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ORIGINAL RESEARCH

Anticandidal action of polyurethane foam: a new modifier with functionalized isothiouronium group

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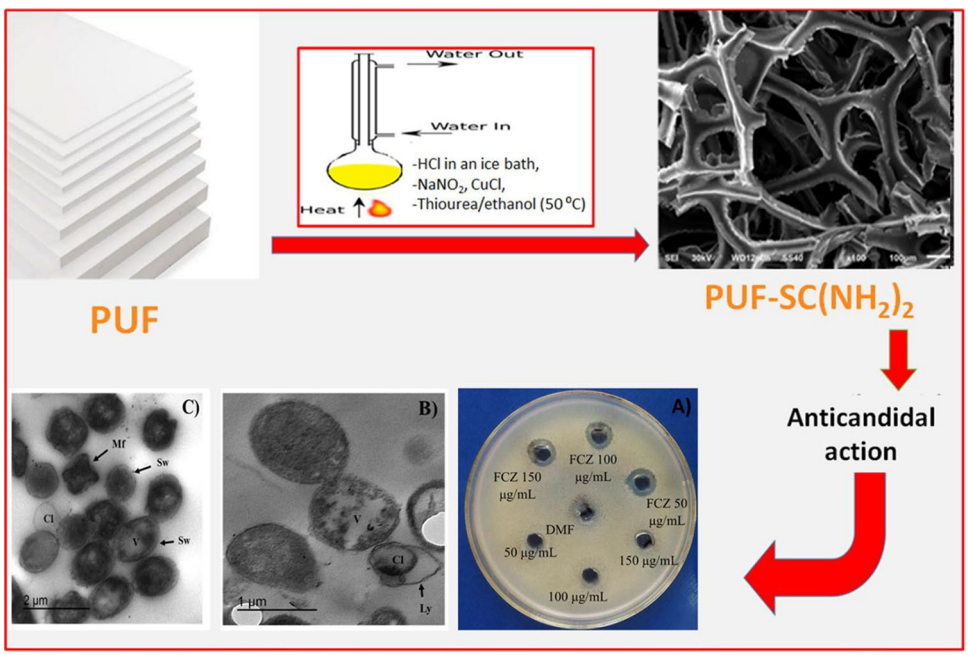
Abstract

A novel sorbent of isothiouronium polyurethane foam, PUF-SC$(NH_2)_2$, was synthesized from low-cost raw materials (a commercial polyurethane foam). The prepared PUF-SC$(NH_2)_2$ was characterized with different tools, the infrared spectra and Boehm test demonstrated the presence of several active groups in the material matrices of PUF-SC$(NH_2)_2$. The diffraction analysis and images of the scanning electron microscope showed that the surface structure was amorphous, and Cu(II) salt crystals were embedded on its surface. The polyurethane foam, as a modifier, was applied to enhance antimicrobial activity, and its anticandidal action was studied against Candida albicans ATCC 10,231. Agar well-diffusion test showed a significantly biocidal action of PUF-SC$(NH_2)_2$. The anticandidal action was dependent on PUF-SC$(NH_2)_2$ dose, while the microbial inhibition increased with increases in PUF-SC$(NH_2)_2$ dose and the microbial growth stopped at 26 µg/mL. The PUF-SC$(NH_2)_2$-treated yeast was studied by transmission electron microscope (TEM). TEM micrographs showed severe morphological changes in the yeast cells including the disruption of the cell membrane structure and the appearance of large vacuoles as well as separation between cell membranes and cell walls. The results indicated that this green synergy of PUF-SC$(NH_2)_2$ may have a promising potential in antifungal therapy as an effective biomaterial and other biomedical applications.

