Antifungal Properties of *Dracaena cinnabari* Resin Extracts Against *Candida albicans*

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Abstract

Background: Candida albicans is the most prevalent fungal pathogen in humans, capable of causing a range of clinical infections from mucocutaneous conditions like oral thrush to life-threatening systemic diseases. While Candida species are typically part of the normal oral flora in about 75% of the global population, the rising resistance to antifungal drugs has become a significant concern. This highlights the urgent need to explore alternative antimicrobial agents, including natural phytochemicals derived from plants, as potential substitutes for synthetic chemicals to address the growing issue of antifungal resistance. Methods: This study aimed to evaluate the antifungal properties of Dracaena cinnabari resin extracts (methanol and water) against Candida albicans. The antifungal activity was assessed using the direct contact agar diffusion test, while the minimal inhibitory concentration (MIC) of the extracts was determined through the broth dilution method. Results: The antifungal susceptibility tests demonstrated that C. albicans was susceptible to both methanol and water extracts of D. cinnabari resin, with zones of inhibition measuring 32.2 ± 0.8 mm and 29.0 ± 1.1 mm, respectively. The MIC values ranged between 2.50 and 5.00 mg/mL for both extracts. Conclusion: The antifungal effectiveness of D. cinnabari resin extracts was comparable to that of the miconazole control, showing significant potential as a natural treatment option against Candida albicans. These findings suggest that Dracaena cinnabari resin could play a valuable role in the treatment and management of candidiasis, particularly oral candidiasis.

Keywords: Dracaena cinnabari, Candida albicans, Antifungal resistance, Natural products, Oral candidiasis

Significance | This study determined Dracaena cinnabari's resin as a promising natural antifungal agent against Candida albicans, particularly in oral candidiasis.

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Introduction

Candida species are fungi that grow as yeasts and deficient of the complete sexual cycle, they have a potential to appoint in the parasexual cycle, where they are thought to be obligated diploid can mould as true filamentous hyphae and pseudohyphae cells (Berman, 2012). *Candida albicans* is the topmost constant of human fungal pathogens. *C. albicans* is a multiform fungus which has the possibility to rise as stretched ellipsoid cells with narrowing at the septa (also called as pseudohyphae), oblong-shaped budding yeast or as parallel wall true hyphae. *C. albicans* can result in two most types of diseases which are superficial infections (vaginal or oral thrush) and lethal systemic infections. They exist in the mouth of 75% of the world population as normal flora. The capability of *C. albicans* to infect is influenced by fitness attributes and virulence factors. Rapid adjustments to alterations in pH of the surrounding

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environment, dominant
nutrient addition systems, metabolic adaptability, and potent stress response are considered as fitness attributes. Examples of virulence factors are expression of invasions and adhesions on the cell's surface, morphological changeover of yeast and hyphal forms, biofilms formation, thigmotropism, hydrolytic enzymes secretion and phenotypic switching. (Mayer *et al.,* 2013).

C. albicans, oral streptococci co-infections are correlated with increased prevalence of tooth surface caries and oropharyngeal diseases. *C. albicans* associated with *Streptococcus gordonii, S. sanguinis, and S. oralis* increase biofilm formation and bacterial colonization. Furthermore, *C. albicans* paired with bacterial infections are related with stomatitis in denture wearing persons, *C. albicans* partners with bacterial communities have been found in periodontal pockets and root canals. Development of early childhood caries are caused by *C. albicans*–streptococcal biofilms. (Koo *et al*., 2018). Furthermore, a study conducted by Hamid Badali (2013) reported that the occurrence of endocarditis caused by *Candida* spp. has increased even with antifungal therapy and surgery. A study conducted by Okonkwo *et al*.,(2013) stated that *C. albicans* remains as a main cause of oral thrush especially in HIV infected persons. On the other hand, based on a study conducted by Bassetti *et al*., (2018) showed that for the past twenty years, a variety of antifungals had been developed and showed therapeutic efficiency in fungal infections. Sanglard and Odds (2002) stated that *Candida* species become resistant to antifungal agents by several mechanisms which result in treatment failure for infections caused by *Candida* spp.

