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Antifungal activity of marine algal extracts against some pathogenic fungi isolated from human infection-related habitats

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Abstract
In the present study, a total of 100 fungal isolates from infection-related environments were collected and identified from central laboratory of Ain Shams University Specialized Hospital from July to November (2022). It was observed that between 100 of patients with fungal infections, patients aged between 20- 70 years old (72 cases), females (56 cases), isolates from outpatient clinics (66 cases), fungal infections with the first infection (84 cases) and single fungal infection had the higher rate of cases (76 cases). Highest number of fungal infection isolates were from personal belongings (34 isolates), urine catheters and cultures (26 isolates), bed sheets (13 isolates), blood cultures (11 isolates), vaginal swabs (10 isolates), bronchial wash tube (4 isolates), and only two isolates from wound cultures. *Candida albicans* represented the highest ratio (40 isolates), *Candida tropicalis* (17 isolates) and *Microsporum canis* (15 isolates). Ethanolic extract of brown alga *Sargassum giganteifolium* showed the highest antifungal activity against *Candida tropicalis* (22mm), ethyl acetate extract of red alga *Actinotrichia sp.* had high antifungal activity against *Candida tropicalis* and *Candida Parapsilosis* (18 and 20 mm.), respectively, petroleum ether extract of green alga *Caulerpa racemosa* showed moderate antifungal activity against *Microsporum canis* (16mm). TEM showed ultra-structural effects of ethanolic extract of brown alga *Sargassum giganteifolium* against *Candida tropicalis*, the rupture of the fungal cell wall which led to deformation of outer cell shape, loss of internal cellular components and shrinking of cytoplasm were observed.

Keywords: Fungal infections, *Candida tropicalis*, *Candida parapsilosis*, *Microsporum canis*, *Sargassum giganteifolium*, *Caulerpa racemose*

Introduction
Every year, there are over 150 million cases of severe fungal infections worldwide, which result in about 1.7 million deaths. These numbers are increasing because of a number of medical and societal developments in recent decades that have facilitated the spread of fungal diseases. Furthermore, multidrug-resistant fungi, such as the highly virulent strain of *Candida auris*, have emerged as a result of long-term therapies and preventative usage of antifungal medications in high-risk individuals (Kainz *et al*., 2020) [30]. Understanding the elements that lead to the rising incidence and dissemination of fungal diseases is necessary for developing effective prevention measures. For instance, deforestation can increase human-wildlife contact, which increases the risk of zoonotic fungal diseases, and migration and travel around the world can foster conditions that are conducive to fungal development and transmission. Conversely, fungal diseases may be able to spread to new areas due to changes in climate that affect their geographic distribution (Nnadi and Carter, 2021) [40]. Invasive candidiasis can develop in immunocompromised patients with diabetes, chronic liver disease, chronic renal illness, or those who need frequent blood transfusions. A recent meta-analysis comprising 34 studies and 29 risk factors found that the most important risk factor for invasive candidiasis in critically sick patients was the use of broad-spectrum antibiotics (Thomas-Rüddel *et al*., 2022) [54].
According to Corzo-León *et al*. (2019) [16], 25% of people worldwide suffer from human skin fungal infections (SFIs). According to Xiao *et al*. (2020) [59], the incidence of fungal

bloodstream in intensive care unit patients was 0.38%. Dermatophytes, the most common pathogenic fungi in the US, produce skin illnesses that can be divided into three categories according to their habitat: geophilic (growing in soil), zoophilic (growing on animals), and anthrophillic (growing on humans) (Boddy *et al.,* 2016) [14]. They are classified into seven clades, numbered A through G. *Trichophyton* species are found in clade A, *Epidermophyton floccosum* species are found in clade B, and *Microsporum* species are found in clades C and F (De Hoog *et al*., 2017) [18].

The most frequent invasive *Candida* infection is a bloodstream infection called candidemia. In North America, *Candida* is one of the most common causes of infections linked to healthcare (Weiner-Lastinger *et al*., 2020) [58]. *Candida albicans* is the most prevalent kind of fungus that causes urinary tract infections, and complicated UTIs had a greater treatment failure rate when fungal species caused systemic or invasive damage (Luu and Albarillo, 2022) [35]. Depending on the population and region, it has historically been estimated that 70-75% of women of reproductive age have vulvovaginal candidiasis (Benedict *et al*., 2018) [13]. According to Zhang *et al.* (2018), 110 5.04% of the fungal strains recovered from 1,310 thermal burn lesions had the common constituent mixture of *Candida parapsilosis*, *Aspergillus flavus*, *Candida albicans* and *Candida tropicalis*. *Aspergillus*, *Fusarium* and *Candida* are the most prevalent and responsible for 70% of the fungal species that cause keratitis out of the 105 known pathogenic mycotic species of keratitis (Niu *et al*., 2020) [39]. The primary cause of superficial fungal infections, dermatophytes including *Trichophyton rubrum* and *Trichophyton mentagrophytes*, have recently begun to pose a danger to antifungal resistance, which has been shown in some of the most prevalent species (Kruithoff *et al.,* 2024) [32]. Fluconazole, itraconazole, and voriconazole resistance in *C. tropicalis* has been steadily rising (Wang *et al*., 2021) [61]. Only a few antifungal drugs are now available for therapeutic use because humans and fungi share a eukaryotic structure. Additionally, the growing use of currently available antifungal drugs to treat fungal infections has resulted in an increase in drug resistance in *Candida* species. However, several antifungal drugs with different mechanisms of action are authorized for use in clinical settings to treat fungal infections (Ahmady *et al*., 2024) [3].

In addition to producing a wide range of bioactive chemicals, marine algae are abundant in essential nutrients. Terpenoids, carotenoids, proteins, peptides, alkaloids, phlorotannins, diterpenes, tocopherols, and tocotrienols are all of great interest as polyphenolic ingredients (Suleria *et al.,* 2020) [51]. The therapeutic effects of marine seaweeds' bioactive substances include anticoagulant, immunomodulatory, anticancer, antitumor, antioxidant, antiallergic, anti-inflammatory, hypoglycemic, antiobesity, antimicrobial, antifungal, and antiviral qualities (Cui *et al*., 2018; Hentati *et al.,* 2018) [17, 27]. Algal extracts contain bioactive substances such as pigments like carotenoids (carotene xanthophyll), chlorophylls, and phycobilins (phycocyanin, phycoerythrin), which have antibacterial, antiviral, antifungal, antioxidative, anti-inflammatory, and antitumor properties, as well as compounds like carbohydrates, proteins, minerals, oil, fats, and polyunsaturated fatty acids. Antioxidants include polyphenols, tocopherols [vitamin E], vitamin C, and mycosporine-like amino acids (Gullón *et al.,* 2020) [25].

Commercial and biomedical applications have made use of Rhodophyta (carrageenans, porphyran, and agars), Phaeophyta (alginates, fucans, laminarin, and fucoidans), and Chlorophyta (ulvans, among others) polysaccharides. Derived oligosaccharides can boost defence responses and protection activity against pathogens in plants (Tanna and Mishra, 2019) [52]. It is commonly recognized that marine algae contain a variety of fatty acids, sterols, and other lipid compounds. These lipids are crucial to the ecology and physiology of marine algae and are used in many different industries, including the manufacturing of biofuel, food, medicine, and cosmetics (Ahmed *et al.,* 2024) [4].

Freshwater algae are less mineral-rich than marine algae, claim Abu Hafsa *et al.* (2021) [2]. This led to the conclusion that macroalgae may include trace elements such as Ca, Zn, I, Co, Mg, Mn, Cd, Se, Fe, and K, all of which are necessary for preserving animal health. Marine algae include phenolic compounds such as flavonoids, phenolic acids, phlorotannins, tannins, and catechins. The kind and yield of phenolic compounds that are extracted are greatly influenced by the species of seaweed. Numerous biological actions, such as antioxidant, antitumor, anticancer, antibacterial, antiviral, antiobesity, antiproliferative, anti-inflammatory, and antidiabetic properties, have been associated with polyphenols that are isolated from seaweeds (Gómez-Guzmán *et al*., 2018) [24].

