

SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PhD)

Investigation of the Effects of Fungal-Derived Quorum Sensing Molecules on *Candida auris*

by Noémi Balla

Supervisor: Renátó Kovács, Ph.D.



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by Noémi Balla biotechnologist MSc

Supervisor: Renátó Kovács, Ph.D.

Doctoral School of Pharmaceutical Sciences, University of Debrecen

Head of the **Defense Committee:** Attila Bácsi, Ph.D., D.Sc.

Reviewers: István Lekli, Ph.D.

Enikő Egediné Fehér, Ph.D.

Members of the Defense Committee: István Lekli, Ph.D.

Enikő Egediné Fehér, Ph.D.

Marianna Domán, Ph.D.

István Varga, Ph.D.

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Introduction

Fungi constitute a highly diverse group within the eukaryotic domain of life, the true species richness of which remains only partially explored to date. It is estimated that approximately 2.2–3.8 million fungal species may exist worldwide; however, only around 300 of these have been described as capable of causing human disease. Among clinically relevant fungal pathogens, opportunistic yeasts are of particular importance, especially members of the genus *Candida*, which represent some of the most common etiological agents of human fungal infections.

The significance of invasive fungal infections has steadily increased over recent decades, paradoxically partly as a consequence of advances in modern medicine. Immunosuppressive therapies, organ transplantation, treatment of hematological malignancies, the widespread use of intensive care, and the increasing application of invasive medical devices (such as central venous catheters) all contribute to the growing proportion of susceptible patient populations. In parallel, the number of cases associated with antifungal resistance has increased globally. The extensive and often prolonged use of antifungal agents—not only in human medicine but also in agriculture and veterinary practice—exerts selective pressure on fungal populations present both in the environment and within the host, facilitating the selection and spread of resistant strains. The spread of resistance has particularly severe consequences in cases of invasive candidiasis, as delayed or inadequate therapy is associated with increased mortality, prolonged hospitalization, and rising healthcare costs.

The clinical importance of fungi is further amplified by global warming and anthropogenic environmental changes, which are associated with the emergence of new pathogens that were previously rarely observed or underdiagnosed. These organisms frequently exhibit reduced antifungal susceptibility and/or resistance to multiple drug classes. In recent years, increasing attention has been paid in clinical practice to pathogens such as *Candida auris*, azole-resistant *Aspergillus* species, and *Lomentospora prolificans*, which present new epidemiological and therapeutic challenges in clinical settings. It is noteworthy that *C. auris* represents a significant threat not only because of its multidrug resistance but also due to its remarkable ability to adapt to hospital environments, persist on surfaces for prolonged periods, and cause nosocomial outbreaks.

One of the fundamental determinants of fungal pathogenicity is phenotypic and morphological plasticity. Many species are capable of transitioning from a yeast form to filamentous or pseudohyphal morphologies, a process often associated with biofilm formation. Morphological switching and biofilm development represent key components of fungal virulence. These processes facilitate colonization and invasion of host tissues, enhance tolerance to environmental stress, and substantially contribute to resistance against antifungal agents.

Biofilm-associated infections are particularly difficult to treat, as the extracellular matrix of biofilms reduces drug penetration, while metabolic heterogeneity among cells diminishes the vulnerability of targeted biological processes. Consequently, clinical management often requires removal of invasive devices, implementation of combination therapies, or even innovative modifications of therapeutic strategies.

Collectively, these factors highlight that the limitations of the current therapeutic repertoire are becoming increasingly evident in the fight against invasive candidiasis and newly emerging multidrug-resistant *Candida* species. Although several promising developments have been initiated in recent years, the number of available antifungal drugs remains limited, and the diversity of their mechanisms of action is still far less extensive than that observed in antibacterial therapy. Among the most promising new antifungal agents are ibrexafungerp, rezafungin, novel itraconazole derivatives, and VT-1161, which may offer improved pharmacological properties, better clinical applicability, and in some cases a broader spectrum of activity. In parallel, alternative therapeutic approaches are also under investigation, including high-dose administration of existing antifungal agents, antifungal lock therapy, and various combination strategies aimed at exploiting synergistic interactions and reducing biofilm-associated resistance.

The clinical relevance of resistance and biofilm-associated persistence also justifies the exploration of novel intervention strategies that do not exclusively target fungal growth but rather aim to reduce pathogenicity through modulation of virulence factors. Within this conceptual framework, quorum sensing signaling and fungal-derived quorum sensing molecules (e.g., farnesol, tyrosol) have attracted considerable attention, as they have been shown in several *Candida* species to influence morphogenesis, biofilm formation, and, under certain conditions, responsiveness to antifungal agents. Quorum sensing molecules applied at supraphysiological concentrations may potentially contribute to the development of novel

strategies for the treatment of biofilm-associated infections, particularly in pathogens for which current first-line therapies show limited efficacy or where rapid resistance development poses a significant risk.