Graphical Abstract



Keywords Isothiouronium polyurethane foam · Anticandidal activity · *Candida albicans* · Minimal inhibition concentration

Extended author information available on the last page of the article

Abbreviations

UV/Vis	Ultraviolet-visible
FTIR	Fourier-transform infrared
pH_{pzc}	Point zero charge
XRD	X-ray diffraction
EDX	Energy-dispersive X-ray
SEM	Scanning electron microscopy
PUF-SC(NH_2)$_2$)	Isothiouronium polyurethane foam
TEM	Transmission electron microscope

Introduction

Polyurethane foam (PUF) represents a class of polymeric materials that have found extensive applications in industrial and medical fields [1, 2]. PUF can be incorporated into many products, such as fibers, furniture, liquid coatings, adhesives, paddings, elastomers, paints, and integral skins [3–6]. PUF is replacing older polymers for various reasons, such as their thermal conductivity, low density, light-weight and interesting mechanical, structural and convenient characteristics [7–9]. Other advantages of PUF include their high tensile strength and melting points which make them more durable [10, 11].

The PUF surface is susceptible to contamination by many microorganisms especially *Candida* species, where *C. albicans* form a biofilm on the surface of PUF [12, 13]. This has attained great attention as an infectious agent that causes deep mycosis in immune-compromised patients [14]. In addition, Candidiasis is a common disease for the pathogenic certain groups of *Candida albicans* [15]. Although many drugs have been verified to be effective against *Candida* spp., their continuously developed resistance remains very hard to overcome. Therefore, the studies demonstrated the design of antimicrobial polyurethane foams by reduction of its microbial action by incorporation of camphor [16], *N*-halamine [17], silver nanoparticles [18], and sub-nanometer [19] to enhance PUF antimicrobial activity. Already, several studies have been developed to improve antimicrobial PUF properties [20–22].

It is well-known that heterocyclic compounds containing nitrogen and sulfur have a biological activity, such as thiourea and its derivatives [23, 24]. A few compounds of thiourea have shown bactericidal and fungicidal activities [25, 26]. Isothiouronium, $[RSC(NH_2)_2]^+$, where R = alkyl, aryl, is a functional group and the acid salt of isothiourea. Isothiouronium has become the focus of interest in the recent past owing to its antimicrobial activities [27]. Al-Wahaibi et al. [28] have reported the in vitro antimicrobial activity of adamantane–isothiourea hybrid derivatives against certain standard strains of pathogenic bacteria and the yeast-like pathogenic fungus *C. albicans* [28]. Also, many isothiourea derivatives were synthesized and shown in vitro antifungal activity toward the clinically relevant strains of *Candida* species [29]. In this respect, the antimicrobial behaviors of acyl thiourea derivatives of chitosan against pathogenic fungi (*Alternaria solani*, *Fusarium oxysporum* f. sp. *vasinfectum*, *Colletotrichum gloeosporioides* (Penz.) *Saec*, and *Phyllisticta zingiberi*) were investigated by Zhong et al. [30]. On other hand, thiourea, isothiouronium compounds and their derivatives constitute an important class of compounds, which exhibit a wide range of antimicrobial activities and play an important role in many chemical and biological processes [31].

The present study highlights the synthesis of PUF foam functionalized with isothiouronium group (-SC(NH_2)$_2$) for improving the microbial resistance of PUF-SC(NH_2)$_2$ against *C. Albicans*.

Experimental

Materials and reagents

The culture media and chemicals were purchased from Sigma Aldrich Chemical Pvt., India). Fluconazole (Diflucan) was purchased from Pfizer Inc., New York, NY.

The pathogenic yeast, *C. albicans* ATCC10231, the strain was kindly obtained from the culture collection of Botany and Microbiology Department, Faculty of Science, Damietta University, Egypt.

Pretreatment of PUF: commercial open cell flexible PUF sheets (d = 12 kg/m^3) were supplied by Foamex Company for foam production, Damietta, Egypt. The PUF sheets were sliced to a cubic shape (0.125 cm^3). An amount of 10 g PUF was soaked in 200 mL of 0.1 mol/L HCl, and PUF cubes were washed with distilled water followed by ethanol and dried in a desiccator.

PUF-SC(NH_2)$_2$: a 50 mL $NaNO_2$ (0.5 mol/L) was added to the pretreated PUF form PUF-N_3^+ Cl^- salt which was followed by addition of 50 mL of 0.5 mol/L CuCl. The product was refluxed with 15 g thiourea in 200 mL ethanol at 50 °C. PUF-SC(NH_2)$_2$ was washed thoroughly with distilled water and with acetone and left to dry at room temperature.