Marine algae are rich in natural bioactive compounds that have been shown to have antibacterial, antiviral, antifungal, hypolipidemic, antioxidant, antidiabetic, and anti-inflammatory effects. They produce secondary metabolites with biological activity that may be employed as therapeutic agents (Veluchamy and Palaniswamy, 2020) [55]. Because it contains a range of bioactive chemicals with biological activity in the food, pharmaceutical and cosmetic industries, such as phlorotannins, carotenoids, and fucoidans, *Ulva prolifera* is an important member of the green algae family (Abd El Hafez *et al*., 2020) [1]. Marine algal crude extracts of the green algae *Ulva lactuca* and the red algae *Corallina elongata* showed therapeutic potential against diabetes and its effects (Hussein *et al*., 2023) [28].

Zubair *et al.* (2019) found that a methanol extract of the seaweed *Turbinaria ornata* inhibited the growth of *Candida albicans*. Depending on the concentration, the inhibition zones' diameters changed: 25% (12.6 mm), 50% (14.81 mm), 75% (19.66 mm), and 100% (29.3 mm).

Specimens of the brown seaweed *Hormophysa cuneiformis* were collected from the rocky littoral zone in the Hurghada region of Egypt's Red Sea coast. Eight pathogenic fungi were investigated for *in vitro* antifungal activity using specific crude polar (methanol and ethyl acetate) and non-polar (chloroform and petroleum ether) extracts of the often-overlooked brown marine alga *Hormophysa cuneiformis*. The findings demonstrated that the chloroform extract exhibited antifungal efficacy against every fungal isolate that was investigated; the minimum inhibitory concentrations (MIC) varied between 0.78 and 6.25 µg/ml, which is quite comparable to the typical antifungal medication amphotericin B (0.63 µg/ml) (Rashad and El-Chaghaby, 2020) [44].

Materials and Methods

I) Isolation and identification of some pathogenic fungi

A survey was carried out on 100 of pathogenic fungal isolates that were cultured in Central Laboratory of Ain

Shams University Specialized Hospital during the period from July to November (2022), isolates were collected from the samples which came to the Microbiology Unit from the internal departments and the outpatient clinics. Pathogenic fungi were isolated from different infection-related environments. A survey carried out for the predisposing factors of the obtained fungal isolates from human fungal infections that were diagnosed as fungal cutaneous infection.

Each patient's personal belongings (scarfs, hats, socks, T-shirts, sunglasses, and gloves), bed linens, urine catheters, blood cultures, and tubes from internal organs were among the related environments from which fungi were isolated. Information was gathered to analyze the circumstantial conditions of each patient, including gender, age, the location of the infection, and medical history (first or recurrent infection).

Every sample that was gathered on a Petri dish was cultivated using sterile Sabouraud's dextrose agar (SDA) medium that had the following composition: 20 g of agar, 40 g of dextrose, and 10 g of peptone/L. Chloramphenicol (0.5 g/L) was given to inhibit bacterial growth in addition to cycloheximide (0.5 g/L), which inhibits the growth of most saprophytic fungi except dermatophytes. After being divided across Petri dishes with a diameter of 9 cm, the medium was left to harden. In order to obtain the purest growth, the collected infected specimens were plated, and the culture plates were cultured at 35°C for yeas-like fungus and at 25°C for filamentous fungi. Each sample was then split into three replicas.

The isolated mushrooms were identified by morphological and microscopical examination in accordance with the following references: Moubasher (1993) [36], Klich (2002) [31] and Samson *et al*. (2010) [47]. The isolated fungi were also photographed using a light microscope set to 400 X magnification.

Using the API 20 C Aux approach (API system, Montalieu, France), which is based on 19 carbohydrate assimilation tests plus a negative control, other yeast-like isolated fungi were also identified by measuring the turbidity of cupules. Following the manufacturer's instructions, the kit was utilized (Barnett *et al*., 1990) [11]; all isolated samples that were identified were kept at 4 °C for future use.

II) Collection and identification of some marine algal species

The algal species were collected from Hurghada city (27° 15′ 58.45″N, 33° 48′ 57.09″E), the Red Sea coast of Egypt. Algal species were identified according to Aleem (1993) [6] and Coppejans *et al.* (2009) [15]. Six algal species were used in this study; namely, brown alga *Sargassum giganteifolium*, green alga *Caulerpa racemosa*, red alga *Jania rubes*, red alga *Actinotrichia sp*., brown alga *Turbinaria turbinate* and brown alga *Dictyota dichotoma*. Successive extraction was carried out with different solvents (Ethanol, Methanol, Ethyl acetate, Diethyl ether, Petroleum ether and Acetone).

III) Preparation of marine algal extract

The extraction process was carried out according to Al-Fatimi *et al*., (2007) [5]. After being cleaned and allowed to air dry on absorbent paper at room temperature (between 25 °C and 30 °C) in the shade, the materials were ground into a fine powder using an electric mill. Ethanol, Methanol, Ethyl Acetate, Diethyl Ether, Petroleum Ether, and Acetone were used in successive extraction. The ground material was soaked in the appropriate solvent (1:15 v/v) in a conical flask, sealed with cotton wool, and then placed on a rotary shaker set at 150 rpm for 72 hours at room temperature between 25 °C and 30 °C. Separate extractions using various solvents were performed on each sample. Filter paper (Whatman No. 1) was used to filter the extracts. The resulting thick residues (crude extracts) were placed in an airtight bottle at -20 °C after being dissolved in dimethylsulfoxide (DMSO) to a final amount of 10 ml.

IV) Antifungal assay

The growth of isolated fungus from a variety of infections was used to test the antifungal activity of several algae extracts. Three replica plates were made for each algal extract, and three wells with a diameter of 5 mm were filled with 100 µl of the extract. After that, the plates were incubated for 10-14 days at 25 °C for filamentous fungi and 2-7 days at 35 °C for yeast-like fungi. Using the well diffusion method, 36 algal extracts were tested for antifungal efficacy against the isolated fungus (Bauer *et al*., 1966) [12].

1. After being prepared, sterilized, and inoculated with a fungal suspension, Sabouraud's dextrose agar medium (SDA) was transferred into sterile Petri dishes with a diameter of 9 cm and allowed to harden.
2. The spore suspensions of fungal isolates in present study were prepared by mixing a portion of fungal growth with 2 ml of sterile saline solution.
3. Three wells of 5 mm were formed in the plate of solidified Sabouraud's media using cork borer for each antifungal test separately.
4. Drop 100 µL of the examined algal extract in each well, (3 replica plates were prepared as mentioned previously for each algal extract), then the plates were incubated at 25 °C for 10-21 days for dermatophytes, 25 °C for 10-14 non-dermatophytes, and at 35 °C for 2-7 days for yeast- like fungi according to the growth rate of each tested fungus.
5. The antifungal activities of the tested algal extracts against the fungal strains were confirmed by forming inhibition zone around the wells which were measured and expressed in mm in diameter, stander deviations were estimated.

The antifungal activity of some commercial antifungals was examined against the growth of isolated fungi from various infections. Three wells of 5mm diameter were prepared and loaded with 100 µl of antifungal suspension (3 replica plates were prepared for each commercial antifungal). Then the plates were incubated at 25 °C for 10-21 days for filamentous fungi, and at 35 °C for 2-7 days for yeast- like fungi.

