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2,5-Dimethyl-4-hydroxy-3(2H)-furanone as an Anti-biofilm Agent Against Non-*Candida albicans Candida* Species

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Abstract

Background The predominance of non-*Candida albicans Candida* (NCAC) species causing health-care-associated infections has increased over the last decade pertaining to their ability to form biofilms on medical devices. These biofilm-associated infections are challenging to treat as they are resistant to antifungal agents and evade host-immune response resulting in a high risk of device failure or biomaterial removal. Thus, to minimize the risk of biofilm-associated infections, preventing biofilm formation is the best approach which is mediated by the quorum quenching process.

Methods The present study investigated the modulatory effect of 2,5-dimethyl-4-hydroxy-3(2H)-furanone (DMHF) on NCAC biofilm formation and also assessed the effect of the DMHF-coated catheters on biofilm formation of NCAC. The NCAC isolates studied were *Candida tropicalis*, *Candida glabrata* and *Candida krusei* isolated from catheter tip, urine and blood, respectively.

Results DMHF at a concentration of 30 µg/mL showed an inhibitory effect against NCAC biofilms at various stages and was statistically significant ($p \leq 0.05$) against the various concentrations (50–5 µg/mL) tested and also among the three phases of experiment. The furanone content on coated catheters ranged from 170 to 750 µg and release of furanone from the coated catheter was about 15 µg for 30 days. The effect of DMHF-coated catheters on NCAC biofilm formation was observed by the scanning electron microscopy which revealed the absence of NCAC adherence on DMHF-coated catheters.

Discussion This study provides a design to develop furanone-coated biomaterials which could be implemented in healthcare settings to reduce medical device-associated infections. The excellent biological performance, combined with their antimicrobial properties, suggests that 2,5-dimethyl-4-hydroxy-3(2H)-furanone could be an effective anti-infective coating for implantable devices.

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Catheter coating · Implantable devices · Scanning electron microscope

Introduction

Recent advancement in health sciences has led to the increased use of indwelling medical devices (IMD) for the betterment of the patients. Unfortunately, infections from biomedical implants via biofilm formation are caused by opportunistic pathogens such as *Candida* species and are currently a significant global threat to mankind. Colonization of yeast cells on the catheter surfaces occurs within 24 h, and several factors facilitate this process. The contamination of urinary catheters occurs either by endogenous translocation from the gut or exogenously by intra- or extraluminal colonization. The central venous catheters get contaminated by extraluminal migration of the skin resident flora along the catheter from the skin at the catheter insertion site. Candida colonized on the biomaterial surface, multiply to form a microcolony which eventually matures to a biofilm by matrix production and quorum-sensing signals.

The biofilm disperses and is responsible for subsequent infection dissemination and bloodstream infection [1, 2]. Quorum sensing (QS) plays a dynamic role in biofilm formation by releasing autoinducers or signaling molecules. Biofilm-associated infections are generally polymicrobial in vivo, and the establishment of biofilm along with its dissemination and drug resistance is mediated by these signaling interactions [3].

Polymicrobial biofilms are difficult to treat as they are recalcitrant to antimicrobial agents and host-immune response. This tolerance has led to device failure and subsequent removal of the device or biomaterial. Thus, to minimize the risk of biofilm-associated infections, preventing biofilm formation is the best approach. This is achieved by quorum quenching process in which the QS mechanism is interrupted by inhibiting either the signal synthesis or binding of signaling molecules or even inhibiting the binding of signal transduction cascade [3, 4]. There are a wide range of QS inhibitors, among which few natural compounds such as brominated furanone, garlic, ursine triterpenes, corosolic acid and Asiatic

acid, ginseng and 3-indolyl acetonitrile are being studied for its anti-biofilm properties [3, 4]. Furanone is produced naturally by the red algae *Delisea pulchra*, which prevents fouling on the surface of the algae. Natural and synthetic furanones have shown anti-biofilm properties in both gram-negative and gram-positive bacteria [3]. Our studies (preliminary data) on the modulatory role of QS molecules (farnesol, homoserine lactone and DMHF) on biofilm formation on three phases—adherence and subsequent biofilm formation, preformed biofilms and planktonically growing cells on clinical NCAC isolates showed that furanone exhibited higher inhibitory effect against NCAC biofilms in comparison with farnesol and homoserine lactone. Indwelling biomaterials are usually within the body for a time span ranging from 48 h to several days. Thus, to prevent biofilm formation on these indwelling biomaterials, a controlled drug delivery system on the coated biomaterial is mandatory. This requires the use of a polymer that is biocompatible, biodegradable and a potent applicator in controlled drug delivery. Polycaprolactone (PCL) is one of those kinds of polymers with excellent physical and biological properties of biocompatibility with other polymers, has high permeability to drugs, biodegradable and excreted from the human body. This has paved the way for its potential application in controlled drug delivery systems in the present biomedical era [5, 6].