Natural products have been widely used in our daily lives such as in cooking, food flavouring, as preserving agents and in medications. It is known to have multiple benefits which include both antifungal and antibacterial properties. By definition, natural products are products that are made by a living organism (Roberts and Caserio, 2021) and its examples include herbs and spices. Its use as an alternative to synthetic drugs has been a growing interest for years and research on its effectiveness is still active (Newman and Cragg, 2020). The increasing interest in natural product alternatives may stem from the need to overcome the growing incidence of drug resistance among microorganisms as well as the interest in utilizing the various benefits of natural products.

A study conducted by Ray Hovijitra *et al* (2016) showed that essential oils derived from cinnamon bark and sweet basil leaves have effect on both sessile forms of *C. albicans*. Both essential oils also proved to successfully eradicate them at higher concentrations than their minimum inhibitory concentrations (MIC) (Hovijitra *et al,* 2016). Another study by Łopusiewicz and Mizielińska (2017) reported that cumin, rosemary and fennel essential oils show antifungal properties with fungi such as *Bortrytis cineria* and *Mucor circinelloids*, which exhibits the most sensitivity towards the oils. In the same study, it showed that cumin oil inhibits growth of *Aspergillus niger, Aspergillus clavatus* and *Rhizopus oryzae* at higher concentration as well (Łopusiewicz and Mizielińska, 2017).

In a separate study conducted by Freire et al, they had tested three different types of essential oils and phytochemical components which are derived from natural product for their antifungal activity against *C.albicans* isolated from denture wearers. The essential oils namely are oregano, ginger and peppermint which the phytochemical components tested on are citral and limonene that are usually derived from citrus peel (Freire, et al., 2017). The study had found that citral had shown the most antifungal response towards *C.albicans* among the products used in which it requires the least amount of minimum inhibitory concentration(Freire, et al., 2017). Many studies proved that natural products have the potential in inhibiting fungal diseases. This allows greater possibilities in discovering other natural products that have antifungal properties.

Dracaena cinnabari is an endemic wild tree and one of the six arboreal species of the genus found on Socotra island, Yemen. (Marrero *et al,* 1998). *Dracaena cinnabari* is called dragon blood tree because of its deep red resin and its uniquely strange appearance where it appears upturned, densely packed crown appearing like an uprightly held umbrella (Ibrahim, 2018). The deep red resin within the tree is called dragon's blood which has been a traditional medicine by many cultures since decades such as early Greeks, Arabs and Roman (Gupta et al., 2008).

Based on many studies, the resin extract of *Dracaena cinnabari* can be used for treating dysentery, eczema, diarrhoea, haemorrhage, external ulcers and respiratory disease (Milburn, 1984). Furthermore, Ibrahaem., 2018 stated that the root can be used in rheumatism; whereas the leaves can be used to relieve flatulence by adding it as a carminative ingredient. The extract of *Dracaena cinnabari* exhibits couples of properties such as antimicrobial, antifungal and antiviral activity, antitumor and cytotoxic activity, antihemorrhagic activity, Immunomodulatory activity, antiulcer and antidiarrheal activity, antioxidative activity, anti-inflammatory activity, mutagenic and antimutagenic activity. Moreover, *Dracaena cinnabari extract* showed an effective value together with ethyl acetate against pathogenic fungal strains (Abu-Taleb, 2013). In dentistry, authors mentioned that resin can be used by grinding into powder and rubbed on teeth to treat tooth decay or tooth cleaning (Al-Fatimi, 2018).

The need to study natural products' antifungal properties stems from the increasing antifungal resistance incidence. The current study is aiming to investigate the potential antifungal effect of *Dracaena cinnabari* resin extract on *C. albicans*. This natural extract could seize a role in the treatment planning and management of candida disease, especially oral candidiasis in humans.