Two commercial antifungal agents were examined to determine their antifungal activity against the isolated cutaneous fungi, one of them was itraconazole capsule and the other was grisofulvin tablet, following well diffusion method as the same protocol of testing the natural agal extracts (Bauer *et al*., 1966) [12], where suspensions of antifungal agents were prepared for both of itraconazole and griseofulvin as follow:

- **For itraconazole:** by mixing the contents of one capsule (100 mg) with 10 ml of dist. Water to obtain a concentration of 10 mg/ml.

- **For griseofulvin:** by mixing one tablet (125 mg) with 12.5 ml of dist. Water to obtain a concentration of 10 mg/mL.

V) Examination of ultrastructure of fungal cells

This assay was conducted to investigate the impact of brown alga *Sargassum giganteifolium* ethanol extract on the ultra-structure of *Candida tropicalis*, which was found to exhibit the highest antifungal activity of the ethanol extract in the current study. The brown alga *Sargassum giganteifolium* ethanol extract, which was made using the previously determined MIC, was mixed with the selected fungal isolate after it had been grown on SDA liquid medium. After that, the combination was kept in a shaking incubator set to 60 rpm for the entire night at the right temperature. To collect the cell pellet in a sterile Eppendorf tube, the treated mixture was centrifuged again after being washed with sterile saline solution and centrifuged for 20 minutes at 3000 rpm (Richards and Cavill, 1976) [45].

The obtained cell pellets were fixed by adding 1 millilitre of 2.5% glutaraldehyde that had been buffered in 0.1 M phosphate buffer saline (PBS) with a pH of 7.4 in order to fix the cellular protein content and cease all cultural reactions. After that, the pellets were kept in the refrigerator for two hours at 4 °C. The fixed samples were washed with 1% osmic acid for 30 minutes to fix the lipid cell content. They were then rinsed three times with PBS for 10 minutes each, then they were dehydrated for 30 minutes in increasing ethanol concentrations (30, 50, 70, 90, and 100% alcohol). The dehydrated samples were then infiltrated with acetone for an hour to guarantee that all of the cell contents were fully fixed. A plastic mould was then made by embedding them in araldite 502 resin. To make sure the sample preparation was satisfactory, these were then cut into semi-thin sections using an ultra-cut microtome (LEICA ultracut UCT, Japan), stained with 1% toleudine blue, and inspected. Ultimately, uranyl acetate was used to stain ultra-thin sections, and lead citrate was used as a counterstain. The full-stained ultra-thin slices were examined and photographed at the appropriate magnification using a transmission electron microscope (JEOL-JEM-100SX, Japan). The high voltage was 80 KV, and the beam current was 60µA (Ardenne and Beischer, 1940) [8].

Results

I) Isolation and identification of some pathogenic fungal isolates

Pathogenic fungi were isolated from different infection-related environments. A survey for the predisposing factors of the obtained fungal isolates from human fungal infections was conducted during the period from July to November 2022, that were be diagnosed as fungal cutaneous infection.

From Table 1, the fungal infections were observed to be common among patients aged between 20- 70 years old (72 cases =72 % out of total fungal infections), followed by the patients whom ranged between newborns and 20 years old (28 =28 % out of total fungal isolates), more common among females (56 cases = 56 % out of total fungal infections) more than males which recorded only (44 cases = 44 % out of total fungal isolates), isolates from outpatient clinics were more common (66 cases = 66%) than those from the hospital internal departments (34 cases = 34% out of total fungal isolates), a high rate of fungal infections was recorded with the first infection recorded (84 cases = 84 %) while recurrent infections (16 cases = 16 % out of total fungal isolates) and single fungal infection had the higher rate of cases (76 cases= 76 %) more than those of fungal infections which combines with bacterial infections (24 cases= 24 % out of total fungal isolates).

From Table 2, the highest rate of fungal infection isolates were from Personal belongings of patients whose injury was diagnosed as fungal infection (34 isolates), isolates from urine catheters and urine cultures were represented by 26 isolates, then bed sheets were also represented an important source of isolates by a rate of 13 isolates, and 11 isolates from blood cultures were recorded, vaginal swabs represented a source for 10 isolates, four isolates from the bronchial wash tube were recorded, and only two isolates from wound cultures.

Candida albicans was isolated by the highest ratio (40 isolates) from all sources from different fungal infections, from urine cultures and urine catheters (14 isolates), followed by the isolates from blood cultures (7 isolates) and vaginal swabs (6 isolates), and isolated from bed sheets and from Personal belongings of patients whose injury was diagnosed as fungal infection (4 isolates for each source of isolates), three isolates from bronchial wash tubes, the lowest incidence rate of *Candida albians* was from wound cultures that showed only two isolates, Seventeen isolates of *Candida tropicalis* isolates were isolated from all sources, six of them from urine cultures and urine catheters, 4 isolates from blood cultures and 3 isolates from the Personal belongings of patients whose injury was diagnosed as fungal infections, only two isolates from each of vaginal swabs and bed sheet. *Microsporum canis* was represented in 15 isolates, mainly isolated (10 isolates) from Personal belongings compared with 5 isolates from bed sheets, which was illustrated in Table 2 and Photo 1.

Candida parapsilosis showed 11 isolates, the high ratio of incidence in urine cultures and urine catheters (6 isolates) followed by Personal belongings of patients whose injury was diagnosed as fungal infection that showed (3 isolates), then isolates from vaginal swabs (2 isolates) only. *Trichophyton rubrum* was isolated from 10 resources, from the personal belongings of patients whose injury was diagnosed as fungal infections (8 isolates), then from bed sheets (2 isolates). *Trichophyton mentagrophytes* was isolated only from the personal belongings of patients whose injury was diagnosed as fungal infections (6 isolates). *Aspergillus fumigatus* was isolated only from bronchial wash tube (1 isolate only), which showed in Table 2 and Photo 1.

II) Antifungal activity of marine algal extracts against the isolated pathogenic fungi Antifungal activities of crude extracts of six species of marine seaweeds represented by one Chlorophyta (*Caulerpa racemosa*), three Phaeophyta (*Sargassum giganteifolium*, *Turbinaria decurrens* and *Dictyota dichotoma*) and two Rhodophyta (*Jania rubens* and *Actinotrichia Sp.*) (Photo 2) were tested against seven pathogenic fungi (*Candida albicans*, *C. tropicalis*, *C. parapsilosis*, *Trichophyton rubrum*, *T. mentagrophytes*, *Microsporum canis* and *Aspergillus fumigatus*). According to the data, methanol was the most effective solvent and demonstrated the largest inhibition against the fungi under test (23.7%). Ethyl acetate (22.56%), ethanol (20.13%), petroleum ether (15.92%), diethyl ether (15%), and acetone (2.65%) were next in line.

Extracts of species belonging to Rhodophyta (*Jania rubens* and *Actinotrichia sp.*) were the most potent against the isolated fungi followed by Phaeophyta (*Sargassum giganteifolium*, *Turbinaria decurrens* and *Dictyota dichotoma*) and finally Chlorophyta (*Caulerpa racemosa*) as recorded in Table 3. The best solvent for extracting antifungal chemicals from the green alga *Caulerpa racemosa* was ethyl acetate, which was followed by ethanol, petroleum ether, methanol, and diethyl ether. The maximum activity, however, was found in methanol and ethyl acetate extract against *C. parapsilosis* (14±0.7 mm) and petroleum ether extract against *M. canis* (16±0.8 mm). Whereas, diethyl ether and petroleum ether extracts against *T. mentagrophytes* and ethanol extract against *T. rubrum* recorded (12±0.6 mm). However, acetone could not extract the active antimicrobial compounds from *C. racemosa* hence did not show any antifungal effect (Table 3).