The aim of the present study was to assess the modulatory effect of 2,5-dimethyl-4-hydroxy-3(2H)-furanone (DMHF) on non-*Candida albicans Candida* (NCAC) biofilm formation and also to evaluate the anti-biofilm activity of DMHF along with PCL-coated catheter materials on NCAC biofilm using scanning electron microscopy.

Materials and Methods

Catheter Materials

The catheter materials used in this study were procured from the hospital pharmacy associated with the study centre: Sterile Foley's urinary catheters—latex (BARDEX, Kedah, Malaysia) and silicone (RUSCH, Kamunting, Malaysia); and central line catheter—polyurethane (BRAUN, Melsungen, Germany). These catheters were aseptically cut into

pieces of 1 cm in length and used for the experimental studies.

NCAC Isolates

The NCAC isolates were obtained from the Clinical Microbiology Laboratory attached to the study centre. *Candida tropicalis* was isolated from Foley's catheter tip of patient suffering from urinary tract infection; *Candida glabrata* from urine of patient suffering from urinary tract infection; and *Candida krusei* from blood of a neonate suffering from sepsis. The isolates were preserved in potato dextrose agar slants at 4 °C.

Modulatory Effect of 2,5-Dimethyl-4-Hydroxy-3(2H)-Furanone (DMHF) on Non-*Candida albicans Candida* (NCAC) Biofilm Formation

A stock solution of 1 mg/mL of 2,5-dimethyl-4-hydroxy-3(2H)-furanone (DMHF) (Sigma-Aldrich, USA) was prepared in sterile distilled water, and the working concentrations of 5–50 µg/mL DMHF were prepared. The modulatory effect was studied in three phases, viz., effect on the adherent cells and subsequent biofilm formation; effect on preformed biofilms; and effect on planktonic cells. Appropriate control experiments without furanone treatment were put up for all the three phases [7].

For the effect on the adherent cells and subsequent biofilm formation, 100 µL of the standardized yeast cells containing 1×10^6 cells/mL in Sabouraud Dextrose Broth (SDB) were added into the wells of the microtitre plate and incubated for 4 h at 35 °C. Following the initial incubation, the medium was aspirated and non-adherent cells were removed by thoroughly washing the plate with sterile phosphate-buffered saline (PBS). 100 µL of the working concentrations of furanone were added to the adherent cells, incubated at 35 °C for 24 h, and the semi-quantitative measurement of the biofilm growth was measured spectrophotometrically at 450 nm by adding 20 µL of a tetrazolium salt (WST-CCK8) to the plates and incubating for 4 h at 37 °C in 5% CO_2.

For the effect of furanone on preformed biofilms, 100 µL of the standardized yeast cells containing 1×10^6 cells/mL in SDB were added into the wells of the microtitre plate and incubated for 24 h at 35 °C. Following the incubation, the medium was aspirated and the plate was washed with sterile PBS and 100 µL

of the working concentrations of furanone were added and further incubated for 24 h at 35 °C and the semi-quantitative measurement of the biofilm growth was measured spectrophotometrically at 450 nm by adding 20 µL of a tetrazolium salt (WST-CCK8) to the plates and incubating for 4 h at 37 °C in 5% CO_2.

For the effect on planktonic cells, 100 µL of the working concentrations of furanone were added to the wells of the microtitre plate containing 100 µL of the standardized yeast cells containing 1×10^6 cells/mL in SDB and incubated for 24 h at 35 °C and the semi-quantitative measurement of the biofilm growth was measured spectrophotometrically at 450 nm by adding 20 µL of a tetrazolium salt (WST-CCK8) to the plates and incubating for 4 h at 37 °C in 5% CO_2.

