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BIOMEDICAL SCIENCES

Farnesol modulation of *Rhodotorula mucilaginosa* in biofilm and planktonic forms

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Abstract: Biofilms are important to the virulence of human pathogenic fungi, and some molecules have been found to play key roles in the growth and regulation of fungal biofilms. Farnesol, one of these molecules, is well-described for some microorganisms but is still scarcely known for *Rhodotorula* spp. This study aimed to evaluate the influence of farnesol on the biofilm of *R. mucilaginosa*. Initially, screening with 0.2 mM to 2.1 mM of farnesol was evaluated against planktonic forms. A concentration of this compound was then chosen and evaluated for its effect on biofilm in formation and on preformed biofilm after 24, 48 and 72 hours. The impact of farnesol was evaluated by colony-forming units (CFU) counts, determination of metabolic activity and quantification of total biomass. In the presence of 0.9 mM, farnesol was able to decrease the CFU number, at 48 hours, when the biofilm was in formation, although it did not affect the preformed biofilms. Thus, our results show that farnesol exerts a modulating activity during biofilm formation for *R. mucilaginosa*, with this compound reducing the metabolic activity and total biomass of the biofilms.

Key words: Biofilm, farnesol, quorum sensing, *Rhodotorula* sp.

INTRODUCTION

Biofilms are important to the virulence of human pathogenic fungi (de Barros et al. 2020). Studies have shown that microorganisms dispersed from a biofilm are able to cause severe infections, which have a greater association with mortality compared to their counterparts in planktonic form. In fact, it is estimated more than 65% of human fungal infections involve the formation of biofilms (Sardi et al. 2014). Consequently, more than 500,000 deaths per year are caused by biofilm-associated fungal infections (Sardi et al. 2014). Fungi organized in biofilms acquire greater resistance to most antifungal agents. Thus, this issue represents a major problem for clinicians, as the antifungal dose required to eradicate the biofilm can exceed the highest concentrations of that which is therapeutically attainable. In this sense, in the last decade, the events associated with the formation of biofilm by human fungal pathogens have received considerable attention, but in contrast to the extensive literature on biofilms of *Candida* spp., little attention has been paid to emerging fungal pathogens, such as *Rhodotorula* spp. (Nunes et al. 2013, Gharaghani et al. 2020, Jarros et al. 2020).

Rhodotorula spp. are particularly important to food, bioconversion and bioenergy industries, due to their biotechnological potential, such as the large production of carotenoids, as well as of unicellular proteins and microbial lipids (Kong et al. 2019). In the literature, only the species *R. mucilaginosa*, *R. glutinis* and *R. minuta* are described as being of medical interest, with *R. mucilaginosa* being the most commonly found in infections (García-Suárez et al. 2011). Invasive

infections caused by *R. mucilaginosa* are mainly associated with underlying immunosuppression or cancer, and with the use of central venous catheters or other invasive medical devices (Almeida et al. 2008, Tuon & Costa 2008). All of these devices provide the necessary surfaces for the formation and establishment of biofilms, which have been considered key to human infections caused by this genus (Del Pozo & Cantón 2016). In previous studies, our research group showed that *R. mucilaginosa* was able to colonize and transpose the acellular dermal matrix used in the reconstruction of the dermis of burn patients (Jarros et al. 2018). Recently we proved that isolates found colonizing chronic renal patients were virulent to *Tenebrio molitor* larvae and efficient in forming biofilm (Jarros et al. 2020).

Some molecules have been found to play an important role in the growth and regulation of fungal biofilms. These molecules are produced continuously during cell growth in quantities proportional to cell mass, leading to a coordinated expression of target quorum-sensitive (QS) genes (Ramage et al. 2002, Mosel et al. 2005). In *C. albicans*, it is well-described that farnesol blocks filamentation and the formation of biofilm in a manner dependent on concentration and time (Ramage et al. 2002, Mosel et al. 2005). In addition, farnesol can affect the production of some virulence factors in species of *Candida* (de Barros et al. 2020). It has been reported that farnesol also influences growth, especially in the early stages of biofilm development in other yeasts and filamentous fungi (Kischkel et al. 2019). Nevertheless, the influence of farnesol on *R. mucilaginosa*, in terms of clinical interest, has scarcely been investigated (Nishino et al. 1982, Gliszczyńska & Wawrzeńczyk 2008, Agustín et al. 2019). Thus, this study aimed to deepen knowledge of this known QS compound on the biofilm of *R. mucilaginosa*.

