to their anti-parasitic effectiveness are also used as insecticides, and additionally used because of their ability to fully grasp medication interactions.

The results of this study highlight the potential of *C. myrrha* and *C. molmol* aqueous extracts as promising antifungal agents against common *Candida* infections. The presence of a variety of antimicrobial compounds, particularly terpenes, contributes to the observed inhibitory activity. However, further research is necessary to elucidate the specific mechanisms of action of these compounds and to evaluate their efficacy in *in vivo* models. Additionally, studies on the potential toxicity and safety of these extracts are essential before considering their clinical application. Further study is also required to thoroughly examine the potential of these water extracts as revolutionary anti-fungal drugs, including their efficiency against diverse *Candida* strains, their mechanisms of action and main components.

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