Coating of DMHF Along with Polymer Matrix onto the Catheter Materials

50 mg of DMHF was added to 38% w/v of poly-caprolactone solution in di-chloro methane-containing 30% w/w dibutyl phthalate as plasticizer and vortexed well. This constitutes the coating mixture. The catheters were dip-coated manually by dipping the catheter materials vertically into the coating mixture for about 10 s and then air-dried. The process was repeated twice with an interval of about 5–10 min and was ensured that the previous coating was completely dry before each successive coating was performed. All the coated catheters were air-dried and observed for their stability for 24 h.

Standard Plot of DMHF in Phosphate Buffer pH 7.4

Standard plot of was performed to determine the concentration of DMHF. 5.0 mg of DMHF was dissolved in 5.0 mL of methanol to obtain a stock solution of 1000 µg/mL. From the above stock solution, 100 µg/mL solution was prepared and suitable dilutions were made to obtain concentrations of 4, 6, 8, 10, 12, 14, 16 and 18 µg/mL. The absorbance was measured at 289 nm using UV spectrophotometer (UV1601PC, Shimadzu, Japan).

DMHF Content of the Coated Catheters

The amount of DMHF coated on the catheter materials was measured. 5 mL of methanol was taken in clean

test tubes, and the biomaterials each of 1 cm in length and with varying diameters (latex of 4 mm diameter, silicone of 6 mm in diameter and polyurethane of 3 mm in diameter) were placed in each tube and ultrasonicated for 15 min. The biomaterials were removed, and the solution was centrifuged at 10,000 rpm for 10 min. About 100 μL of the supernatant was taken in a clean tube, and 900 μL of the buffer (PBS pH 7.2) was added. The absorbance was measured by UV spectrophotometer (Shimadzu) at 289 nm against blank polymer solution. The drug content of the coated biomaterials was calculated using the regression equation.

Release of DMHF from the Coated Catheters

The coated catheters were placed in sterile vials containing 10 mL of PBS (pH 7.4). The vials were allowed to stand for 30 days without any disturbance at room temperature. 1 mL of the sample was withdrawn at intervals of day 1, 3, 5, 10, 15 and 30, and the absorbance was measured using UV spectrophotometer at 289 nm. The medium was replaced with 1 mL of fresh PBS after every withdrawal to ensure the maintenance of sink condition.

Anti-biofilm Activity of DMHF on the Coated Catheters Using Scanning Electron Microscopy

The coated catheter materials were gas sterilized and degassed for 7 days at room temperature to prevent the interference of ethylene oxide in the microbial study. Each of the coated material was placed in the wells of Nunclon tissue culture plates, and 800 μL of SDB was added to the wells. 200 μL of inoculum (1×10^7 CFU/mL) consisting of the NCAC strains (*C. tropicalis* was inoculated onto latex catheter; *C. krusei* onto polyurethane catheter and *C. glabrata* onto silicone catheter) were added to the wells and incubated overnight at 35 °C for biofilm formation. The materials were washed with sterile PBS, air-dried and subsequently dehydrated in a series of ethanol washes (70% for 10 min, 95% for 10 min and 100% for 20 min), completely air-dried and observed under the SEM [8].

Statistical Analysis

The software version 16.0 IBM SPSS was used to generate descriptive statistics of data. The experiments were repeated thrice, and the experimental data were expressed as a mean ± standard deviation. Two-way ANOVA was used and its corresponding post hoc analysis was done. $p < 0.05$ was considered statistically significant among the different concentrations tested and also among the three phases.

Results

Modulatory Effect of Furanone with NCAC Biofilms

The effect of furanone on NCAC biofilms showed effective inhibition at all the three phases—viz—the adherence and subsequent biofilm formation, preformed biofilms and planktonically growing cells (Fig. 1) when compared with their respective controls. The inhibitory effect of furanone against NCAC biofilms had no statistical difference ($p = 1$) at all the three stages. Among the various concentrations (50–5 μg/mL) used to study the modulatory effect of furanone on NCAC biofilms, a concentration of 30 μg/mL was effective in inhibiting the adherence of NCAC species (statistical significance $p = 0.008$, among the different concentrations tested and also among the three phases).