Instruments

The X-ray diffraction (XRD) patterns of PUF-SC(NH_2)$_2$ were recorded by X-ray X'Pert powder diffractometer (Philips, D8-Brucker Model, Germany), equipped with a Ni filter and Cu K_α-radiation (λ = 1.5418 Å) at 40 kV and 30 mA. Infrared (IR) spectra were carried out using a KBr disc (KBr pellet) on a Jasco FTIR-410 spectrometer (Germany) in 4000–400 cm^{-1} region. All absorbance measurements were performed with a Jasco UV/Vis Spectrometer v-630 (Jasco, Japan). Scanning electron microscopy (SEM)

images at different magnifications were obtained using a Jeol instrument (JSM-6510LV, USA) with an energy dispersive X-ray spectroscopy EDX analytical system.

Anticandidal activity

Agar well-diffusion method: the anticandidal activity of PUF-SC(NH_2)$_2$ was investigated against *C. albicans* ATCC10231 using an agar well-diffusion method according to the guidelines of Clinical and Laboratory Standards Institute [32]. In brief, about 0.5 McFarland standard ($1–2\times10^8$ CFU/mL) of the pathogenic yeast was prepared and inoculated into autoclaved cool molten Sabouraud dextrose agar (SDA) medium. Next, the inoculated agar media were poured into sterile Petri dishes in triplicates. After solidification, seven small wells (5 mm) were punched using a sterile cork borer and 200 µL of 50, 100 and 150 µg/mL of PUF, PUF-SC(NH_2)$_2$ and fluconazole (antifungal) were prepared and added separately. The plates were incubated at 30 °C for 48 h. After the incubation time, inhibition zones were measured in millimeters (mm).

To acquire a minimal inhibition concentration (MIC) a Sabouraud dextrose broth (SDB) was prepared, distributed into 100 mL conical flasks, autoclaved and inoculated by 100 µL of *C. albicans* (0.5 McFarland standard ($1–2\times10^8$ CFU/mL)) in two sets of conical flasks containing different dosages (5–50 µg/mL) of PUF, PUF-SC(NH_2)$_2$ and fluconazole concentrations. The inoculated flasks were incubated at 100 rpm at 30 °C for 24 h. The growth was measured spectrophotometrically at 600 nm against negative control by measuring the optical density (OD) to determine the MIC value. Similarly, negative controls were exclusively made of PUF-SC(NH_2)$_2$. The growth inhibition percentage was calculated using the following formula:

$$\text{Growth inhibition (\%)} = \left[\frac{ODc - ODt}{ODc}\right] \times 100$$

where ODc and ODt resemble the OD of the control and tested sample, respectively [33].

For transmission electron microscopy study of treated *C. albicans* the ultrastructure of PUF-SC(NH_2)$_2$ was treated using *C. albicans* (MIC, 26 µg/mL) using TEM (Jeol JEM-2100, Japan, Electron Microscope Unit, Mansoura University, 200 kV).

Statistical analysis

The data were statistically analyzed using the software system SPSS version 18. All values in the experiments were expressed as mean ± standard deviation (SD).

Results and discussion

Characterization of PUF-SC(NH_2)$_2$

The FTIR spectrum of PUF-SC(NH_2)$_2$ is shown in Fig. 1. Absorption bands of isothiouronium –SC(NH_2)$_2$ groups are reported at 2044 cm^{-1} [34]. While the N–H bands are observed at 3281 cm^{-1} due to the extension of the conjugation system after addition of –SC(NH_2)$_2$ group to the PUF matrix. The conjugation system refers to the negative charge in the isothiocyanates group that contributes equally between sulfur and nitrogen, thus thiocyanates can act as a nucleophile at either sulfur or nitrogen. In addition, the other groups appear at 2927 and 2875 cm^{-1} (C–H), 2277 cm^{-1}

