The influence of farnesol and tyrosol on *Candida* spp. virulence traits

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Abstract

Introduction **Intercellular communication helps regulate the cell density and the virulence traits in yeasts and bacteria. The study aims to identify the effects of quorum sensing molecules (QSMs) like farnesol and tyrosol on *Candida* spp. virulence traits.**

Methods **The effects of farnesol and tyrosol were studied on the growth rate of *Candida albicans*, *Candida parapsilosis*, *Candida krusei*, *Candida auris*, and *Candida guilliermondii* at different time points, on a 48 hours incubation period. The growth rate was assessed spectrophotometrically. The biofilm formation abilities of *Candida* spp. were assessed by crystal violet staining technique. Moreover, the expression of *C. albicans* virulence genes (*ALS3*, *HSP70*, *SAP2*) was analyzed as a response to 100 µM farnesol and tyrosol, by RT-PCR.**

Results **Generally, farnesol was found to inhibit the growth rate and biofilm formation mostly in non-*albicans* species, while tyrosol exerted a non-consistent response on the different *Candida* species. The expression of *ALS3* and *HSP70* in *C. albicans* was upregulated by the QSMs.**

Conclusions **Both farnesol and tyrosol are involved in the regulation of *Candida* spp. virulence mechanisms, dependent on the used concentration and exposure time and in a species-dependent manner.**

Keywords **Farnesol, tyrosol, *Candida*, growth rate, biofilms, *ALS3*, *HSP70*, *SAP2***

Introduction

Fungi, as well as bacteria, communicate through quorum-sensing molecules (QSMs), signaling molecules that regulate a wide range of cellular functions, including the expression of virulence factors. As *Candida* spp. are opportunistic pathogens, the expression of virulence factors is crucial for the occurrence of the disease. Farnesol, tyrosol, tryptophol, and phenylethanol are the main QSMs used by *Candida* spp.[1]

Farnesol is a metabolite of the mevalonate/sterol synthesis pathway,[2] an acyclic sesquiterpene alcohol with anti-inflammatory properties.[3] Tyrosol is a phenylethanoid involved in germ tube formation, adherence, and biofilm

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formation. Both farnesol and tyrosol modulate a wide range of cellular functions in *Candida* spp.[4] and despite being considered potential adjuvants in preventing and treating *Candida* infections, their role is still incompletely elucidated. As virulence is multifactorial, how yeast cells communicate and regulate their cellular processes can be considered a virulence factor.[5]

The study aims to analyze the effects of farnesol and tyrosol on the growth rate and biofilm formation ability of five *Candida* spp., as well as to study the effects of the mentioned QSMs on the expression of *ALS3*, *SAP2* and *HSP70*, virulence genes in *C. albicans*.

Besides studying *C. albicans*, the current study fills a gap in the literature by including non-*albicans* species like *Candida parapsilosis*, *Candida guilliermondii*, *Candida krusei*, and *Candida auris*, as most studies focus on *C. albicans*, the most isolated *Candida* spp.

Methods

The growth rate of *Candida* spp. in the presence of farnesol and tyrosol

To assess the growth rate, a 0.5 McFarland inoculum was created by mixing fresh cultures of *C. albicans* ATCC 10231, *C. krusei* ATCC 6258, *C. parapsilosis* ATCC 22019, *C. auris* CBS 10913, and *C. guilliermondii* IC184 (Cantacuzino Institute, Romania) in saline solution (approximately 1-3 × 10^6 fungal cells/mL). From each inoculum, 10 µL were transferred in Sabouraud dextrose liquid medium (Oxoid, UK) with or without added substances. The QSM farnesol (95%, Sigma-Aldrich, USA) and tyrosol, 2-4(-hydroxyphenyl)ethanol (98%, Sigma-Aldrich, USA), were added in a final concentration of 100 µM. The 100 µM concentration was chosen for comparability with other studies.[6,7]

All samples were incubated for 48 hours at 37°C. The optical density (OD) was read spectrophotometrically, by using the Eppendorf BioPhotometer® D30 (Eppendorf, Austria), immediately after creating the mix (H0), after 6 hours (H1), after 9 hours (H2), after 12 hours (H3), after 24 hours (H4) and after 48 hours of incubation (H5). Before every reading, each sample was vortexed for 10 seconds. Blank probes for the spectrophotometer consisted of Sabouraud medium mixed with the farnesol and tyrosol, in the studied concentrations and without added substances for the control. The experiment was performed in triplicate.