Coating of DMHF Along with Polymer Matrix onto the Catheter Materials

The percentage coating for different catheters ranged from 17.15 ± 4.08, 17.90 ± 0.07 to 21.30 ± 1.83 for different biomaterials latex, silicone and polyurethane, respectively. The latex and silicone materials are highly hydrophobic, whereas polyurethane is amphiphilic in nature.

DMHF Content of the Coated Catheters

The DMHF content of coated polyurethane catheter was high and least for silicone catheter (Table 1).

Fig. 1 Interaction of 2,5-dimethyl-4-hydroxy-3(2H)-furanone (30 µg/mL) with NCAC biofilms. Two-way ANOVA was performed, and p value of 0.006 ($p < 0.05$) was considered statistically significant among the three different phases
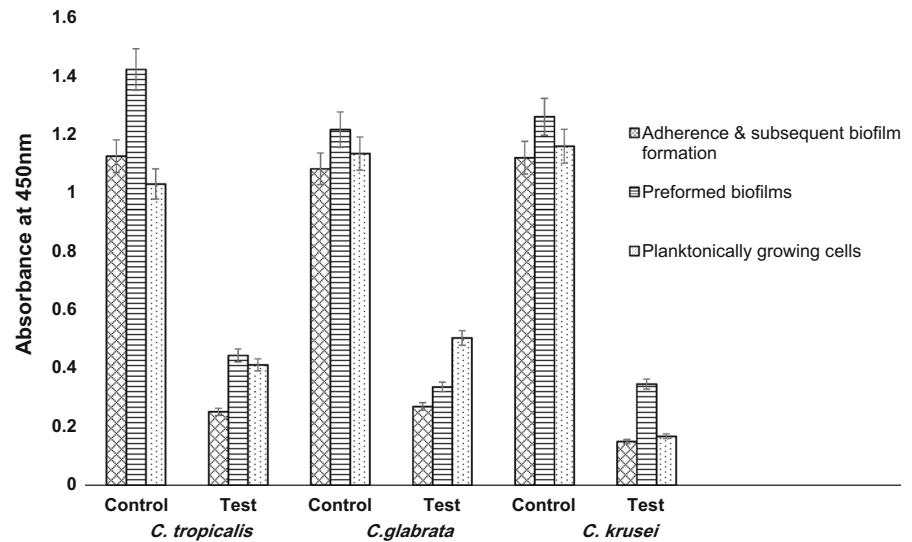

Table 1 Percentage coating and drug content of catheters

Biomaterials	% Coating	Drug content (µg/mL)
Latex	17.15	176.5
Silicone	17.9	94.9
Polyurethane	26.3	4967.5

Release of DMHF from the Coated Catheters

The in vitro release profile for the coated catheters is shown in Fig. 2. The release profile showed less than 3% DMHF release at the end of 30 days for coated silicone catheters, thus retaining a higher amount of the DMHF on the catheter to provide protective action against NCAC species, while about 12% DMHF was released from the coated polyurethane and latex catheters, respectively. However, more than 85% of DMHF was retained on the coatings to show inhibitory action against the NCAC species in both biomaterials.

Anti-biofilm Activity of DMHF on the Coated Catheters Using SEM

The anti-biofilm activity of DMHF-coated catheters revealed complete inhibition of NCAC cell adherence on the furanone-coated catheters (Fig. 3c, d) when compared with the polymer-coated catheters (control) (Fig. 3a, b). All the three catheter materials (latex, silicone and polyurethane) showed similar effect with

the respective NCAC species—*Candida tropicalis, Candida glabrata* and *Candida krusei*. Yeast adherence was seen on the untreated catheters after 24 h of incubation (Fig. 4). *Candida* species showed varied degree of adherence on the catheter, which is due to the surface characteristics of the catheter biomaterial.

Discussion

Hospital acquired infections are a public health concern, contributing to the morbidity and mortality of patients. The incidence of nosocomial candidiasis has increased throughout the world, with the epidemiological surveillance in the USA, showing 5–10% of patients in the hospitals acquiring the nosocomial infection. Of these, about 80% of fungal infections are caused by *Candida* species [9, 10]. Recent advancement in health sciences has led to the increased use of indwelling medical devices (IMD). Several studies report the IMD-associated biofilm infections such as intravenous catheters, prosthetic heart valves, urinary catheters, orthopedic devices, cardiac pacemakers, intrauterine devices, biliary tract stents, breast implants, contact lenses and voice prosthesis [11]. These infections are challenging to treat as it involves multi-drug-resistant opportunistic pathogens like Candida species. The adherence primarily depends on the glycoproteinaceous conditioning film of the catheter that alters the chemical characteristics of the material from its original form, along with the physicochemical