MATERIALS AND METHODS

Strains and culture conditions

This study was conducted with the reference strain *R. mucilaginosa* ATCC 64684 plus two clinical isolates of *R. mucilaginosa* from an oral colonization. *C. albicans* ATCC 90028 was used as the control in the same experiments. For the clinical isolates, the collection of biological samples and the cultivation method were performed as described previously (Pieralisi et al. 2016, Jarros et al. 2020).

These yeasts were deposited at the Microbial Collections of Paraná Network-TAX online and at the Medical Mycology Laboratory, Laboratório de Ensino e Pesquisa em Análises Clínicas of Universidade Estadual de Maringá (LEPAC), with the identification codes: CMRP3462 (MK453051; Genbank) and CMRP3463 (MK453052; Genbank). The yeasts were stored in Sabouraud Dextrose Broth (SDB; Difco™, USA) with glycerol at –80 ºC. All samples were cultured on Sabouraud Dextrose Agar (SDA; Difco™, USA) with chloramphenicol (0.1%) and incubated at 25 ºC for up to 3 days (Moț et al. 2017). Before experiments, yeasts were subcultured in chromogenic medium CHROMagar™ *Candida* (Difco, USA) to check the culture purity.

Preparation of farnesol

Farnesol (trans, trans-farnesol; Sigma-Aldrich, MO, USA) was prepared in 7.5% methanol (v/v) and diluted in RPMI 1640 medium (Roswell Park Memorial Institute, Gibco) to achieve the desired concentrations for each assay (Fernandes et al. 2016).

Screening for the ideal concentration of farnesol against *R. mucilaginosa*

Twenty farnesol concentrations (0.2 mM to 2.1 mM) were first tested against planktonic cells of *R. mucilaginosa* in order to choose

the best concentration for the subsequent experiments determining the effect of farnesol on this species. For this evaluation, the minimal inhibitory concentration (MIC) was determined according to the Clinical and Laboratory Standards Institute M27-A2 4th document (2017) and Fernandes et al. (2016). Cell suspensions were tested with farnesol solutions in 96-well microplates (Nunclon Delta; Nunc) incubated for 48 hours at 25 ºC. Negative (medium only) and positive (medium and inoculum) controls were used. The reading was performed according to Xia et al. (2017), measuring the metabolic activity by 2,3-bis (2-methoxy-4-nitro-5-sulfophenyl)-5-(phenylamino)-carbonyl-2H-tetrazolium hydroxide (XTT; Sigma-Aldrich, USA) reduction assay (Negri et al. 2016). The absorbance values at 492 nm for the XTT assay were standardized according to inhibition percentage.

The minimal fungicidal concentration (MFC) was evaluated according to Salci et al. (2017) by exposing the yeasts to four farnesol concentrations close to the MIC.

Rhodotorula spp. growth kinetics in the presence of farnesol

For the determination of the growth kinetics of *Rhodotorula* spp., the 0.9 mM concentration of farnesol was selected based on the minimum reducing concentration of the metabolic activity of ATCC 64684 *R. mucilaginosa* planktonic cells. The method was performed with slight modifications that were previously described (Tobaldini-Valerio et al. 2016). Prior to testing, fungi were subcultured on SDA, and the inoculum was adjusted to 1–5 × 10^7 yeasts/ml in RPMI 1640 medium using a Neubauer chamber. Then, the yeast suspension was grown in the presence of farnesol. The RPMI 1640 medium without farnesol was used as a positive control. Test suspensions were incubated at 25 ºC. At predetermined time points (0, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48 hours), serial dilutions were performed on SDA for determination of the colony-forming units (CFU). Following incubation at 25 ºC for 48 hours, the number of CFU/mL was determined.