The mean OD of the samples was compared to the mean OD of growth control (Δ-Index). A Δ-Index value that exceeds or equals the threshold of 1.25 was considered an indicator of growth stimulation, while an Δ-Index value ≤0.75 is equivalent to growth inhibition. If the Δ-Index values ranged between 0.75 and 1.25, the influence of the studied QSMs on the growth rate was considered insignificant.

The biofilm formation of *Candida* spp. in the presence of farnesol and tyrosol

C. albicans ATCC 10231, *C. krusei* ATCC 6258, *C. parapsilosis* ATCC 22019, *C. auris* CBS 10913, and *C. guilliermondii* IC184 were mixed in saline solution to create suspensions of 0.5 McFarland units. Stock solutions containing farnesol (200 µM) and tyrosol (200 µM) were created in RPMI medium. From each inoculum, 10 µL were transferred in the stock solutions and then distributed in the sterile 96-well microtiter plates. The first wells contained inoculum with stock solutions (200 µM). Through serial dilutions, decreasing concentrations of farnesol and tyrosol were created (100 µM, 50 µM, and 25 µM). The plates were incubated at 37°C for 24 hours to allow the cells to attach to the wells. After the incubation, the wells were washed with deionized water, stained with crystal violet, and then discolored with acetic acid. Samples without added substances served as growth control. The samples were read through spectrophotometry at 620 nm. The experiment was performed in triplicate. The biofilm formation rate was expressed in a percentage form, compared to each growth control.

C. albicans virulence gene expression in the presence of farnesol and tyrosol

Cells from a fresh culture of *C. albicans* ATCC 10231 were incubated overnight in a shaking water-bath, at 37°C, in Sabouraud liquid medium (Oxoid, UK) (approximately 3×10^7

cells/mL). From this inoculum, 1 mL was distributed in a 1.5 mL sterile tube. The mixture was centrifuged at 5000 rpm for 5 minutes. The sediment was resuspended in 1.5 mL of culture medium with the tested substances (with the final concentrations of 100 µM) and incubated for 3 hours, at 37°C in the thermomixer, to allow the substances to exert an effect over the yeast cells. After the incubation, the samples were centrifuged (5000 rtm/5 minutes) and the sediment was resuspended in TE buffer (500 µL). The total fungal RNA was extracted after physical and chemical lysis, by using column purification.