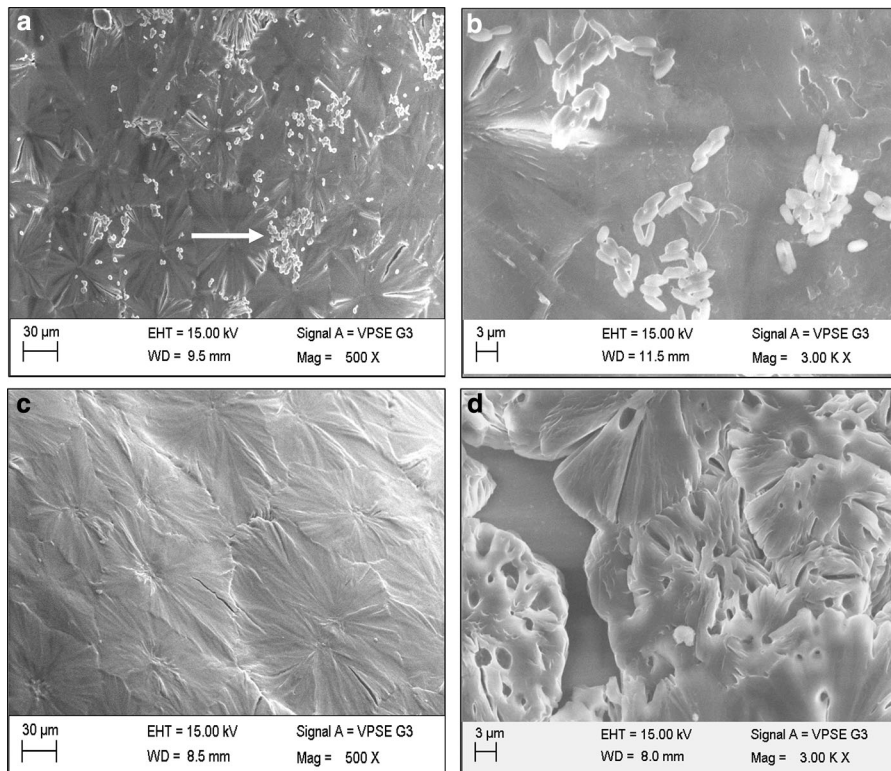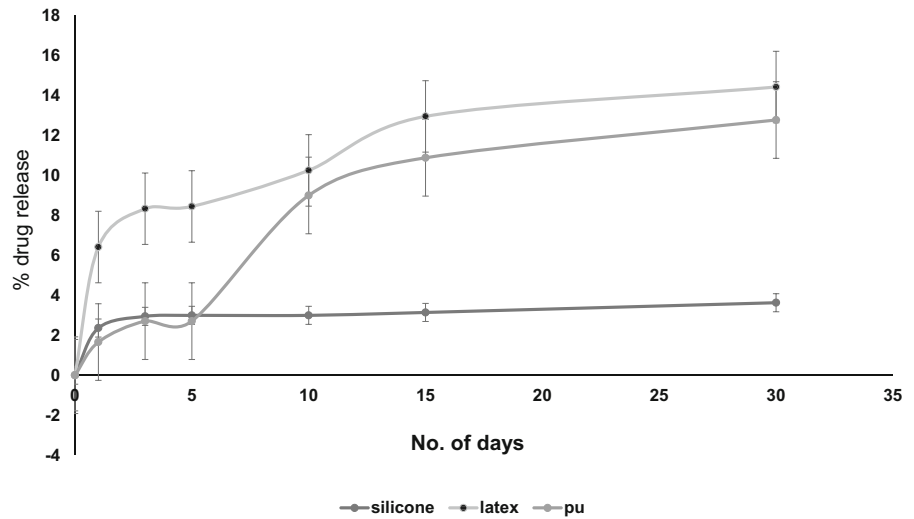**Fig. 2** In vitro release profile for DMHF in PBS

Fig. 3 SEM of polymer-coated (control—**a** and **b** with varying magnification) and furanone with polymer-coated catheters (**c** and **d** with varying magnification). Note the adherence of NCAC (*C. tropicalis*) on the controls (shown by an arrow) and the absence of NCAC on the furanone with polymer-coated catheters

characteristics such as surface roughness, hydrophobicity and electrostatic interactions. To overcome the defensive nature of biofilms, a surface that can resist or minimize the initial adherence of yeast is needed to prevent the subsequent biofilm formation, thereby reducing the mortality by nosocomial infections.