Farnesol influence on *R. mucilaginosa* biofilm

To evaluate the influence of farnesol on biofilm formation, as well as on preformed biofilms, the methods of CFU evaluation, quantification of metabolic activity (XTT) and quantification of total biomass (CV) were used. These methodologies were based on Kischkel et al. (2019), with modifications. As a control, a similar experiment without farnesol was performed with the yeast suspension. *R. mucilaginosa* ATCC 64684 was first subcultured into SDB and grown for 18 hours with shaking at 110 rpm at 25 ºC.

On biofilm formation

The grown cultures were harvested, washed twice with phosphate-buffered saline (PBS; pH 7.2), adjusted to a concentration of 1 × 10^7 cells/mL in RPMI 1640 medium and farnesol at concentration 0.9 mM was added. The plates were then incubated with agitation at 110 rpm at 25 ºC for 24, 48 and 72 hours. After each incubation period, the CFU, XTT and CV quantifications were performed, according to Fernandes et al. (2016) and Jarros et al. (2020).

On preformed biofilm

Firstly, the biofilm was formed according to the previous section without the addition of farnesol. After the incubation times (24, 48 and 72 hours), 0.9 nM farnesol was added and the plates were incubated again under the same conditions for 24 hours. After each incubation period, the CFU, XTT and CV quantifications were performed (Fernandes et al. 2016, Jarros et al. 2020).

Statistical analysis

All tests were performed in triplicate and on three independent days. Data with a non-normal distribution were expressed as the mean ± standard deviation (SD). Significant differences among means were identified using the two-way ANOVA test, followed by Bonferroni multiple-comparison test. The data were analyzed using Prism 5 software (GraphPad, San Diego, CA, USA). Values of $p < 0.05$ were considered statistically significant.

RESULTS

Firstly, it was evaluated whether farnesol had influence on the growth of yeast in its planktonic form through determinations of the MIC and MFC. Figure 1 shows that farnesol does not exert fungicidal action. The evaluation of the metabolic activity measured by the reduction of XTT allowed for the definition of the MIC as 0.9 mM, since it was the lowest concentration that provided the greatest reduction in metabolic activity of *R. mucilaginosa* ATCC 64684. Based on this, the concentrations of 1.1 mM, 1.0 mM, 0.9 mM, 0.8 mM and 0.7 mM were chosen for the subsequent MFC assays.

The confidence of these findings was ensured by the results found for *C. albicans* ATCC 90028, which was used as a control. Despite the significant reduction in metabolic activity observed for both *R. mucilaginosa* and *C. albicans*, the SDA plate culture for the MFC assay relies on the viability of these cells, even after exposure to high farnesol concentrations, which indicated that farnesol was not fungicidal (Fig. 1b).

With regard to *R. mucilaginosa* ATCC 64684 growth kinetics, Figure 2 shows that, in untreated cells, there was a significant increase in growth from 16 hours, while in farnesol-treated cells, the significant growth started from 24 hours, suggesting a retardation. Additionally, in the presence of 0.9 mM farnesol, it was possible to observe a reduction in growth of