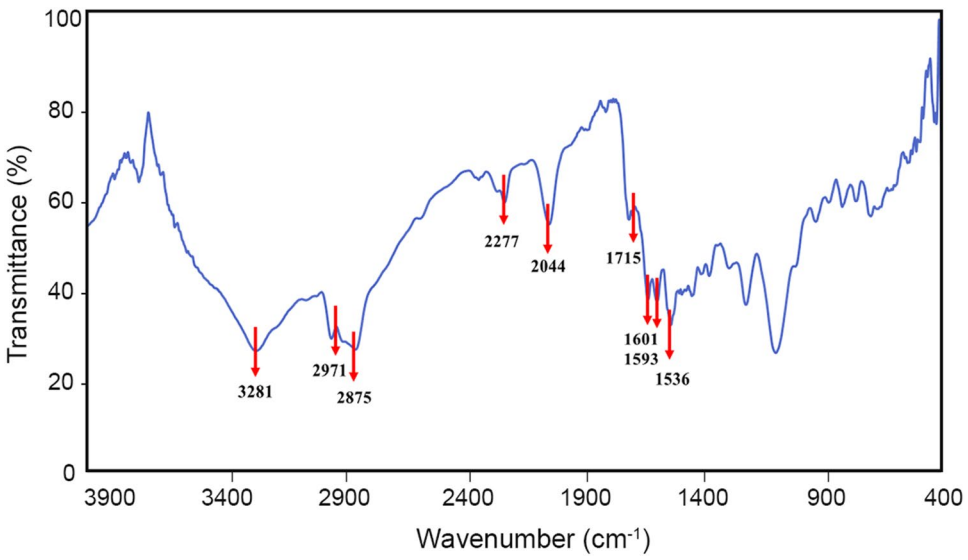


Fig. 1 FTIR spectrum of PUF-SC(NH_2)$_2$

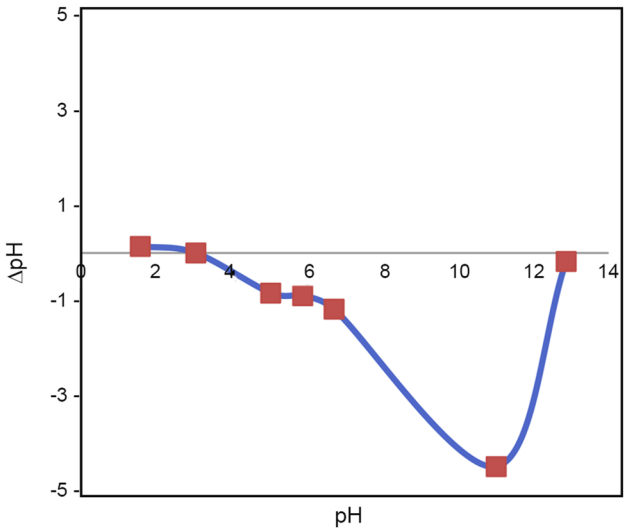


Fig. 2 pH_{pzc} of PUF-SC$(NH_2)_2$

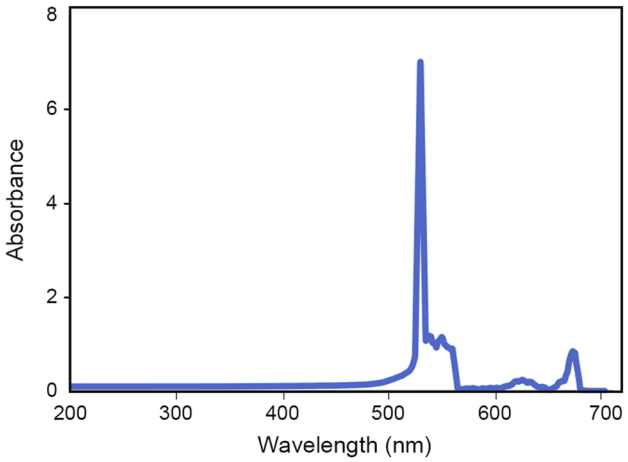


Fig. 3 Nujol mulls method of PUF-SC$(NH_2)_2$

(NCO), 1712 cm^{-1} (C = O), 1601 and 1593 cm^{-1} (C = C), and 1536 cm^{-1} (COC) [35]. The surface charge of PUF-SC$(NH_2)_2$ has been evaluated at different pH values (pH 1–14) using HCl and NaOH [34]. The pH_{pzc} value of PUF-SC$(NH_2)_2$ is found to be 3.05 (Fig. 2). The pH_{pzc} depends on all the functional groups that are present and the net charge on PUF-SC$(NH_2)_2$ surface is equal to zero. Based on pH_{PZC} value, the surface of PUF-SC$(NH_2)_2$ would be positively charged at pH values lower than 3.05 due to the protonation of surface functional groups in an acidic medium. However, over a pH value of 3.05, the surfaces of PUF-SC$(NH_2)_2$ would carry a net negative charge. This is consistent with the value of Boehm titration, showing the dominance of acidic groups on the surface of PUF-SC$(NH_2)_2$.

The electronic spectrum of PUF-SC$(NH_2)_2$ was obtained using the Nujol mulls method (Fig. 3). Two peaks have appeared at 529 and 674 nm due to the groups that increase hydrogen bonding and conjugated system [34, 35]. Electrons were delocalized by the transitions (π–π* and n–π*), where sulfur and nitrogen in isocyanate are electron donner (lone pair electrons).

The surface functional groups of PUF-SC$(NH_2)_2$ were determined using Boehm titration. The oxygenated functional groups (carboxylic groups, lactonic, and phenolic) which referred to the acidic sites of sorbent were calculated. The carboxylic groups, lactonic, and phenolic were 0.1, 0.1, and 0.4 mmol/g. The basic sites (1.0 mmol/g) of PUF-SC$(NH_2)_2$ were higher than the acidic sites (0.6 mmol/g) due to the basicity of isothiouronium.