Materials and Methods:

1. Dracaena cinnabari (DC) resin extract preparation

The resin of DC was obtained from the Socotra Island located in Yemen, where the Environmental Protection Authority of Yemen is the authority that distinguishes and verifies the plant samples. A voucher specimen of the resin (DC/2013-8/ 122) was placed at the herbarium of the department of Pharmacognosy, Faculty of Pharmacy, University of Sana'a, Yemen. An electrical blender was used to ground the DC extract into powder, which had aided the extraction process. A 50g of the powdered DC resin was placed into a 1L conical flask and later macerated with methanol (500ml methanol was added, where the proportion of 1g of dried and ground DC was to 10ml methanol (1:10)). The high polarity of methanol allows greater efficacy towards the extraction of polar phytochemicals such as phenolics and flavonoids (Anwar et al, 2010). The conical flask was placed on a shaker at 100 rpm at room temperature for about 3 days. The resultant extract was then filtered using a fine muslin cloth. A Whatman filter paper of Grade 1-Circles that measured at 150mm was later used to remove the crude part. Under reduced pressure at 40 °C, the Eyela rotary evaporator was used to separate the methanol from the extract and thus, a gummy red resin extract was produced. A dry powder extract weighing at 28.0g was then obtained using a freeze dryer. The extract was wrapped with aluminium foil in order to prevent possible photo-oxidation. The extract was later stored at 4°C until it was used. The methanol extract was later dissolved in a 10% DMSO solution before its usage. (Al-Afifi, et al, 2018).

2. Media and fungal suspension preparation

Candida albicans was used in this research. It was cultivated on a Sabouraud Dextrose agar (SDA). *C. albicans* was inoculated from frozen tubes using the loop transfer method, and added into 3mL slant nutrient broth. It was later subjected to 200rpm shaking culture. *C. albicans* from that culture was then placed onto a suitable solid medium and incubated overnight. Designated colonies were later transferred to a proper liquid medium and incubated for 4–6 hours in order to achieve log phase growth. Stock cultures remained at -80°C in growth broth containing 25% sterile glycerol.

3. Direct contact agar diffusion tests

Based on the previously described method, disk diffusion test was carried out with a few alterations (Quan et al., 2006; Li et al., 2015). *Candida albicans* was the main and only fungal tested. The test began by spreading uniformly 3ml of aliquoted solution of 5Å~105cells/ml suspension onto different sets of Mueller Hinton agar (MHA) plates. Then, aliquots containing *Dracaena cinnabari* are later placed on the agar. As for negative control, a filter paper disc containing 1% dimethyl sulfoxide will be used. Beside that, the filter disks with 6mm diameter containing Miconazole which is the current common medication was placed onto the agar surface as a positive control. The plates was incubated at 35◦C for 24 hours. The diameter of growth inhibition zones were later measured and recorded after incubation.

4. Minimum inhibitory concentration (MIC) by broth dilution method

Anti-fungal susceptibility tests regarding C. *albicans* isolates will be implemented based on the NCCLS reference which is a method of microdilution. Sequential two-fold dilutions of the approved materials will be arranged in RPMI-1640 medium (Sigma Aldrich, St. Louis, MO, USA) and will be buffered to pH 7.0 with 3-N-morpholino propane sulfonic acid buffer (MOPS), EMD Chemicals, (Gibbstown, NJ, USA) in ninety six-well microtiter plates with a concluding volume of 100 µL. Initial concentration of DC dissolved in medium used was 10mg/mL then 2-folded serial dilutions were carried out on flat-bottom 96 –well plate (Nunclon™, Denmark). The concluding concentrations of the extracts will be in the range between 0.04 and 5.00 mg/mL for DC. Negative control was used by add the suspension without any drug and was regarded as the drug-free control.The plates was incubated for 24-hour at 37°C. Amount of MIC will be interpreted directly as the primary concentration where no fungal growth is detected.