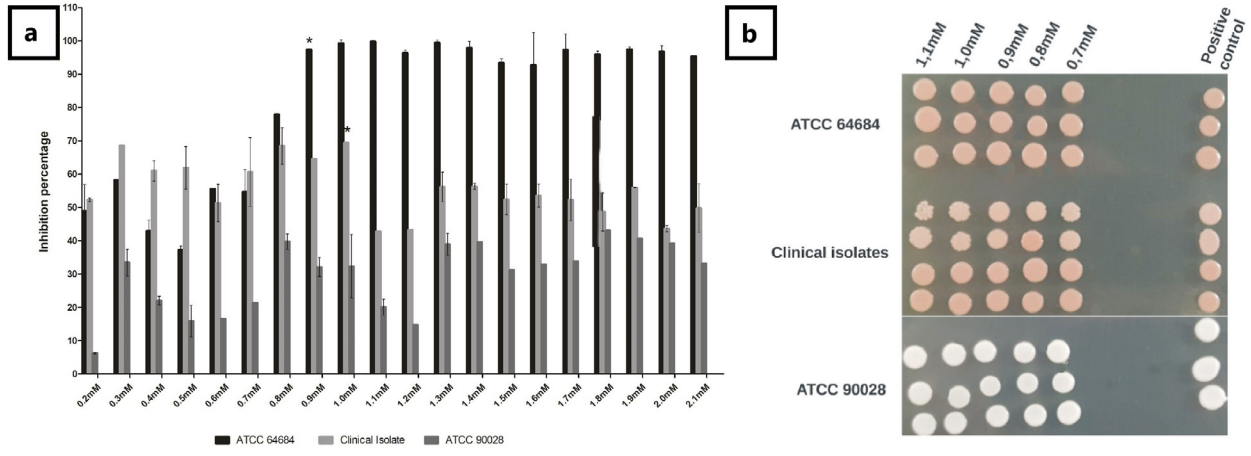

Figure 1. Screening the effect of farnesol concentrations (0.2 mM to 2.1 mM) on planktonic cells of *Rhodotorula mucilaginosa*: (a) The minimal inhibitory concentration (MIC) based on the metabolic activity (XTT) of *R. mucilaginosa* ATCC 64684 plus the average for clinical isolates of *R. mucilaginosa* (CMRP3462 and CMRP3463) and *Candida albicans* ATCC 90028; (b) Evaluation of the minimal fungicidal concentration (MFC) at concentrations of 1.1 mM, 1.0 mM, 0.9 mM, 0.8 mM and 0.7 mM. Farnesol was not able to inhibit the growth of yeasts, but its action was observed in the interference of metabolic activity. *Statistical difference between strains. All tests were performed in triplicate and on three independent days. Data with a non-normal distribution were expressed as the mean ± standard deviation (SD).

the farnesol-treated cells, with statistical significance, in the number of CFU/mL between 16 and 20 hours.

The effects of farnesol on *R. mucilaginosa* biofilm formation were evaluated (Fig. 3), first by quantifying the CFU (Fig. 3a). Biofilm in formation, treated with farnesol at a concentration of 0.9 mM suffered a significant reduction in the recovered CFU number at 48 hours compared with the untreated control. There was a significant increase of the metabolic activity in untreated biofilm at 72 hours (Fig. 3b). However, there was a significant reduction in cellular metabolism when biofilm in formation was treated with farnesol. This was observed at all evaluated times (24, 48, and 72 hours), in comparison to the untreated control, but the 48-hour time-point was crucial, as the metabolic activity was significantly lower than 24 and 72 hours. The 48-hour time-point also stood out due to a significant increase in total biomass compared to the other evaluated times (24 and 72 hours) for the untreated control (Fig. 3c). However, for farnesol-treated biofilm in formation, there was a significant reduction at all times (24, 48 and 72 hours).

On the other hand, regarding preformed biofilm by *R. mucilaginosa*, no statistical differences were found in the CFU count between farnesol-treated and untreated biofilms (Fig. 4a), showing that there was no influence on the biofilm at different times (24, 48 and 72 hours). In terms of metabolic activity (Fig. 4b), there was a significant reduction in the metabolism of farnesol-treated preformed biofilm compared to untreated biofilms, similarly to that which occurred for biofilm in formation. Finally, according to Figure 4c, preformed and untreated biofilms had a significant increase in total biomass in 24 hours. However, the addition of farnesol at a concentration of 0.9 mM provoked a significant reduction in total biomass