The energy-dispersive X-ray spectrometry (EDX) was used to evaluate the chemical composition of PUF-SC$(NH_2)_2$ as illustrated in Fig. 4. The weight percentages of PUF-SH were carbon (77.4%), oxygen (21.5%), sulfur (0.9%) and copper (sourced from the catalyst, 0.2%). The presence of sulfur and copper elements in PUF-SC$(NH_2)_2$

Fig. 4 EDX of PUF-SC$(NH_2)_2$

increased the surface activity. Thus, PUF-SC$(NH_2)_2$ can be used as a powerful tool for anticandidal activity.

The XRD patterns of PUF-SC$(NH_2)_2$ showed a characteristic diffraction line of PUF as broad diffraction bands at 2θ, 22.5° (Fig. 5). It is clear that the PUF-SC$(NH_2)_2$ amorphous character is usually observed for the aromatic isocyanate-based PUF [36, 37].

The surface morphology of PUF-SC$(NH_2)_2$ was investigated using a scanning electron microscope (SEM) (Jeol SEM-6400JSM-6360LV, Japan) at magnifications from 100 × to 20,000x. Figure 6a, b represents SEM images of PUF-SC$(NH_2)_2$ matrix at magnifications of 100 × and 500x. The matrix contains many spaces, channels, and cells, which are irregular in size and shape. The crystals of Cu(II) salt that appeared on the surface of PUF-SC$(NH_2)_2$ in Fig. 6c, d confirmed the result of EDX analysis.

Anticandidal activity

Isothiouronium polyurethane foam, PUF-SC$(NH_2)_2$, showed a good anticandidal effect with highly significant different values ($P < 0.05$) between the yeast and the diameter of the inhibition zone, as shown in Table 1 and Fig. 7. The concentrations of 150 µg/mL of PUF-SC$(NH_2)_2$ and fluconazole showed a higher biocidal action against the yeast than lower concentrations that showed a dose-dependent manner of PUF-SC$(NH_2)_2$ anticandidal action.