In Phaeophyta, *Dictyota dichotoma* was the most effective species followed by *Sargassum giganteifolium* and then *Turbinaria decurrens* (Table 3). Ethanol extract of *Sargassum giganteifolium* recorded highest antifungal activity against the pathogenic fungi followed by ethyl acetate and then methanol, diethyl ether and petroleum ether. Ethanol extract yielded the highest inhibition zone against *C. tropicalis* (22±1.1 mm) followed by ethyl acetate and diethyl ether extracts that showed 14±0.7 mm inhibition zones as antifungal effect against both of *T. rubrum* and *C. albicans*, then methanol extracts (12±0.6 mm) against *C. tropicalis* and *M. canis*. Also, inhibition zone of 12±0.6 mm was detected by ethyl acetate extracts against *A. fumigatus* and acetone extracts against *C. parapsilosis* and *T. rubrum.* Highest antifungal activity among the extracts of brown alga *Turbinaria decurrens* extracts was recorded for methanol, followed by ethanol and diethyl ether.

The highest inhibition zones were recorded for extraction of brown alga *Turbinaria decurrens* by ethanol solvent (16±0.8 mm) against *C. tropicalis*, followed by methanol extract (14±0.7) against *C. parapsilosis*, then, methanol extracts which showed activity of (12±0.6) against *C. tropicalis*, *M. canis*, and diethyl ether (12±0.6) against *C. albicans*, as shown in Table 3. However, ethyl acetate, petroleum ether and acetone could not extract the active antimicrobial compounds from *Turbinaria decurrens* hence did not show any antifungal effect.

The highest activity was recorded among the different extracts of brown alga *Dictyota dichotoma* was the petroleum ether, followed by ethyl acetate, methanol, diethyl ether and finally ethanol, no antifungal activity for acetone extract of *Dictyota dichotoma*. Highest activity expressed by inhibition zones are also the petroleum ether (16±0.8 mm) against *A. fumigatus*, followed by methanol extract against *A. fumigatus*, ethyl acetate extract against *M. canis* and *T. mentagrophytes*, diethyl ether extract against *C. albicans*, petroleum ether extract against *C. albicans* and *T. mentagrophytes*, which recorded inhibition of zones (14±0.7 mm) for all of them, then ethanol and methanol which showed activity of (12±0.6 mm) against *C. parapsilosis* and *M. canis* respectively there isn't any activity for acetone extract against any fungal isolates. In Rhodophyta, the results showed that *Actinotrichia sp.* is the most potent species compared to *Jania rubens* and all tested marine algal species (Table 3). The efficiency of tested solvents for extracting the active antimicrobial compounds from *Actinotrichia sp.* could be arranged in the following order: Methanol > ethanol > ethyl acetate > diethyl ether > petroleum ether. Acetone extract did not show any antifungal effect. However, the highest antifungal activities were detected in ethyl acetate extract of *Actinotrichia sp.* (20±1.0 and 18±0.9 mm) against *C. parapsilosis*, *C. tropicalis*, respectively. Antifungal activity represented by 14±0.7 mm inhibition zone was detected in petroleum ether extract against *C. albicans*, diethyl ether against *M. canis*, and methanol extract against *C. parapsilosis* and *T. rubrum* (Table 4).

In *Jania rubens*, the highest antifungal activity was observed in ethyl acetate extract (10±0.5, 16±0.8 mm), followed by petroleum ether extract (10±0.5, 14±0.7 mm), diethyl ether, ethanol and finally methanol. The highest activity was detected in ethyl acetate (16±0.8 and 14±0.7 mm) against *C. albicans and C. tropicalis*, respectively. Also, 14±0.7 mm inhibition zone was detected in petroleum ether against *C. tropicalis* and *M. canis*, ethanol extract against *C. parapsilosis.* Thereafter, ethyl acetate and petroleum ether and diethyl ether recorded (12±0.7 mm) against *M. canis*, *C. parapsilosis*, *T. mentagrophtes* and *A. fumigatus*, respectively.

III) Examination of ultrastructure of fungal growth under the effect of the most potent algal extract by transmission electron microscope (TEM)

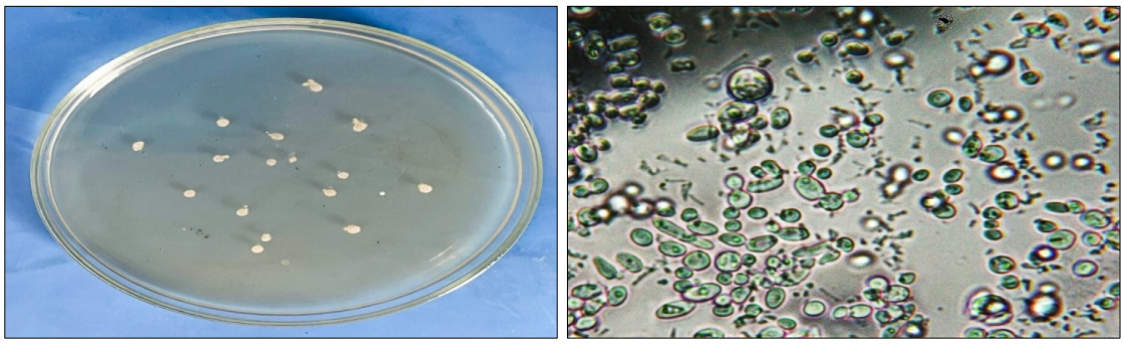
As be observed in Photo 3, Transmission electron microscope (TEM) showed ultra-structural effects of ethanolic extract of brown alga *Sargassum giganteifolium* against *Candida tropicalis*, the rupture of the fungal cell wall which led to deformation of outer cell shape and loss of internal cellular components and shrinking of cytoplasm were observed.

Table 1: Survey of different residential conditions and predisposing factors affecting the incidence of human fungal infections during the period from July to November (2022).

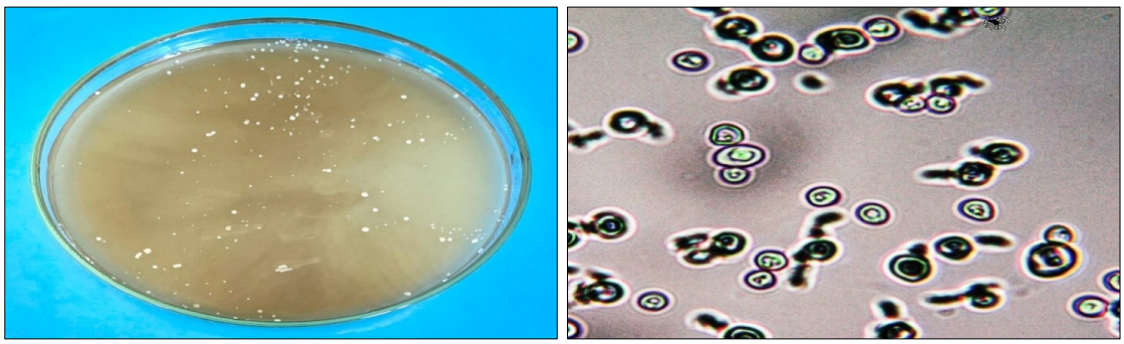
Predisposing factors	Most frequent category	No. of cases	Least frequent category	No. of cases
Age	More than 20 years old	72	Newborns to 20 years old	28
Gender	Females	56	Males	44
Location of isolates	Out- patient clinics	66	Hospital Internal departments	34
History of infection	First time infection	84	Recurrent infection	16
Condition of infection	Single infection	76	Combined with bacterial infection	24

Table 2: Fungal species that isolated from infection-related environments during the period from July to December (2022).