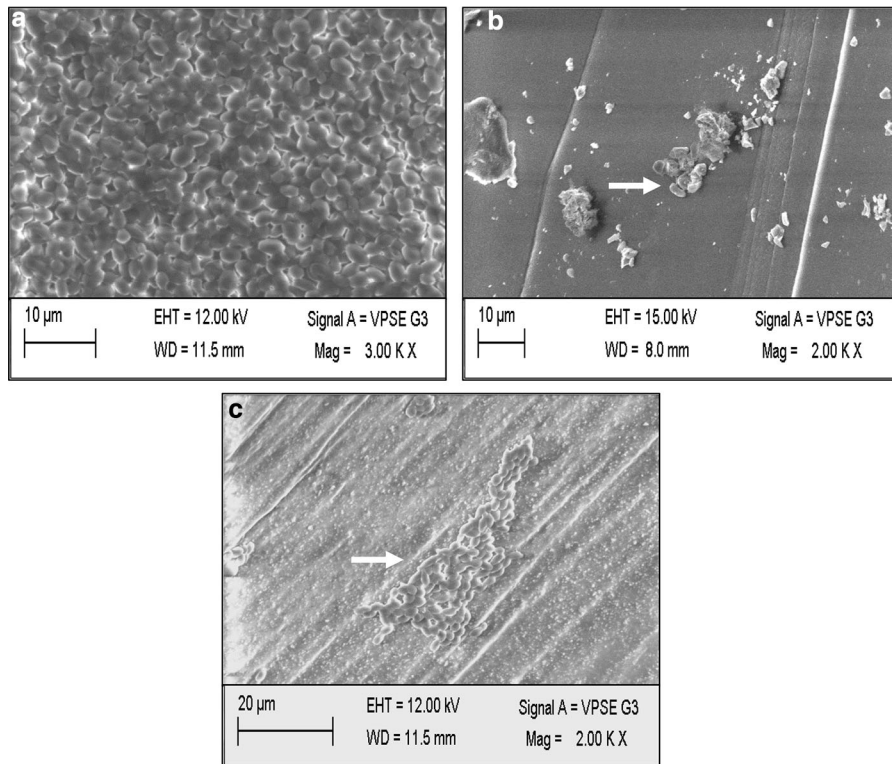There are several approaches in preventing biofilm formation—hand hygiene techniques and skin

Fig. 4 SEM of untreated catheters. **a** *Candida tropicalis* on latex; **b** *Candida glabrata* on silicone; and **c** *Candida krusei* on polyurethane

antiseptics during catheter handling, use of antifungal-impregnated catheters (polyenes and echinocandins), devices coated with antimicrobial peptides (liposomal amphotericin B), synthetic or semi-synthetic chemicals, biofilm-disruptive agents with drugs (AMP with DNAse), plant extracts, antimicrobial metal ions like silver, cation chelators (EDTA) and molecules that directly target persister cells (sugars, ADEP4 and antimicrobial peptides) [1, 2].

Naturally occurring brominated furanones isolated from *Delisea pulchra,* marine algae exhibited QS activity by the AI-2 signal pathway which is seen in both gram-positive and gram-negative bacteria. 2,5-dimethyl-4-hydroxy-3(2H)-furanone (DMHF) or furaneol is an aromatic compound found in berries, pineapples and various processed foods and is used extensively in food flavoring process. It is produced during the Maillard reactions between sugars and amino acids. The antioxidative activity of DMHF exhibits an anti-cataract and anti-carcinogenic effect in mice [12]. DMHF displayed antibacterial activity against antibiotics resistant strains along with anti-

candidal activity against *C. albicans*. It also showed the non-hemolytic effect on human red blood cells and arrested the cell cycle progress of *C. albicans* at the S and G2/M phase [12, 13].