The anticandidal ratio for 26 µg/mL of PUF-SC$(NH_2)_2$ (MIC value) against *C. albicans* was 91% as shown in Figs. 8

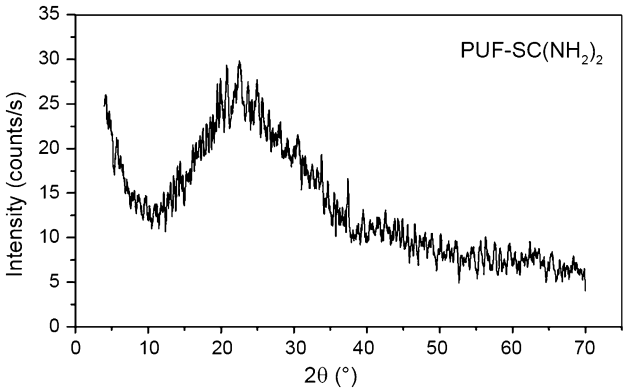


Fig. 5 XRD pattern of PUF-SC$(NH_2)_2$

Table 1 Anticandidal activities of the synthesized foams in comparison with fluconazole as standard drugs against *C. albicans*

Ligands	Concentration (µg/mL)	Zones of inhibition (mm ± SD)
PU	50	- ve
	100	- ve
	150	- ve
ITPUF	50	9.00 ± 0.06
	100	11.00 ± 0.03
	150	13.00 ± 0.03
Fluconazole	50	12.00 ± 0.03
	100	14.00 ± 0.03
	150	16.00 ± 0.03

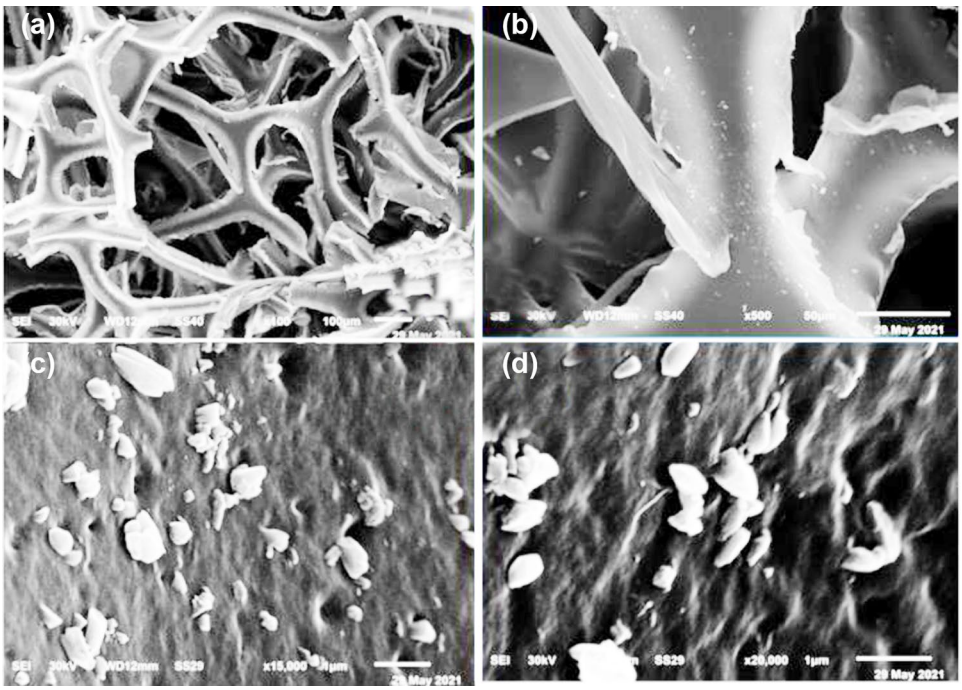


Fig. 6 SEM images of PUF-SC$(NH_2)_2$ at magnifications of 100 × and 500x: **a**, **b**, at magnifications of 15,000 × and 20,000x; **c**, **d**, respectively