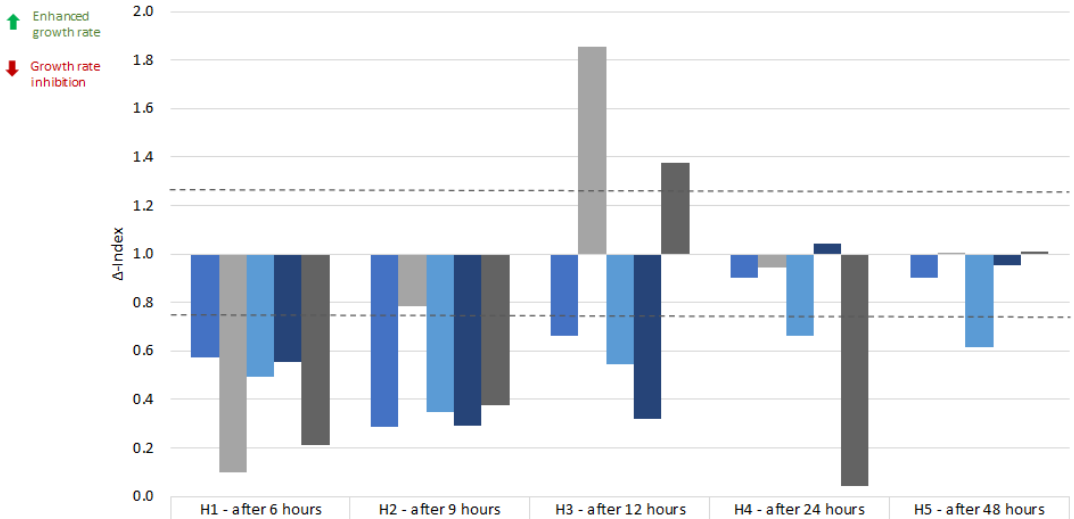
Because of the thick yeast cell wall, the samples were heated at 95°C, then frozen at -70°C in two freeze-thaw cycles of 10 minutes each. Lyticase (150 units per each sample) (from *Arthrobacter luteus*, Sigma-Aldrich, USA) was added for the chemical digestion of the fungal cell wall. To allow the digestion to take place, the samples were incubated at 37°C for one hour. The reaction was stopped by heating the tubes at 94°C for 10 minutes. Silica-based spin columns were further used, according to the producer's protocols (IndiSpin Pathogen Kit, Indical Bioscience, Germany). After purification, a volume of 25 µL elute was obtained. The samples were then treated with 1 µL DNase I (Thermo Scientific, UK), according to the producer's instructions (the elute, the reaction buffer and the enzyme were incubated for 30 minutes at 37°C; 1 µL EDTA was added to each sample after the incubation period and the samples were incubated again at 65°C, for 10 minutes).

The purity and the concentration of the extracted RNA, required for adapting the volume of the elute to participate in the reaction, were evaluated by nanodrop reading (Eppendorf BioPhotometer D30, Eppendorf Austria GmbH). The RNA was adapted to 1 µg/µL for each sample. For reverse transcription, the GoScript Reverse Transcription System (Promega, USA) was used. Each sample was incubated with 1 µL of oligoNT primers for 5 minutes at 70°C and the samples were allowed to chill on ice for 6 minutes. During this time, a mix containing MgCl2, Reaction Buffer, PCR Nucleotide Mix, and Reverse Transcriptase was prepared. Fifteen microliters from the mix were incubated with 5 µL of the RNA-oligoNT mixture for 5 minutes at 25°C (annealing), 60 minutes at 42°C (extension), and 15 minutes at 70°C (the inactivation of the enzyme). RT-PCR was performed using the following primers: ACT1 (FW 5'–TTG TTG ACC GAA GCT CCA ATG–3', REV 5'–ACG TGA GTA ACA CCA TCA CCA–3'), *ALS3* (FW 5'–CCA CTT CAC AAT CCC CAT C–3', REV 5'–CAG CAG TAG TAG TAA CAG TAG TAG TTT CAT C–3'), *HSP70* (FW 5'–TGG TAT TCC ACC AGC TCC AAG–3', REV 5'–CAA CTT CTT CAA CAG TTG GTC CAC–3'), *SAP2* (FW 5'–GAT GCT GCC ACG GGA CAA AT–3', REV 5'–AGA AGC AGC AAA TTC GGA AGC–3'). A sample with added substances served as the positive control. Samples without added substances served as a negative control. The experiment was performed in triplicate. To quantify the expression of the virulence genes, the threshold cycle (CT) value of the targeted gene was normalized against a housekeeping gene (here, ACT1). If the 2^ΔΔCt value (2^ΔCt of the housekeeping gene/ ΔCt of the analyzed virulence gene) is <0.5, the QSM inhibits the gene expression; a value ≥0.5 and ≤1.5 equals no effect on the gene expression, while a 2^ΔΔCt value >1.5 stands for the stimulation in terms of gene expression.