In the present study, the NCAC species, *C. tropicalis, C. glabrata,* and *C. krusei*, were studied for the effect of the DMHF-coated catheter on their biofilm formation, as they were predominantly isolated from medical implants, urine and blood, respectively. *C. tropicalis* was tested for biofilm formation on DMHF-coated latex urinary catheter, *C. glabrata* on silicone urinary catheter and *C. krusei* on polyurethane central line catheter. The choice of the NCAC isolates was made depending upon their prevalence, site of isolation and their ability to cause biofilm-associated infection.

In our study, the 2,5-dimethyl-4-hydroxy-3(2H)-furanone inhibited biofilm formation of NCAC at all three stages (adherence and subsequent biofilm formation; preformed biofilms; planktonically growing cells). This inhibitory effect was seen equally in all the NCAC species. A study in Korea reported the

antimicrobial activity of 2,5-dimethyl-4-hydroxy-3(2H)-furanone against antibiotic-resistant clinical strains. The antifungal activity against *C. albicans* showed a MIC of 10–20 µg/mL [12]. The inhibitory concentration of DMHF in our study was 30 µg/mL against the NCAC species, although the range of concentrations (50–5 µg/mL) proved inhibitory effect on NCAC biofilms.

In our study, the coating of the catheter with DMHF was done with a PCL polymer solution to enable a sustained release of DMHF from the catheters. The polymer matrix, PCL, a polyester of polyglycolic acid (PGA), poly-L-lactide (PLLA) is commercially prepared by either ring-opening polymerization of €-caprolactone using a variety of catalysts or via a free radical ring-opening polymerization of 2-methylene-1-3-dioxepane. The physical properties such as hydrophobicity, semi-crystalline structure, good solubility and low melting point (59–64 °C) along with its distinguishing features such as compatible blends with catheters, slow biodegradation and higher permeability of drugs make it a potent copolymer for the use in controlled drug delivery system [6].

The percentage of DMHF coating varied among the catheters which may be due to the varied surface chemistry, surface energy/hydrophobicity and surface roughness of the catheters as described in other studies [14–16]. The DMHF content of the coated catheters also varied depending upon the coating percentage, with polyurethane catheters showing DMHF content of 26.3% when compared with latex and silicone catheters showing 17.15 and 17.9 DMHF content, respectively. The low surface tension and hydrophobic property of silicone may contribute to its coating efficiency [17]. The high coating efficiency of polyurethane could be due to the high uptake of hydrophilic PCL, resulting in a high amount of coating on to the surface of polyurethane catheters. The variation in uniformity of coating on the catheter surface may also contribute to the difference in drug content on the catheters [14]. The release study showed a reduced release of 2.24 µg/mL DMHF (15%) from the catheters at the end of 30 days. This concentration is considered safe [18] as about 85% of the DMHF is retained in the catheter for a controlled delivery in inhibiting yeast adherence.

In our study, the furanone-coated catheters were studied for their effect on biofilms in comparison with a polymer-coated catheter as a control. After 24 h of incubation, SEM studies revealed inhibition of NCAC adhesion on the furanone-coated catheters as reported by Baveja et al. [14]. Studies also report that furanone exhibited its activity in vivo, with a shelf life of 65 days to 2 years [21, 22]. Studies report that furanone-coated catheters such as silicone, PVC, PU, PP, PTFE and PE were effective in reducing the load and slime production of *Staphylococcus epidermidis* ATCC 35984 [19] and *Pseudomonas aeruginosa* [20]. There are several molecules that are currently employed in preventing biofilm formation, and DMHF has an advantage over these alternatives, as they inhibit microbial growth and do not kill the organisms for inducing drug resistance [14]. Further experimentation on the prolonged incubation of NCAC species on DMHF-coated catheters and its cytotoxicity testing is warranted. There are no studies on the effect of furanone on NCAC, and the in vivo activity of the furanone-coated catheters needs to be explored.

Conclusion

The present study provides a preliminary fact on the DMHF-PCL-coated catheters capable of inhibiting the biofilm formation of NCAC species. Further studies on coating the catheters with DMHF-PCL nanoparticles and evaluating their anti-biofilm activity would be an alternative approach. The use of in vivo models for the anti-biofilm activity of the DMHF-PCL-coated catheters remains as the limitation of the study. With the emergence of nosocomial NCAC infections and its association with biofilms, DMHF proves to be a potent anti-biofilm agent for biomaterials.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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