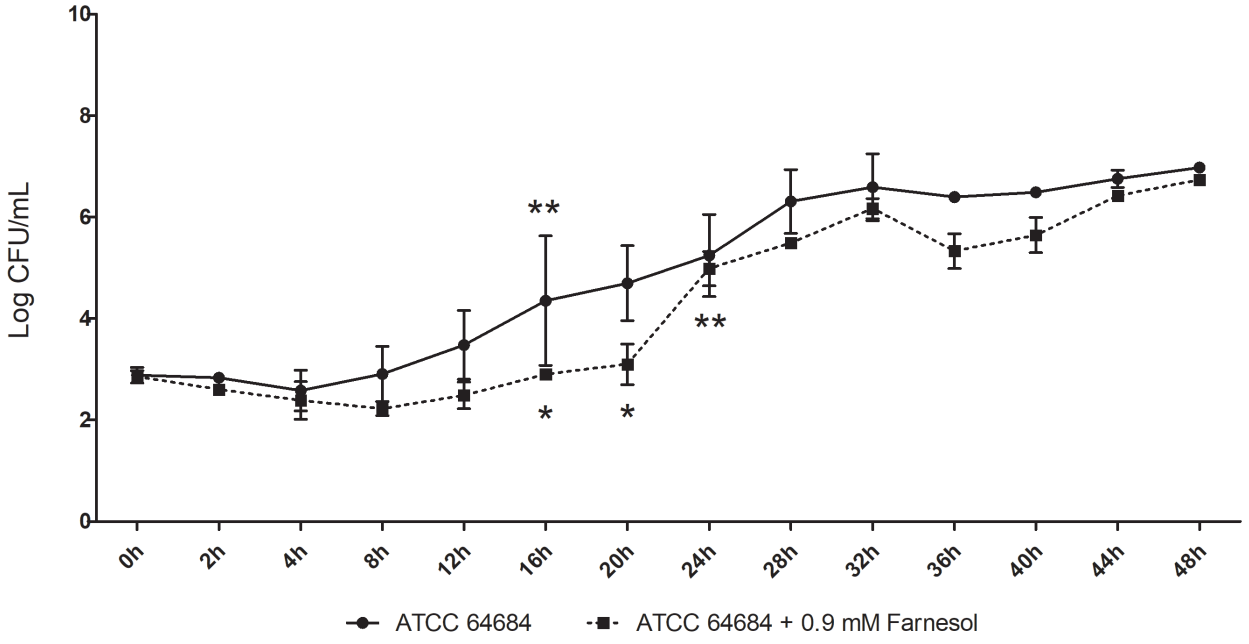

Figure 2. Growth kinetics of planktonic cells of *Rhodotorula mucilaginosa* ATCC 64684 in the presence of 0.9 mM farnesol compared with untreated planktonic cells. *Statistical difference between treated and untreated. **Significant increase over time. All tests were performed in triplicate and on three independent days. Data with a non-normal distribution were expressed as the mean ± standard deviation (SD).