Results

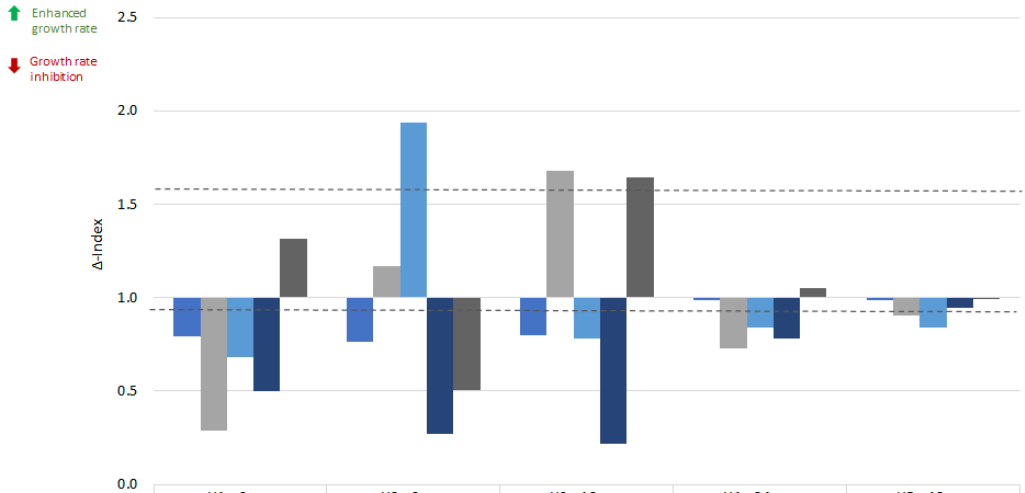
Farnesol (100 µM) generally inhibited the growth rate of the studied *Candida* spp. in the first 6-9 hours. After 12 hours of incubations, the response to farnesol is species-dependent (inhibition for *C. albicans*, *C. krusei* and *C. auris*, and growth stimulation for *C. parapsilosis* and, to a lower extent *C. guilliermondii*). After 12-24 hours, the inhibitory effect of farnesol was consistent for *C. krusei* **(Figure 1)**.

Tyrosol (100 µM) lowered the growth rate of *C. albicans* at all the time points, but the Δ-Index was below the threshold of significance. *C. parapsilosis* and *C. krusei* growth rates were inconsistently affected by tyrosol, while *C. auris* growth was inhibited by tyrosol, with the higher inhibition being observed after 9 and 12 hours of incubation. The effect of tyrosol on *C. guilliermondii* was discontinuous **(Figure 2)**.



	H1 - after 6 hours	H2 - after 9 hours	H3 - after 12 hours	H4 - after 24 hours	H5 - after 48 hours
C. albicans	0.57 ↓	0.29 ↓	0.66 ↓	0.90 –	0.90 –
C. parapsilosis	0.10 ↓	0.78 –	1.86 ↑	0.94 –	1.00 –
C. krusei	0.49 ↓	0.35 ↓	0.54 ↓	0.66 ↓	0.62 ↓
C. auris	0.56 ↓	0.29 ↓	0.32 ↓	1.04 –	0.95 –
C. guilliermondii	0.21 ↓	0.38 ↓	1.38 ↑	0.04 ↓	1.01 –

Figure 1. The effect of farnesol on *Candida* spp. growth rate



	H1 - 6 ore	H2 - 9 ore	H3 - 12 ore	H4 - 24 ore	H5 - 48 ore
C. albicans	0.79 –	0.77 –	0.80 –	0.98 –	0.98 –
C. parapsilosis	0.29 ↓	1.17 –	1.68 ↑	0.73 ↓	0.90 –
C. krusei	0.68 ↓	1.94 ↑	0.78 –	0.84 –	0.84 –
C. auris	0.50 ↓	0.27 ↓	0.22 ↓	0.78 –	0.95 –
C. guilliermondii	1.32 ↑	0.50 ↓	1.64 ↑	1.05 –	1.00 –