5. Statistical analysis

The data were presented as means ± SEM. The data were analyzed using one-way ANOVA and repeated measure one-way ANOVA in SPSS window program version 21.0 (Chicago, SPSS Inc). P value at 0.05 was considered as level of significance. Tukey HSD post-hoc analysis was followed ANOVA with p value less than 0.05.

Results:

1. Dracaena cinnabari (DC) resin extract preparation

Dracaena cinnabari belongs to the family Asparagaceae, also known as dragon blood and originated from Socotra, Yemen (Figure 1a). The part of the plant that is used in this experiment is resin (Figure 1b). Besides, extraction yield for water is 32.67 ± 0.66 % and for methanol is 18.00 ± 0.80 % (Table 1). Every experiment was repeated three times. Values are means of triplicate determination (n = 3) ± standard deviations.

2. Direct contact agar diffusion tests

The Zone of Inhibition was 32.2 ± 0.8 mm and 29.0 ± 1.1 mm, respectively. There was no significant difference with the miconazole (10µg) control which is 31.0 ± 1.3 mm (Table 2. Figure 2b)

3. Minimum inhibitory concentration (MIC) by broth dilution method

The minimum inhibitory concentration (MICs) ranging from 2.50 and 5.00 mg/mL for both *D. cinnabari* methanol and water extracts (Table 3 and Figure 3)

The minimum inhibitory concentration (MICs) ranging from 2.50 and 5.00 mg/mL for both *D. cinnabari* methanol and water extracts.

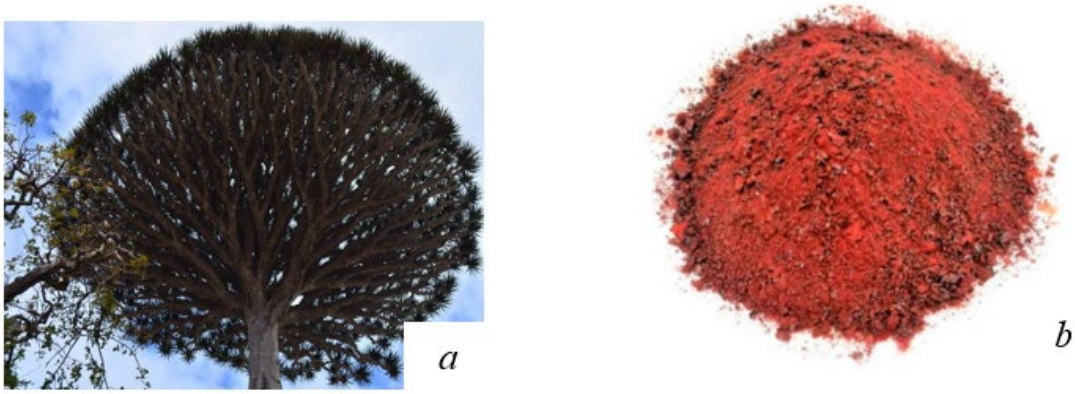

Figure 1.(a) *Dracaena cinnabari,* figure showing an uniquely strange appearance of dragon blood tree. b) Dragon blood tree resin, figure showing deep red resin of *Dracaena cinnabari* resin extract in a powder form.

Table 1. *Dracaena cinnabari* extraction yield percentage by conventional

Plant species	Family	Common name	Plant part used	Country of origin	Extraction yield (%) Water	Extraction yield (%) Methanol
Dracaena cinnabari	Asparagaceae	Dragon blood	Resin	Socotra, Yemen	**32.67 ± 0.66**	**18.00 ± 0.80**

Table 2. Antifungal activity of *Dracaena cinnabari* extracts (50mg/ml) against *Candida albicans*

	Zone of Inhibition (mm)		
Test strain	Water	Methanol	Miconazole (10 μg)
Candida albicans	**29.0 ± 1.1**	**32.2 ± 0.8**	**31.0 ± 1.3**

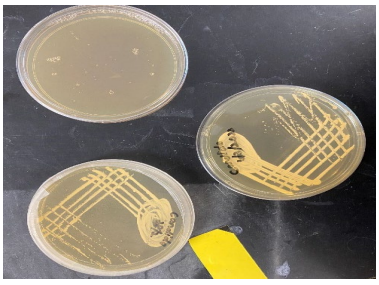

Figure 2(a). *Candida albicans* in Sabouraud Dextrose agar (SDA).