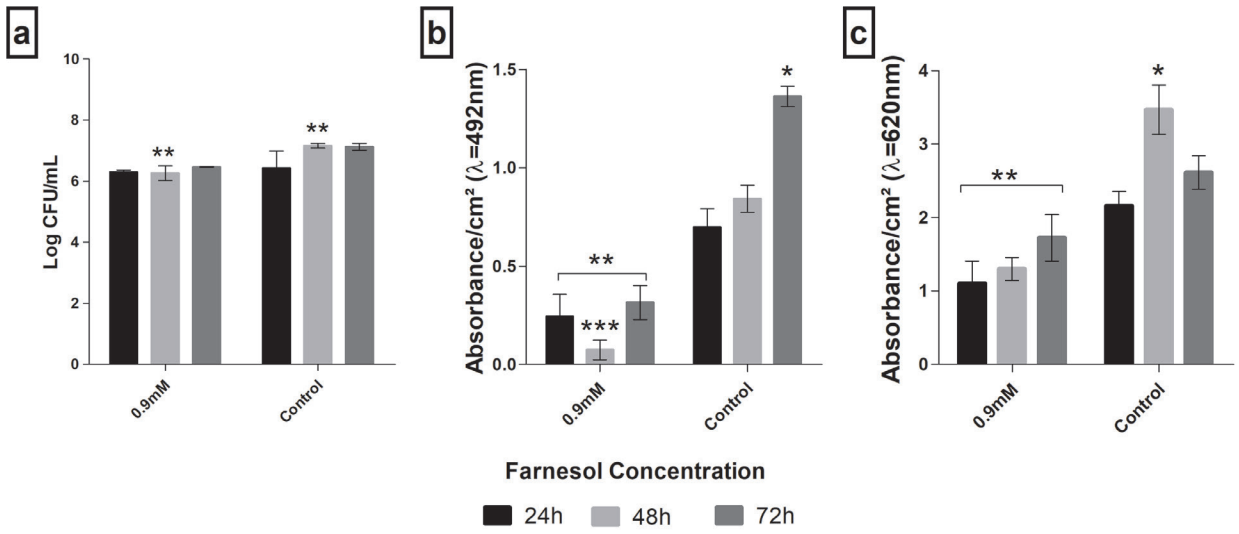

Figure 3. Influence of the concentration of farnesol on *Rhodotorula mucilaginosa* ATCC 64684 biofilm in formation over time by evaluation of three variables: (a) colony forming units (CFU); (b) metabolic activity (XTT); and (c) total biomass production (CV). Farnesol reduced metabolic activity and total biomass and therefore the production of extracellular matrix, since CFU/mL remained high, independent of time. *Statistical difference between controls. **Statistical difference between controls and treated. ***Statistical difference at 24 and 48 hours of treatment. Control: a similar experiment without farnesol. All tests were performed in triplicate and on three independent days. Data with a non-normal distribution were expressed as the mean ± standard deviation (SD).

production in preformed biofilms at 24 and 48 hours. Furthermore, there was a significant reduction in the biomass of treated biofilms at 48 hours compared to those at 24 hours.

DISCUSSION

Microorganisms, in a general way, are able to regulate their cooperative activities and physiological processes through a specific mechanism called QS. They are able to adapt to different biological functions in the environment according to population density through the secretion of self-inducing signaling molecules. Farnesol, an example of a QS detection molecule, is capable of suppressing or activating gene expression (Sebaa et al. 2019). Farnesol is produced as a by-product of ergosterol synthesis, but its mechanism of action remains unknown (Krom et al. 2016). An important role has been found for this molecule in some fungi, such as *C. albicans* (Polke & Jacobsen 2017). However, knowledge so far is usually related to filament regulation (Polke et al. 2018). In the genus *Rhodotorula*, a yeast unable to undergo filamentation, the role of farnesol is still relatively unknown.

This is the first study showing the influence of farnesol on *R. mucilaginosa* biofilm in samples of medical interest. In order to determine the concentrations of farnesol to be tested on the biofilm forms, a range of concentrations (0.2 mM to 2.1 mM) was first tested against the planktonic counterparts (Fig. 1). The best performance in terms of reducing the metabolic activity of the planktonic cells was with 0.9 mM farnesol, data which is very close to that reported by Agustín et al. (2019). At a similar concentration (0.6 mM), farnesol was able to completely inhibit the planktonic cell growth of *Fusarium* spp., with farnesol acting in a dose-dependent manner, at lower concentrations, there was a reduction in filamentation and microconidia (Kischkel et al. 2019).