Figure 2. The effect of tyrosol on *Candida* spp. growth rate

Farnesol in a concentration of 25 µM does not affect the biofilm formation ability of *C. albicans*. Higher concentrations (50, 100, 200 µM) inhibited the formation of *C. albicans* biofilms. A concentration of 100 µM was observed to have the highest inhibitory effect (26%). *C. auris* biofilms were slightly inhibited by 200 µM, and the inhibition decreases with the concentration (a 50 µM concentration of farnesol has almost no effect on *C. auris* biofilm formation rate) (**Figure 3**).

C. albicans biofilm formation ability was inhibited by 36% tyrosol in a concentration of 100 µM, while for *C. krusei*, tyrosol exerted a

stimulating effect on the biofilm production (27-46%) (**Figure 4**).

The expression of *ALS3* was enhanced by both farnesol and tyrosol, in an almost equal amount. Both farnesol and tyrosol stimulated the expression of the *HSP70* gene, but the stimulation by farnesol was higher than the effect of tyrosol. The *SAP2* gene was not influenced by farnesol, but it was inhibited by tyrosol (**Figure 5**).

Discussion

Since their discovery, QSMs have been seen as promising targets for novel therapies,[8] but the anti-QS therapy still has a series of disadvantages,[9] and understanding the effects of these molecules on the virulence traits of microorganisms is crucial for deciding if quorum-sensing-interfering agents or QSMs in different concentrations can be used as antimicrobials. On average, under physiological conditions, *C. albicans* secretes 35.5±16.5 µM of farnesol, while non-*albicans* species secrete lower amounts: *C. parapsilosis* secretes 0.6±0.3 µM, *C. tropicalis* 1.0±0.7, *C. krusei* 0.6±0.1 µM, and *C. guilliermondii* 0.8±0.8 µM.[10]

C. albicans and *C. auris* had a consistent response to farnesol (the growth rates were inhibited on all the measured time points), while other species like *C. krusei*, *C. parapsilosis*, and *C. guilliermondii* had a different response at different time points of incubation. This might be because the response to farnesol is species-dependent, and some species might have adaptive mechanisms. Also, the concentration of farnesol influences the response of the fungal cells. The *Candida* species that showed an inconsistent inhibition of the growth rate might respond to higher concentrations of farnesol, as farnesol is known to inhibit the growth rate of the same *Candida* spp. at specific concentrations.[11]

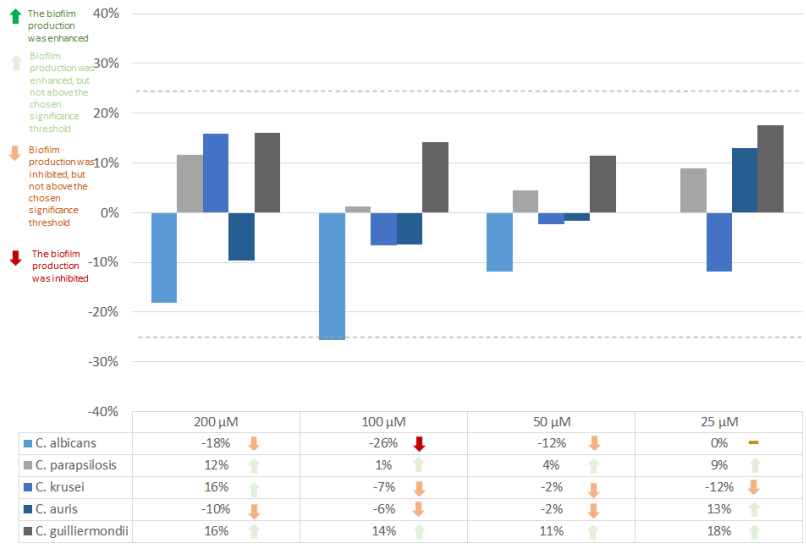
The *Candida* genus is a paraphyletic genus with an increasing number of new species[12] and while considering QSMs substances with potential therapeutic applications for *Candida* infections, their effect should be studied on multiple (ideally on all) species. Our results highlight the fact that farnesol and tyrosol influence the growth rate, but their effects are species-specific and dependent on the used concentration.