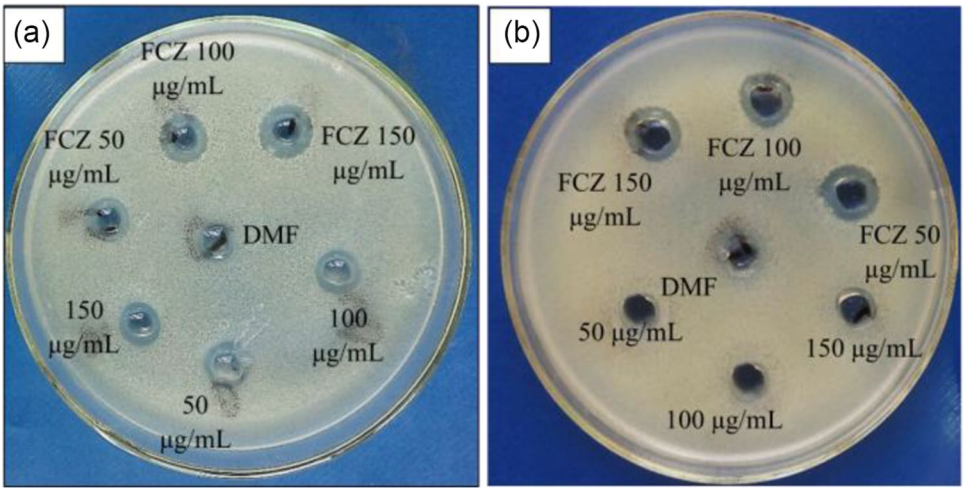


Fig. 7 Anticandidal activities of ITPUF: **a**, and PU: **b**, using agar well-diffusion method where DMF: dimethylformamide and FCZ: fluconazole

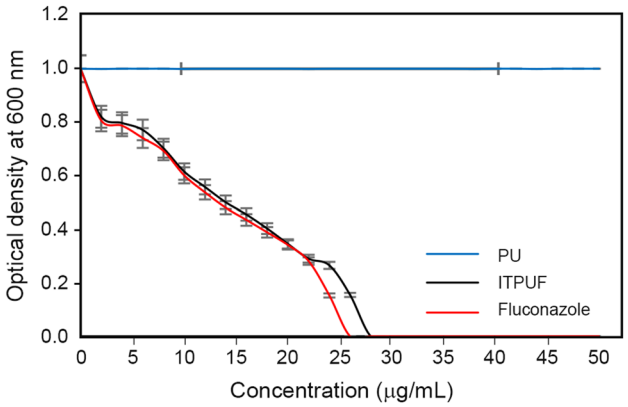


Fig. 8 Minimal inhibition concentration of ITPUF and PU in comparison to fluconazole

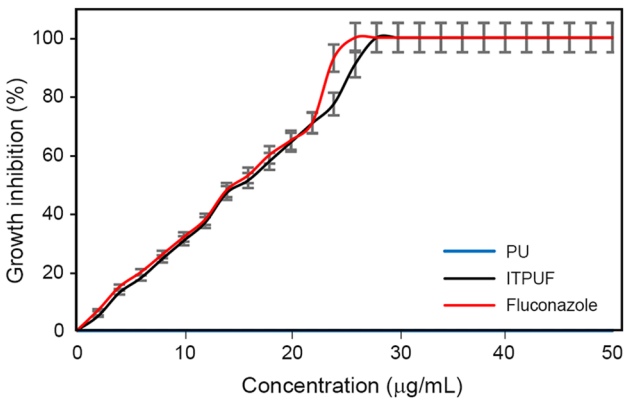


Fig. 9 Growth inhibition percentage of ITPUF and PU in comparison to fluconazole

and 9. Above 26 µg/mL dosage the anticandidal ratios were attained by 100%. Therefore, the anticandidal behavior of PUF-SC$(NH_2)_2$ showed a dose-dependent manner. The minimum bactericidal concentration of polyisothiouronium methyl styrene needed for total killing against four common bacterial pathogens such as: *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Listeria innocua* was found 1% as demonstrated by Cohen et al. [38].

Anticandidal action of PUF-SC$(NH_2)_2$ against *C. albicans* was examined by TEM analysis, as shown in Fig. 10. The untreated *C. albicans* cells showed a normal cell wall, compact cytoplasm, cell membrane and small vacuole. On the other hand, PUF-SC$(NH_2)_2$ caused severe morphological changes in the yeast cells manifested by disruption of the cell membrane structure and the appearance of a big vacuole. This membrane damage was supported by TEM images, where rough membranes and changes in diameter and structure of the outer and inner membranes were observed. PUF-SC$(NH_2)_2$ showed good effects on the separation between cell membranes and cell walls of the treated yeast. It has been shown that the synthesized PUF-SC$(NH_2)_2$ has microbicidal action by killing the tested yeast. The biocidal action of PUF-SC$(NH_2)_2$ foam agrees with its ability for adsorption at water/cell membrane interface which increases its permeability toward the media ingredients. The biological reactions are interrupted within the cell membranes, wall, and cytoplasm. The nanocomposites showed biodegradability as conferred by bacterial degradation. Badawi et al. [39] results showed that the 4-methyl-40-propyloxy-azobenzene isothiouronium dibromo-dichlorocuparate complex revealed a good inhibition action against bacteria (*P. aeruginosa* and *S. aureus*), fungus (*A. flavus*) and yeast (*C. albicans*) as well as confirmed its adsorption ability to the microbial cell membranes.