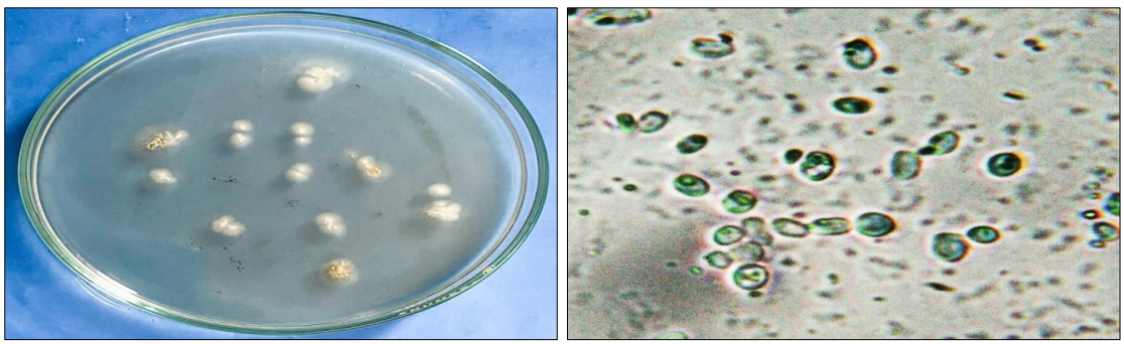
Fungal species	Source of isolates	No. of isolates	No. of total isolates
Candida albicans (Berkhout, 1923)	14	Urine (catheters and cultures)	40
	7	Blood cultures	
	6	Vaginal swabs	
	4	Personal belonging	
	4	Bed sheets	
	3	Bronchial wash tubes	
	2	Wound cultures	
Candida tropicalis (Castellani, 1910)	6	Urine (catheters and cultures)	17
	4	Blood cultures	
	3	Personal belongings	
	2	Vaginal swabs	
	2	Bed sheets	
Microsporum canis (Bodin, 1902)	10	Personal belongings	15
	5	Bed sheets	
Candida parapsilosis (Poll, 1926)	6	Urine (catheters and cultures)	11
	3	Personal belonging	
	2	Vaginal swabs	
Tichophyton rrubrum (Malmsten, 1845)	8	Personal belongings	10
	2	Bed sheets	
Tichophyton mentagrophytes (Blanchard, 1853)	6	Personal belongings	6
Aspergillus fumigatus (Virchow, 1856)	1	Bronchial wash tube	1



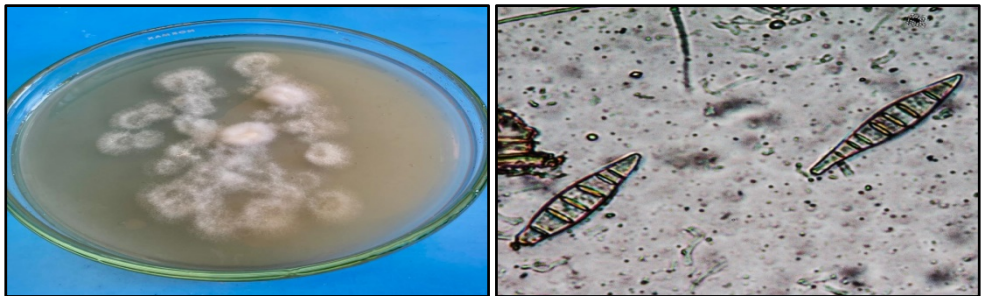
Photos 1- a, b: Culture and microscopic photos for *Candida albicans*



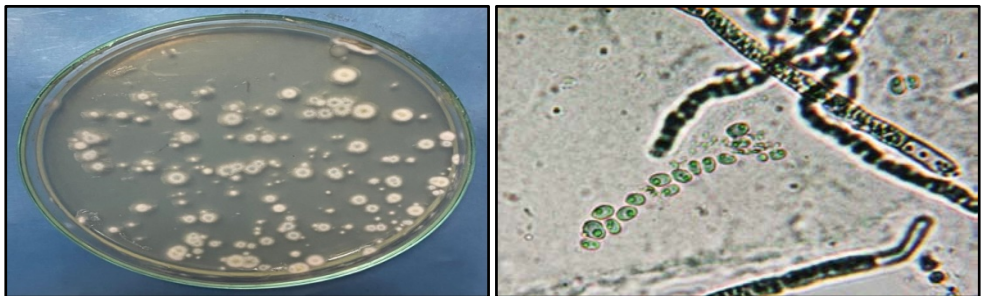
Photos 1- c, d: Culture and microscopic photos for *Candida parapsilosis*



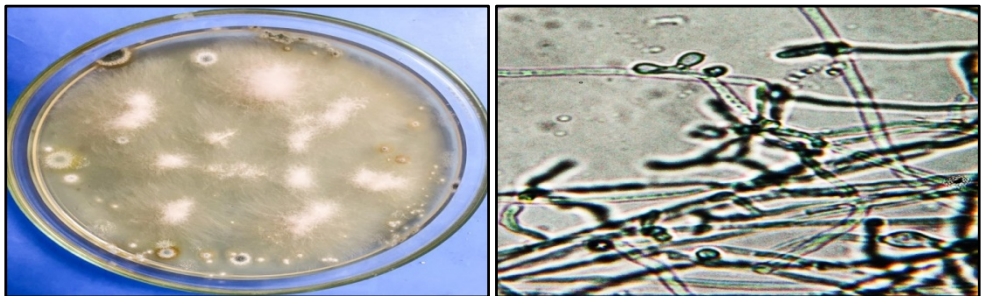
Photos 1- e, f: Culture and microscopic photos for *Candida tropicalis*



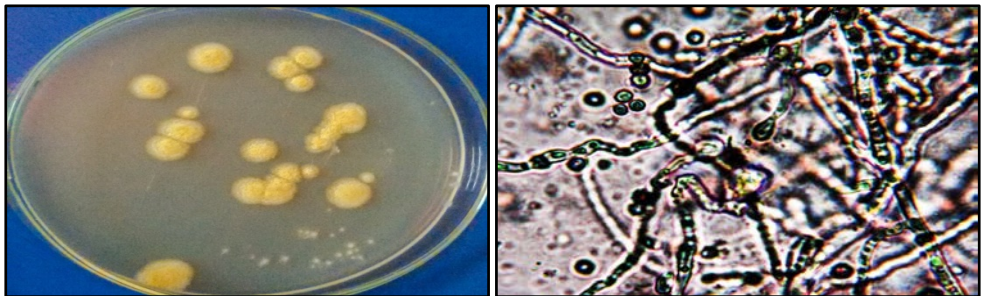
Photos 1- g, h: Culture and microscopic photos for *Microsporum canis*



Photos 1- i, j: Culture and microscopic photos for *Trichophyton rubrum*



Photos 1- k, l: Culture and microscopic photos for *Trichophyton mentagrophytes*



Photos 1- m, n: Culture and microscopic photos for *Aspergillus fumigatus*

Photo 1: Representative photos for some pathogenic fungal isolates.

	
Photo 2-a. Brown alga *Dictyota dichotoma* (Hudson) J.V.Lamouroux, 1809	**Photo 2-b. Brown alga *Sargassum giganteifolium* (Yamada) Okamura, K., 1925**

Photo 2-c. Brown alga *Turbinaria decurrens* (Bory) Bory de Saint-Vincent, 1828

Photo 2-d. Red alga *Jania rubens* (Linnaeus) J.V.Lamouroux, 1816

Photo 2-e. Red alga *Actinotrichia fragilis* (Forsskål) Børgesen, 1932

Photo f. Green alga *Caulerpa racemose* (Forsskål) J. Agardh, 1873

Photo 2: Representative photos for the collected marine algal species.