Rossignol et al. showed that farnesol drastically inhibited the growth rate of *C. parapsilosis* in the first 2 hours of incubation, but this arrest was not connected with a specific stage of the cell cycle. The cells recovered and after 24 hours there was no significant difference between the yeast cells treated with farnesol and the control samples.[13] In our study, the same phenomenon was observed: an initial inhibition was followed by no significant changes after 24 hours. Interestingly, after 12 hours, the growth rate of *C. parapsilosis* was significantly increased.

The effects of tyrosol on the growth rate are less studied as compared with farnesol. Jakab et al. showed that tyrosol (15 mM) inhibits the growth rate of *C. parapsilosis* within 2 hours after addition, without affecting the adhesion of the fungal cells. Cells treated with tyrosol showed a higher production of reactive species.[14] In our study, after 6 hours, the growth rate of *C. parapsilosis* was inhibited, despite using lower concentrations of tyrosol. As farnesol is not the only QSM and interspecies communication is a complex and still incompletely understood subject, the present study fills a gap in the literature and raises questions about how different *Candida* species react to QSMs.

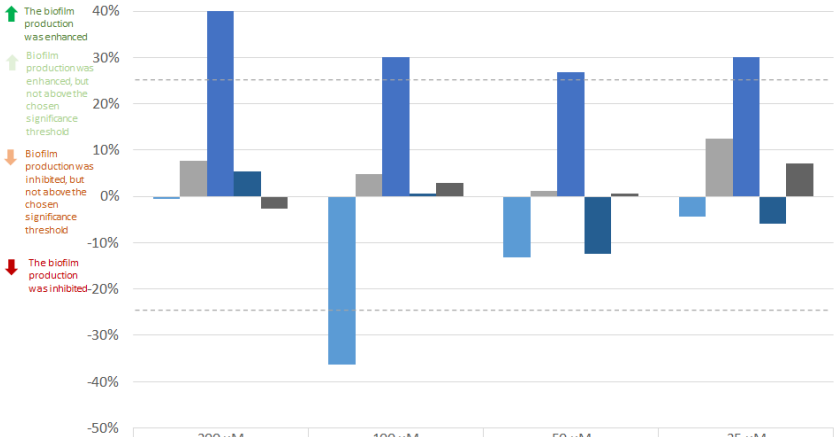
The biofilms formed by non-*albicans* species have a higher metabolic activity[15] and different regulatory networks.[16] The different responses that the studied non-*albicans* species had to farnesol and tyrosol met our expectations in terms of variability.

In *C. albicans*, the *ALS3* gene encodes a cell surface glycoprotein (Als3, agglutinin-like sequence protein 3) that plays a key role in adherence and biofilm formation. By changing the architecture of the biofilm, *ALS3* is involved in the increased resistance exerted by biofilms to antifungal drugs.[17] Higher *ALS3* expression correlates with an enhanced ability of the fungal cells to form biofilms.[18] Both farnesol (100 µM) and tyrosol (100 µM) increase the expression of ALS3. The same concentration of farnesol inhibited the biofilm formation of *C. albicans* and



	200 µM	100 µM	50 µM	25 µM
C. albicans	-18%	-26%	-12%	0%
C. parapsilosis	12%	1%	4%	9%
C. krusei	16%	-7%	-2%	-12%
C. auris	-10%	-6%	-2%	13%
C. guilliermondii	16%	14%	11%	18%