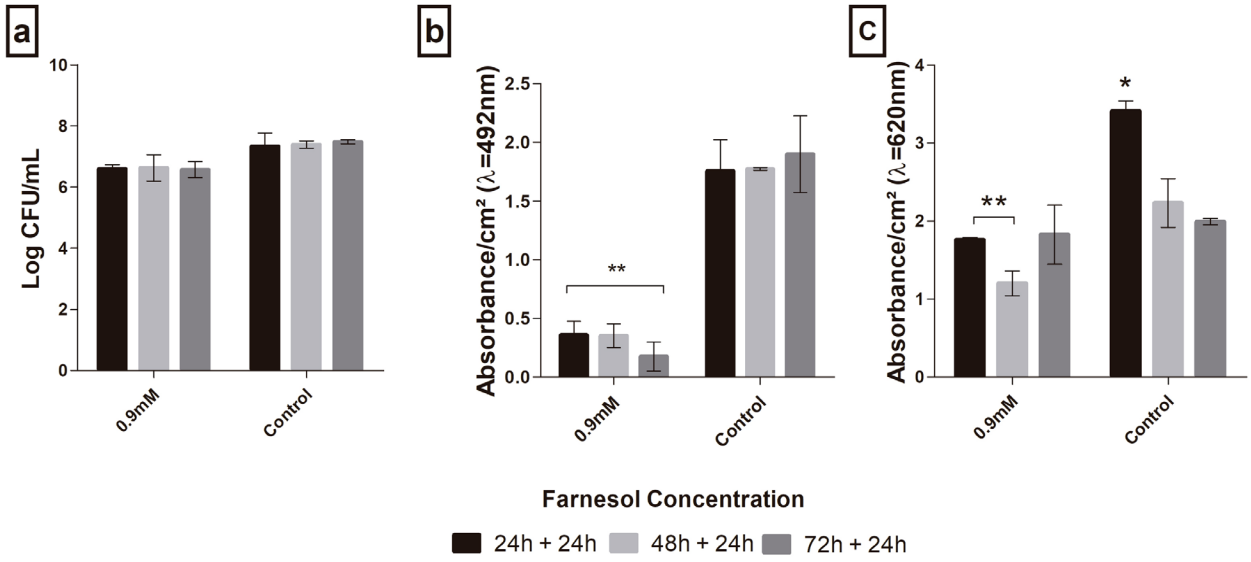

Figure 4. Evaluation of farnesol on biofilm preformed by *Rhodotorula mucilaginosa* ATCC 64684: (a) Colony forming unit (CFU); (b) Metabolic activity (XTT); (c) Total biomass production (CV). *Statistical difference between controls. **Statistical difference between controls and treated. Control: a similar experiment without farnesol. All tests were performed in triplicate and on three independent days. Data with a non-normal distribution were expressed as the mean ± standard deviation (SD).

R. mucilaginosa is an encapsulated yeast, similar to *Cryptococcus* spp., whose infections are also mimicked (George et al. 2016). However, with regard to farnesol susceptibility, divergent results for these two genera were found. Our data show that farnesol did not inhibit the growth of *R. mucilaginosa* in concentrations ranging from 0.7 mM to 1.1 mM (Fig. 1b); nevertheless, the low metabolic activity observed at the different concentrations evaluated (Fig. 1a) justified the concentration chosen for the biofilm assays. On the other hand, Cordeiro et al. (2012) showed that farnesol has an inhibitory effect on strains of the *C. neoformans* species complex.

Regarding the kinetics of farnesol on *R. mucilaginosa* planktonic cells (Fig. 2), there was no structural difference in the adhesion of *R. mucilaginosa* treated with farnesol, in relation to the structure formed in the adhesion (2 hours), as was also described found by Agustín et al. (2019). Corroborating our results, these authors found that the reduction in the number of cells treated with farnesol in the biofilms of multiple species was not evident in the initial phase, but in mature biofilms only. Indeed, little is known about fungi without filaments, but Monteiro et al. (2017) reported that, for planktonic cells of *C. glabrata,* the absence of hyphal elements may have favored the action of drugs. It is possible that this also occurred in *R. mucilaginosa*.

When looking at farnesol-treated biofilm in formation and preformed biofilm, there is generally a 48-hour time-honing, reinforcing data from Agustín et al. (2019). These authors described a significant reduction in the CFU of *R. mucilaginosa*, *C. tropicalis*, *C. krusei* and *C. kefyr* biofilms treated with 0.6 mM farnesol at 48 hours. When the influence of farnesol on biofilm in formation was assessed (Fig. 3), it was observed that there was a reduction in CFU at 48 hours, metabolic activity at all times and concentrations, and total biomass at all times and concentrations evaluated. These results suggest farnesol could be a promising

compound for providing a synergistic effect in association with an antifungal drug in order to eradicate infections with characteristics of dispersion by biofilm, since *in vitro* studies point to farnesol as a specific modulator of the drug efflux pump (Sharma & Prasad 2011, Katragkou et al. 2015). Monteiro et al. (2017) have already been using compounds from the QS as agents associated with oral hygiene products in order to prevent the development of yeasts of the genus *Candida*.

Regarding preformed biofilm, a significant decrease in metabolic activity and total biomass, without a reduction of CFU, was observed (Fig. 4). Thus, it is possible to infer that the decrease in total biomass is related to the decrease in the extracellular matrix (Negri et al. 2016). These results reinforce the idea that farnesol could be used in combination with antifungal drugs, facilitating its penetration and thereby reducing the number of CFU.

CONCLUSION

This study shows farnesol exerts a modulating effect both in biofilm formation as well as on the preformed biofilm for *R. mucilaginosa*. This effect occurs especially in the initial phase of biofilm formation. Moreover, this compound reduced the metabolic activity and total biomass of the biofilm of *R. mucilaginosa*, suggesting that farnesol could be a promising compound for synergistic effect in association with an antifungal drug.

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