Table 3: Preliminary survey for antifungal activity of some marine algal extracts against the isolated pathogenic fungi in the present study, compared with commercial antifungal agents:

Commercial antifungal agents						
	Itraconazole			**Griseofulvin**		
C. albicans	18±0.9			22±1.1		
C. tropicalis	14±0.6			12±0.5		
C. parapsilosis	14±0.7			10±0.5		
M. canis	12±0.6			14±0.7		
T. rubrum	16±0.8			14±0.7		
T. mentagrophytes	18±0.9			14±0.7		
A. fumigatus	12±0.6			16±0.8		
Extracts of green alga (Chlorophyta)						
Caulerpa racemosa						
	Ethanol	**Methanol**	**Ethyl acetate**	**Diethyl ether**	**Petroleum ether**	**Acetone**
C. albicans	8±0.4	0.0	8±0.4	0.0	0.0	0.0
C. tropicalis	0.0	0.0	0.0	0.0	0.0	0.0
C. parapsilosis	0.0	14±0.7	14±0.7	0.0	0.0	0.0
M. canis	0.0	0.0	10±0.5	0.0	16±0.8	0.0
T. rubrum	12±0.6	10±0.5	0.0	0.0	0.0	0.0
T. mentagrophytes	0.0	0.0	0.0	12±0.6	12±0.6	0.0
A. fumigatus	10±0.5	0.0	0.0	0.0	0.0	0.0
Extracts of brown algae (Phaeophyta)						
Sargassum giganteifolium						
C. albicans	10±0.5	0.0	0.0	14±0.7	0.0	0.0
C. tropicalis	22±1.1	12±0.6	0.0	0.0	0.0	0.0
C. parapsilosis	0.0	0.0	0.0	0.0	0.0	12±0.6
M. canis	0.0	12±0.6	0.0	10±0.5	0.0	0.0
T. rubrum	0.0	0.0	14±0.7	0.0	0.0	12±0.6
T. mentagrophytes	10±0.5	0.0	0.0	0.0	0.0	0.0
A. fumigatus	0.0	0.0	12±0.6	0.0	0.0	0.0

Turbinaria decurrens						
C. albicans	0.0	10±0.5	0.0	12±0.6	0.0	0.0
C. tropicalis	16±0.8	12±0.6	0.0	0.0	0.0	0.0
C. parapsilosis	0.0	14±0.7	0.0	0.0	0.0	0.0
M. canis	10±0.5	12±0.6	0.0	10±0.5	0.0	0.0
T. rubrum	0.0	0.0	0.0	0.0	0.0	0.0
T. mentagrophytes	0.0	0.0	0.0	0.0	0.0	0.0
A. fumigatus	0.0	0.0	0.0	0.0	0.0	0.0
Dictyota dichotoma						
C. albicans	0.0	0.0	0.0	14±0.7	14±0.7	0.0
C. tropicalis	0.0	0.0	0.0	0.0	0.0	0.0
C. parapsilosis	12±0.6	0.0	0.0	0.0	0.0	0.0
M. canis	0.0	12±0.6	14±0.7	0.0	0.0	0.0
T. rubrum	0.0	0.0	0.0	0.0	0.0	0.0
T. mentagrophytes	0.0	0.0	14±0.7	10±0.5	14±0.7	0.0
A. fumigatus	10±0.5	14±0.7	0.0	0.0	16±0.8	0.0
Extracts of red algae (Rhodophyta)						
Jania rubens						
	Ethanol	**Methanol**	**Ethyl acetate**	**Diethyl ether**	**Petroleum ether**	**Acetone**
C. albicans	0.0	10±0.5	16±0.8	0.0	0.0	0.0
C. tropicalis	0.0	0.0	14±0.7	0.0	14±0.7	0.0
C. parapsilosis	14±0.7	0.0	10±0.5	0.0	12±0.6	0.0
M. canis	0.0	0.0	12±0.6	0.0	14±0.7	0.0
T. rubrum	0.0	0.0	0.0	0.0	0.0	0.0
T. mentagrophytes	8±0.4	10±0.5	14±0.7	12±0.6	10±0.5	0.0
A. fumigatus	0.0	0.0	14±0.7	12±0.6	0.0	0.0
Actinotrichia Sp.						
C. albicans	10±0.5	10±0.5	0.0	0.0	16±0.8	0.0
C. tropicalis	10±0.5	12±0.6	18±0.9	12±0.6	0.0	0.0
C. parapsilosis	10±0.5	14±07	20±1.0	0.0	0.0	0.0
M. canis	0.0	12±0.6	0.0	14±0.7	0.0	0.0
T. rubrum	10±0.5	14±0.7	0.0	10±0.5	0.0	0.0
T. mentagrophytes	0.0	0.0	0.0	0.0	0.0	0.0
A. fumigatus	0.0	10±0.5	0.0	0.0	10±0.5	0.0

Each value = mean of 3 replica ± Standard deviation Inhibition zones were expressed in mm.

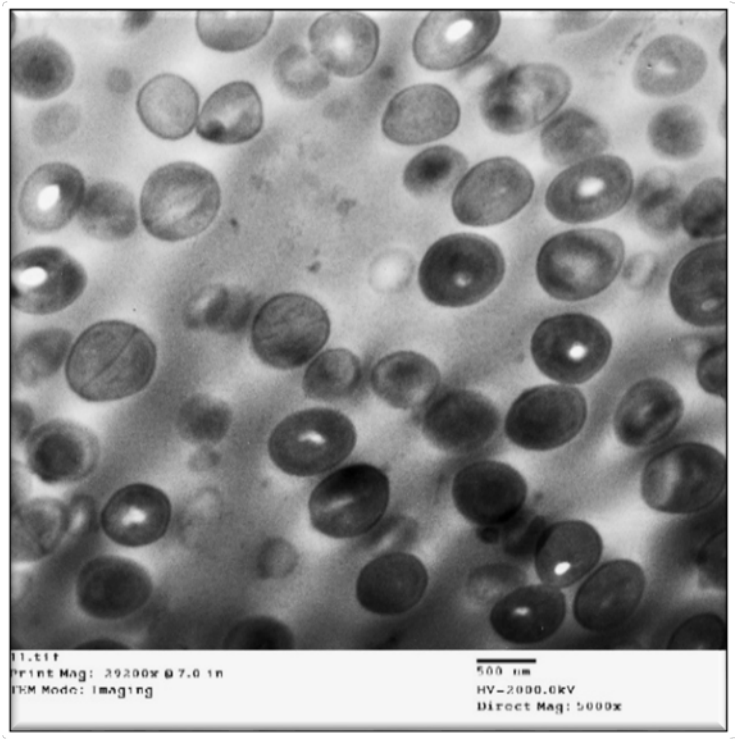
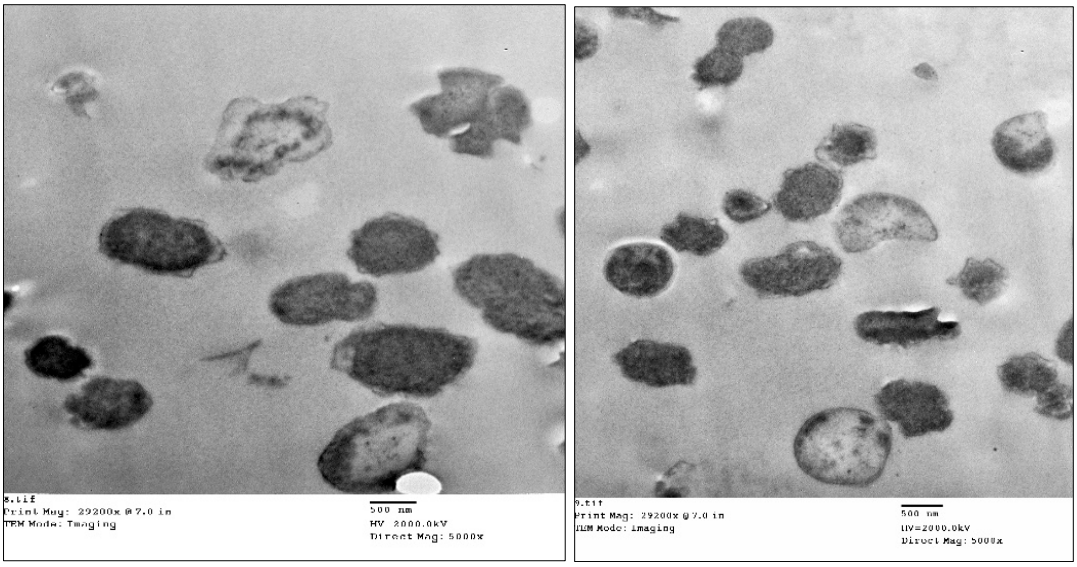
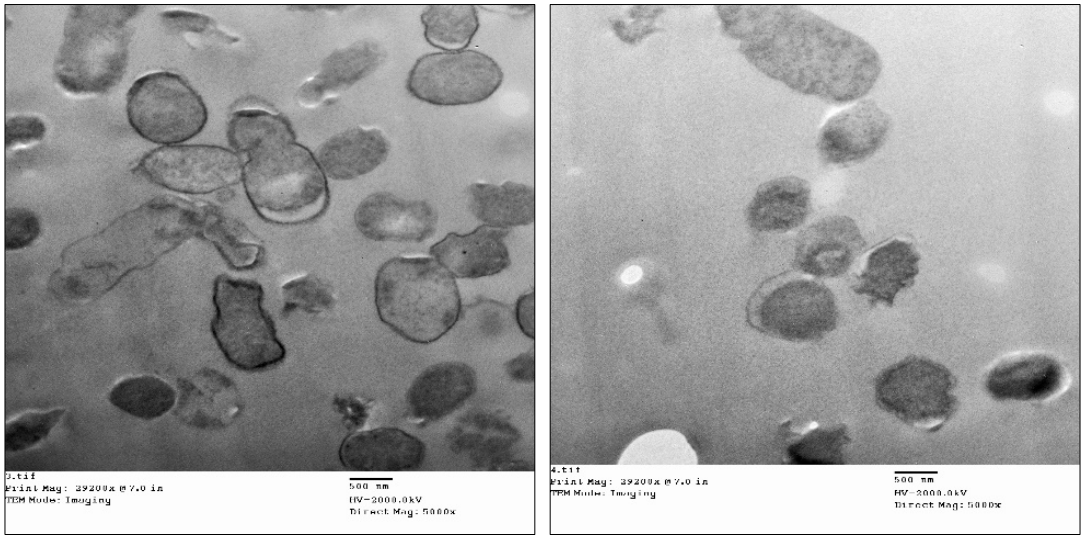