Figure 3. The influence of farnesol on *Candida* spp. biofilm formation



	200 µM	100 µM	50 µM	25 µM
C. albicans	-1%	-36%	-13%	-4%
C. parapsilosis	8%	5%	1%	12%
C. krusei	46%	30%	27%	30%
C. auris	5%	1%	-12%	-6%
C. guilliermondii	-3%	3%	1%	7%

Figure 4. The influence of tyrosol on *Candida* spp. biofilm formation

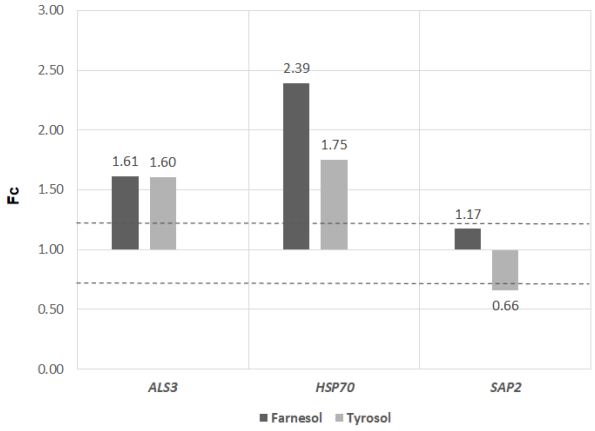


Figure 5. The influence of farnesol and tyrosol on the expression of *ALS3, HSP70, SAP2* in C. *albicans*

the same concentration of tyrosol did not affect the biofilm production ability of *C. albicans*. *ALS3* is expressed exclusively on *C. albicans* hyphae[19] and farnesol influences the *C. albicans* morphology, by inhibiting adenylate cyclase (Cyr1) and thus, inhibiting the hyphal growth.[20] *ALS3* is only a part of the vast regulatory network of genes involved in the production and maturation of biofilms. Fine alterations in the expression of genes can be triggered by various intrinsic or extrinsic factors.[21] We showed that farnesol can influence the expression of *ALS3* and it is one of the many factors that influence the complex network of genes that orchestrate the formation of the *C. albicans* biofilms.

Conclusions

The study of QSM-induced physiological and molecular events can provide new prevention and treatment alternatives for *Candida* spp. infections. In terms of growth rate and biofilm formation ability, different *Candida* spp. have particular responses to farnesol and tyrosol. Generally, farnesol was found to inhibit the growth rate and biofilm formation mostly in non-*albicans* species, while tyrosol exerted a non-consistent response on the different *Candida* species.

QSMs influence the virulence traits of different *Candida* spp. in a species-dependent manner and depending on the concentration. Farnesol and tyrosol have the potential to be used in the future as virulence modulators, but more research is required to properly understand their molecular mechanism of action. Notwithstanding the rarity of some *Candida* spp. like *C. auris* and *C. guilliermondii*, studying their response to QSMs can provide interesting insights about what, when, and how virulence traits are triggered.

Author contributions statement: Conceptualization: CNC, ADM and AM; methodology: CNC, ADM and AM; software: CNC, ADM and AM; validation: CNC, ADM, MM, FT, IBK, AC and AM; formal analysis: CNC, ADM, MM, FT, IBK, AC and AM; investigation: CNC, ADM, MM, FT and AM; resources: CNC, ADM, MM, FT and AM; data curation: CNC, ADM and AM; writing: CNC, ADM and AM; writing, review and editing: CNC, ADM, MM, FT, IBK, AC and AM; visualization: CNC, ADM, MM, FT, IBK, AC and AM; supervision: AM; project administration: AM. All authors read and approved the final version of the manuscript.

Conflicts of interest: All authors – none to declare.

Funding: None to declare.

Ethical approval: The experiments used fungal reference strains. As the study did not involve living animals, humans, or clinical samples, there was no need for Ethics Committee approval. The paper presents experiments conducted fully in vitro that did not involve patients or clinical samples collected from patients, but commercially, well-characterized microbial reference strains. All procedures were conducted following institutional biosafety guidelines.

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