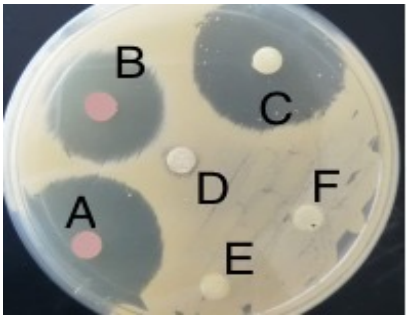

Figure 2(b). Mueller Hinton agar (MHA) plates shows, A; Zone of Inhibition for methanol extract, B; Zone of Inhibition for water extract, C; Zone of Inhibition for miconazole, D, E, F; Solvent (DMSO) as drug-free control in different concentrations.

Table 3. The MIC of *Dracaena cinnabari* water extract and methanol extract against *Candida albicans*

	MIC (mg/ml)
Water Extract	**5.00**
Methanol Extract	**2.50**

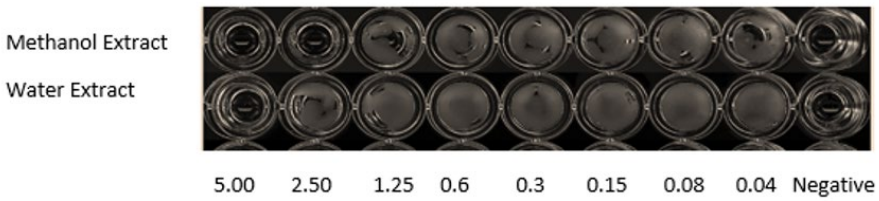

Figure 3. Minimum inhibitory concentration (MIC) of *Dracaena cinnabari* water extract and methanol extract against Candida. For methanol and water extract, the growth inhibition of *Candida albicans* was observed on well of 2.50 and well of 5.00 respectively. No yeast cells were observed to grow in the wells at the minimum inhibitory concentration (MICs) or higher concentrations. Negative; The suspension without any drug was regarded as the drug-free control.

Discussion:

The resin of D. cinnabari contains several flavonoids , including 7-hydroxy-3-(3-hydroxy-4-methoxybenzyl)chroman; 7-hydroxy-3-(4-hydroxybenzyl)-8-methoxychroman; 3-(4-hydroxybenzyl)-8-methyl-enedioxychroman ; 7-hydroxy-3-(4-hydroxybenzyl)chroman ; 7,4′-dihydroxy-3′-methoxyflavan ; 7,3′-dihydroxy-4′-methoxyflavan ; 7-hydroxyflavan ; 4-hydroxy-2-methoxydihydrochalcone ; 4,4′-dihydroxy-2-methoxydihydrochalcone; 4,4′-dihydroxy-2′-methoxychalcone; 7,4′-dihydroxyflavone ; and 7-hydroxyflavan-4-one . (11) and other phytochemicals that attribute various medicinal properties to this multipurpose plant. (Al-Awthan etal, 2021).

The extract of Dracaena cinnabari exhibits properties such as antimicrobial, antifungal and antiviral, antitumor and cytotoxic, antihemorrhagic activity, Immunomodulatory a, antiulcer and antidiarrheal activity, antioxidative activity, anti-inflammatory activity, mutagenic and antimutagenic activity. Moreover, Dracaena cinnabari extract showed an effective value together with ethyl acetate against pathogenic fungal strains (Abu-Taleb, 2013). In dentistry, authors mentioned that resin can be used by grinding into powder and rubbed on teeth to treat tooth decay or tooth cleaning (Al-Fatimi, 2018).