Photo 3-a: Usual cell wall and other intact cellular components of control (non- treated) *Candida tropicalis* cells



Photos 3-b, c: Rupture of cell wall and deformation of outer cell shape of the treated *Candida tropicalis* cells



Photos 3-d, e: Loss of internal cellular components and shrinking of cytoplasm in the treated *Candida tropicalis* cells

Photo 3: Transmission electron micrographs of *Candida tropicalis* cells treated with ethanolic extract of brown alga *Sargassum giganteifolium.*

Discussion

Patients between the ages of 20 and 70 years old had the highest prevalence of fungal infections (72%), followed by patients between the ages of 20 and neonates (28%). Females had a higher prevalence of fungal infections (56%), compared to males (44%). Our results are in line with those of Fanosh *et al.* (2024) [22], who discovered that those aged 17 to 32 were the age group most affected by fungus (60%), followed by people over 35. With 93 out of 155 cases, females were the most affected.

According to the findings, 24% of fungal isolates were also bacterial infections, while 76% of fungal isolates were a single fungal infection. Zhao *et al.* (2021) [61] found that 40.3% of patients had both bacterial and fungal co-infection, while 59.7% of patients had a single fungal infection, which is consistent with our findings.

According to this study, 40% of all isolates from infection-related environments were *Candida albicans*, while 28% of all isolates were a combination of *Candida tropicalis* and *Candida parapsilosis*. This is consistent with Pal *et al.* (2015), who found that *Candida albicans* is the primary cause of most infections.

Microsporum canis, Trichophyton rubrum, T. mentagrophyte and *Candida sp.* were the most common isolates from the personal belongings and bed sheets of the patients of cutaneous fungal diseases, this was in line with Verma *et al.*'s (2024) [56] findings that *Candida albicans*, the most common human skin infection, was found to be associated with dermatophytes, *Candida* spp., *T. rubrum*, or *Malassezia* spp. between the causative agents of fungal infection isolated from patients' personal belongings and bed linens. *Candida albicans* accounted for the same percentage (23%) of the fungal isolates from urine and urinary catheters, according to this investigation. Accordingly, Mughal *et al.* (2024) [37] discovered that, out of 320 patients with UTIs, *Candida albicans* accounted for the greatest number of isolates (60% of all cases), while *Candida tropicalis* accounted for 10%.

Candida albicans was the most common isolated species in cases of candidemia (blood stream candidiasis), accounting for 63.6% of all blood culture isolates. With 36.4% of all isolates, *Candida tropicalis* was the next most prevalent species. Although *Candida albicans* is the most prevalent fungus species that causes candidemia, Kung *et al.* (2018)

[33] reported that infections from non-albicans species, such as *C. parapsilosis* and *C. glabrata*, are increasing, especially in intensive care units. Their findings are consistent with our findings, as *C. tropicalis, C. krusei, C. guilliermondii* and *C. lusitaniae* follow these illnesses.

Results showed that among vaginal swabs *Candida albicans* was the most causative agents (60%) then *Candida tropicalis* and *Candida parapsilosis* which represented by 20% for each. In correspondance with our findings, Jannati *et al*. (2024) [29] arranged the prevalence of fungal species in vagina as follows: *C. albicans* (44.8%), *C. parapsilosis* (5.8%) and *C. tropicalis* (4.2%).

Compared to *Aspergillus fumigatus*, which accounted for 25% of all isolates in this investigation, *Candida albicans* accounted for 75% of the isolates from bronchial wash tubes. Additionally, Shajiei *et al*. (2022) [48] found that *Aspergillus* and *Candida* were the most common causal agents found in ICU patients on mechanical ventilation, whereas *Aspergillus* species were less commonly found than *Candida* species. The findings of this study demonstrated that *Candida albicans* accounted for 100% of the isolates from wound cultures, which was consistent with Ge and Wang's (2022) [23] findings that the primary fungi responsible for chronic wound infection are *Trichophyton rubrum* filamentous fungi and *Candida albicans* yeast.

The results collected demonstrated that the most effective solvent for extracting antifungal ingredients was ethanol. Several marine algae's ethanol extracts demonstrated antifungal activity against the fungal species under investigation. *Sargassum giganteifolium*, a brown algae, had the largest inhibition zone (22 mm) against *Candida tropicalis* when compared to the inhibition zones for itraconazole and griseofulvin, which were 14±0.7 and 12±0.6 mm, respectively. Musbah *et al.* (2019) [38] stated that *Sargassum denticulatum* ethanol extract had a significant effect against *Candida tropicalis* and recorded an inhibition zone of 20 mm, which is consistent with our findings. Accordingly, ethanol and acetone considerably enhanced the antibacterial activity of red and green seaweed extracts (Badr *et al*., 2025) [10]. But according to Al-Saif *et al*. (2014) [7], the best method for creating an algal extract with strong antibacterial properties was chloroform, which was followed by ethanol, petroleum ether, and water. These variations may result from variations in the bioactive metabolites' solubility in the relevant solvents (Osman *et al*., 2010) [42].

Ethyl acetate extracts of various algal specie in marine water had an effect on the growth of examined fungal isolates, ethyl acetate extract of red alga *Actinotrichia sp.* showed antifungal effect against *C. tropicalis* and *C. Parapsilosis* with inhibition zones of diameters of (18, 20 mm) respectively, comparing with inhibition zones of itraconazole and griseofulvin whose diameters were (14±0.7, 12±0.6 and 14±0.7 mm, 10±0.5 mm) for *C. tropicalis* and *C. Parapsilosis* respectively. As the petroleum ether extract of the green alga *Caulerpa racemosa* demonstrated antifungal activity against *Microsporum canis* with an inhibition zone of 16 mm, the present results were consistent with those of Hainil *et al.* (2023) [26], whonoted that the ethyl acetate extract of *Caulerpa racemosa* displayed an inhibition zone with a diameter of 13.5 mm against *Trichophyton mentagrophyte*.