The isothiouronium compounds' mechanism of action is different from the mechanism of classical antibiotics, and

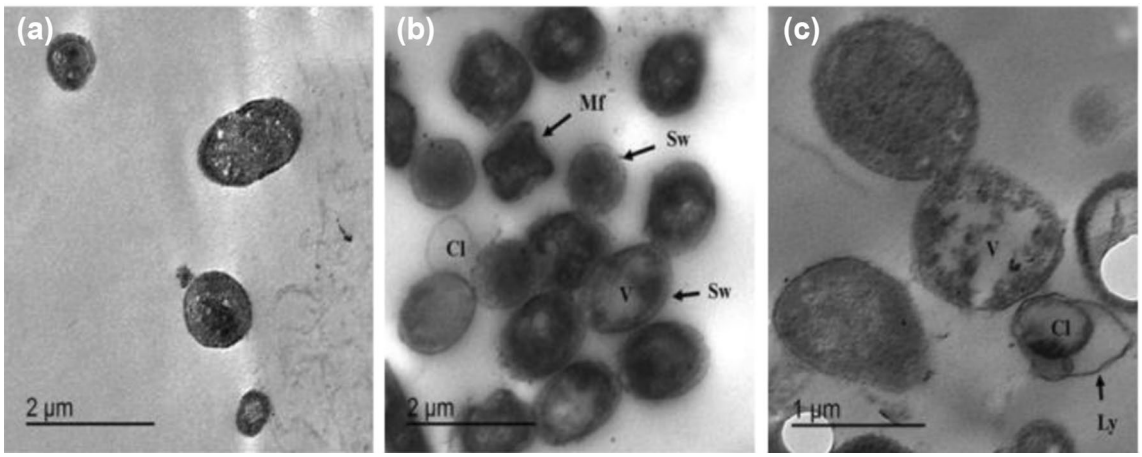


Fig. 10 Anticandidal effect of ITPUF on the ultrastructure of ITPUF-treated *C. albicans*; **b**, **c,** comparing to a negative control (without ITPUF treatment): **a**. There are lysed cell walls (Ly), separated cell wall (Sw), malformed cells (Mf), vacuole (V) and complete cell lysis (Cl)

the microbes exhibit a prolonged sensitivity against them [40]. The exact mechanism that PUF-SC$(NH_2)_2$ may exert antimicrobial activity is not known. There are some hypotheses that when a polymer is functionalized with an antimicrobial group might increase their antimicrobial effect [41]. The isothiouronium terminal amino functional group could bind to peptide terminating with acyl-*D*-alanyl-*D*-alanine (Ac-*D*-Ala-*D*-Ala). Antimicrobial activity of isothiouronium compared to thiourea compounds (which lack a positively charged *N*-terminus group) has a tenfold greater binding constant to Ac-*D*-Ala-*D*-Ala, in a microbial cell-wall model, due to the enhanced acidity of the NH moieties [42].

Conclusions

PUF-SC$(NH_2)_2$ synthesis, characterization and anticandidal activity were studied. The structure and chemical composition of PUF-SC$(NH_2)_2$ indicated that it could be used as anticandidal agent. PUF-SC$(NH_2)_2$ effects on *C. albicans* ultra-structure were studied, where the most sensitive cellular components to ITPUF were the cell wall and cytoplasmic membrane, through which it was disrupted and lost its control on substrate transfer, and consequently, it could not impel the accumulated PUF-SC$(NH_2)_2$ toward outside.

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