Candida albicans is the most common human fungal pathogen which causes disease ranging from oral thrush to systemic candidiasis which can be lethal to the human body. It is found to exist as normal flora in the mouth of 75% of the world population. As mentioned previously, the interest to study antifungal property of natural products are growing due to the ever growing drug resistance towards commercially available synthetic antifungal drugs Naturally available products such as *Dracaena cinnabari,* also known as the dragon blood tree, is a good replacement against synthetic compounds to counteract antifungal resistance. The dragon blood tree's deep red resin has been proven to have significant antioxidative, anti-inflammatory and antimicrobial properties.

Based on the results obtained in this research, the antifungal susceptibility test showed that *C. albicans* is susceptible to both *Dracaena cinnabari* methanol and water extracts. The zones of inhibition were found to be 32.2 ± 0.8mm and 29.0 ± 1.1mm, respectively. There was no significant difference with the miconazole control, which is 31.0 ± 1.3mm. On the other hand, the minimum inhibition concentration (MICs) against *C. albicans* ranged from 2.50 and 5.00 mg/mL for both *D. cinnabari* methanol and water extracts.

Our research has proven that *D. cinnabari* have the antifungal effect on *C. albicans*, this further proves the plant's antifungal properties. A supporting evidence shows that Dracaena cinnabari have antifungal effects on Aspergillus niger (Rajesh K Verma ,2007). In contrast with the research (Nabil A. Albaser, 2020), the antifungal activity was demonstrated by using Methanol and water extracts by using the methanolic solution of the crude resin (20–30 mm) against A. fumigatus, M. gypseum and T. mentagrophytes followed by less polar dichloromethane and ethyl acetate extracts (18 to 20 mm), compared with the antifungal reference nystatin. Previous studies have reported the antifungal activities of D. cinnabari resin (wjpr. 2020). Albaser et al. World Journal of Pharmaceutical Research 225 against three other species C. albicans, A. flavus, and A. niger. These researches show significant evidence on our research result where *Dracaena cinnabari* have indicative antifungal properties on fungi. Our research proves that *Dracaena cinnabari* have antifungal properties that are similar to miconazole where the minimum inhibition concentration against *Candida albicans* are similar.

Dracaena cinnabari is is a potent antifungal agent against *Candida albicans* and it has the ability to kill *Candida albicans*cells in vitro.

Conclusion

Previous studies have reported the antifungal activity of many netural products.. *Dracaena cinnabari* is one of natural products which have a bright future in the treatment of may microbes and further work may lead to relative antitmicrobial agents to be used in clinical settings. Therefore, the investigation of the antifungal properties of *Dracaena cinnabari* resin methanol extract toward *Candida albicans* by direct contact agar diffusion test and the minimal inhibitory concentration (MIC) should be done before further preclinical and even clinical studies. *Dracaena cinnabari* resin bulf.f methanol and water extracts extracts showed a potential antifungal effect against *Candida albicans*. This natural extract could play a role in the treatment planning and management of *Candida spp* diseases, especially oral candidiasis. For further recommendation, *In-vivo* tests for the biological evaluation of antifungal effect of *Dracaena cinnabari* bulf.f resin methanol and water extracts on *Candida albicans* such as animal or tooth model.

Author contributions

R.A.-S. conceived the study, developed the hypothesis, and wrote the manuscript. A.M.A. and A.A.B. contributed to data analysis and manuscript revisions. S.S.S.Z., N.N.H., and L.M.Q. collected data and assisted with the literature review. M.A.A.-G., S.I.A., and A.V.S. provided technical support and data interpretation. V.S. and I.M.F. contributed to the final manuscript revisions. All authors read and approved the final manuscript.

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Competing financial interests

The authors have no conflict of interest.

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