According to reports, ethyl acetate extracts of a variety of marine algae show antifungal properties; *U. lactuca* extracts inhibited *F. solani* and *C. albicans* (El-Nemr *et al*., 2021) [20]. The present results demonstrated that petroleum ether extract of sea algae has moderate antifungal efficacy against *Microsporum*, in comparison to itraconazole and griseofulvin, which had inhibition zones with diameters of 12 and 14 mm, respectively, petroleum ether extract of marine algae had modest antifungal activity against *Microsporum canis*. These results were supported by Sheikh *et al.* (2018) [49], who discovered that petroleum ether was a moderately active solvent against five pathogenic fungus (*Aspergillus flavus, A. fumigatus, A. niger, Candida tropicalis* and *Candida albicans*).

According to the data, the most effective species against the isolated fungi were those of the Rhodophyta (*Jania rubens* and *Actinotrichia* sp.), Phaeophyta (*Sargassum giganteifolium, Turbinaria triquetra* and *Dictyota dichotoma*), and Chlorophyta (*Caulerpa racemosa*). Consistent with our results, Al-Saif *et al.* (2014) [7] found that the extracts of the red algae *Gracilaria dendroides* were more efficient against the tested bacterial strains than those of the brown algae *Dictyota ciliolata* and the green algae *Ulva reticulata*. Among the tested marine algal species, Salvador *et al.* (2007) [46] found that the red algae members had the strongest antibacterial activity. According to Srikong *et al*. (2015) [50], *Gracilaria fisheri* exhibited greater antibacterial activity than *Ulva intestinalis*.

The best solvent for removing antifungal compounds from the green algae *Caulerpa racemosa* was found to be ethyl acetate. According to Sheikh *et al*. (2018) [49], ethyl acetate was found to produce more antibacterial activity from *C. racemosa*, which is consistent with our findings.

In Phaeophyta, *Dictyota dichotoma* was the most effective species followed by *Sargassum giganteifolium* and then *Turbinaria turbinata*. Ethanol extract of *Sargassum giganteifolium* recorded highest antifungal activity against the pathogenic fungi followed by ethyl acetate and then methanol, diethyl ether and petroleum ether. Ethanol extract yielded the highest inhibition zone against *C. tropicalis* (22±1.1 mm). *C. tropicalis* was the most sensitive to extracts of *Sargassum giganteifolium*, followed by *T. rubrum* and *C. albicans*, then *M. canis*. The best yield is obtained from the methanolic extract of *Osmundea pinnatifida* and *Ellisolandia elongata*, followed by the ethyl acetate extract of *Jania rubens*, according to El Mouns *et al*. (2024) [19]. *Chaetomium elatum* and *Chaetomium globosum* were the strains most susceptible to the majority of the organic seaweed extract, in contrast to*Aspergillus steynii*, which exhibited 100% suppression. When compared to other extracts, the ethyl acetate extract of *Osmundea pinnatifida* showed the greatest antifungal activity against *Chaetomium globosum*, with a MIC of 1.95 µg/mL. With a MIC of 7.8 µg/mL, *Ellisolandia elongata*'s methanolic extract exhibited the second-strongest antifungal activity.

The highest inhibition zones were recorded for extraction of brown alga *Turbinaria turbinata* by ethanol solvent (16±0.8 mm) against *C. tropicalis*. *C. parapsilosis* was the most sensitive followed by *C. tropicalis, M. canis* and *C. albicans.* The petroleum ether extracts of *Dictyota dichotoma* produced the highest activity followed by ethyl acetate, methanol, diethyl ether and finally ethanol, no antifungal activity for acetone extract. *A. fumigatus* was the most sensitive, followed by *M. canis, T. mentagrophytes, C. albicans, T. mentagrophytes*, and finally *C. parapsilosis*. According to Lemesheva *et al.* (2023) [34], marine seaweeds

produce a wide range of bioactive metabolites, but brown algae phlorotannins are currently of particular interest because of their potent cytotoxic and antibacterial properties. When tested against most species, the phenoltannin extracts from *Desmarestia aculeata, Fucus vesiculosus* and *Ectocarpus siliculosus* showed the lowest minimum inhibitory concentrations (MIC) (4-25 µg/mL for bacteria and yeast). An examination of the *E. Coli* survival curves showed that a notable cell loss started three to four hours after exposure.

In Rhodophyta, the results showed that *Actinotrichia sp.* is the most potent species compared to *Jania rubens* and all tested marine algal species. The efficiency of tested solvents for extracting the active antimicrobial compounds from *Actinotrichia sp.* could be arranged in the following order: Methanol > ethanol > ethyl acetate > diethyl ether > petroleum ether. However, the highest antifungal activities were detected in ethyl acetate extract of *Actinotrichia sp.* (20±1.0 and 18±0.9 mm) against *C. parapsilosis, C. tropicalis*, respectively. In *Jania rubens*, the highest antifungal activity was observed in ethyl acetate extract followed by petroleum ether extract, diethyl ether, ethanol and finally methanol. *C. albicans and C. tropicalis*, were the most susptable *M. canis, C. parapsilosi, T. mentagrophtes* and *A. fumigatus*. It was elucidated by other studies, as Tariq (1991) [53] recorded that extracts of *Dilsea carnosa, Laurencia pinnatifida, Odonthalia dentata* and *Polysiphonia lanosa* reduced the rate of colony extension in *Microsporum canis* and *Trichophyton verrucosum*, with seasonal variations in the levels of inhibitory activity. In the same way, Azzam *et al*. (2023) [9] tested two green algae (*Ulva flexusoa* and *Enteromorpha intestinalis*) and one red algae (*Griffithsia teges*). The three seaweeds' methanolic extracts were evaluated *in vitro* for their biological activity against *Penicillium expansum* and *Fusarium oxysporum* mycelial growth. The antifungal activity of each of the extracts was evident. The resulting inhibition zone in mycelial growth of *Fusarium oxysporum* as affected by *Enteromorpha intestinalis* methanolic extract was 37 mm, whereas that for *Penicillium expansum* was 32.6 mm.

Ethanolic extract of the brown alga *Sargassum giganteifolium* affected the ultra-structure of *Candida tropicalis*. The effect was mainly on the fungal cell wall that appeared shrunken which caused rupture of cell membrane followed by cellular damage. According to El-Zawawy *et al*. (2020) [21], who reported the antifungal activity of *Cladostephus spongiosus* acetone extract against *C. krusei*, biofilm cells were observed to have a perforated outer membrane with a distorted shape, and a small number of yeast cells with a wrinkled surface were visible. Additionally consistent with our results, *Fusarium moniliforme* cultured on a medium containing *Sargassum muticum* methanol extract displayed vacuoles, large lipid bodies, cytoplasmic disintegration, and a thickening of the cell wall (Nofal *et al*., 2024) [41].

Conclusion

According to the current investigation, *Candida albicans* and *Candida tropicalis* were the most often isolated fungi linked to human fungal infections. The study's findings indicate that the tested marine seaweed crude extract had strong antifungal properties. The most active seaweeds were red ones, which were followed by brown and green seaweeds. Compared to the chlorophyte *Caulerpa racemosa*, the extracts of *Actinotrichia* exhibited the highest activity in Rhodophyta and *Dictyota* in Phaeophyta. *Sargassum giganteifolium*, on the other hand, severely damaged the ultrastructure and had the strongest antifungal action against Candida tropicalis. To identify the chemical identity causing the observed antimycotic effect and to clarify the active ingredients, more research is required.

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