Overall, the increasing burden of invasive candidiasis, the rising prevalence of non-*albicans* species, the spread of multidrug-resistant pathogens (particularly *C. auris*), and the therapeutic challenges associated with biofilms collectively justify the detailed investigation of novel antifungal strategies and alternative virulence-targeting approaches. Accordingly, the present dissertation focuses on the alternative therapeutic characteristics of *C. auris*, as well as the antifungal potential of the quorum sensing system and its associated molecules (farnesol and tyrosol), highlighting their possible role in future therapeutic innovations.

Objective

The aim of the present study was to comprehensively investigate the molecular and physiological responses of *C. auris* to fungal-derived quorum sensing molecules, specifically farnesol and tyrosol. The primary objective of our research was to elucidate the global transcriptional changes that occur in *C. auris* following exposure to these molecules and to determine how these changes contribute to the observed antifungal, growth-inhibitory, and virulence-attenuating effects.

Main objectives:

- To identify transcriptome-wide alterations following farnesol and tyrosol exposure,
- o analyze genes and enzymatic activities involved in the oxidative stress response, as well as to investigate changes in intracellular trace element concentrations (iron, zinc, manganese, copper),
- To map transcriptional modifications in key metabolic pathways, particularly fatty acid and ergosterol biosynthesis, β -oxidation, and nucleic acid synthesis,
- To determine the transcriptional patterns of genes associated with virulence, adhesion, biofilm formation, and drug efflux pumps.

Materials and Methods

Origin and Culture Conditions of *Candida auris* Isolate

For our experiments, we used a *C. auris* isolate (NCPF 8973; accession number: JNANPVY0000000000) previously fully sequenced at the genomic level by our research group. The isolate was obtained from the National Mycology Reference Laboratory in Bristol, United Kingdom. The strain belongs to the South Asian/Indian clade and exhibits a non-aggregating phenotype (Borman et al. 2017). During the experiments, the isolate was stored at -80°C in liquid Bouillon medium containing 20% glycerol. Prior to experimentation, *C. auris* was cultured and maintained on YPD (Yeast Extract Peptone Dextrose) medium (1% yeast extract [Alfa Aesar, USA], 2% microbiological peptone [Oxoid, UK], 2% glucose [VWR International LLC, Hungary], with or without 2% agar depending on whether solid or liquid medium was used; pH 5.6).

Growth Assays of *Candida auris*

For growth experiments, *Candida auris* pre-cultures were incubated in standard YPD broth at 30°C for 18 h with shaking at 2.3 Hz. Subsequently, the cell suspension was diluted with YPD medium to an optical density of 0.1 at 640 nm (OD_{640}), corresponding to approximately $2.5 \pm 0.5 \times 10^6$ CFU/mL. Cultures were then further incubated at 37°C with shaking at 2.3 Hz.

To investigate the effect of tyrosol, cultures were treated with tyrosol at a final concentration of 15 mM following 4 h of pre-incubation. Tyrosol (2-(4-hydroxyphenyl)ethanol; Merck, Hungary) was prepared as a 0.1 M stock solution in standard YPD medium, and the experimental system was established by calculating the required volume of stock solution to achieve the desired final concentration of 15 mM. Growth kinetics were monitored hourly by determining OD_{640} and CFU/mL values. The applied tyrosol concentration was considered safe and, according to our previous studies, was well tolerated by various human cell lines (Jakab et al., 2019). Measurements were performed in six independent experiments, and results are presented as mean $\pm$ standard deviation (SD). Statistical analyses were conducted using paired Student's t-tests in GraphPad Prism version 6.05 (GraphPad Software, LLC, Boston, MA, USA). Differences between tyrosol-treated cultures and untreated controls were considered statistically significant at $p < 0.05$.

The effect of farnesol on the transcriptional response was investigated using the above cultivation protocol with minor modifications. Pre-cultures were incubated in 5 mL YPD medium at 30 °C for 18 h with shaking at 2.3 Hz, diluted to an OD₆₄₀ of 0.1, and subsequently incubated at 37 °C. At the 4-h time point, farnesol was added to the cultures to achieve a final concentration of 75 µM. Farnesol (Merck, Hungary) was obtained as a 3 M stock solution and diluted in 100% methanol to prepare a 30 mM working stock solution. The experimental system was then established by calculating the required volume of the working stock solution to obtain a final concentration of 75 µM. Growth was monitored by determining temporal changes in OD₆₄₀ and CFU/mL values (Nagy et al., 2020). Experiments were also performed in six independent biological replicates, and data are presented as mean ± SD. Statistical evaluation was carried out using paired Student's t-tests, and differences between farnesol-treated and control cultures were considered statistically significant when $p < 0.05$. Microscopic Analysis Following Farnesol Exposure

Morphological and viability changes induced by farnesol were assessed using 75 µM concentration after 0, 4, and 6 hours of incubation at 37 °C. Subsequently, 1 µl of 20 mM propidium iodide (Thermo Fisher Scientific, USA) was added to 999 µl culture. Fluorescently stained cells were incubated for an additional 30 minutes at 37 °C, after which 10 µl of suspension was placed on a glass slide and examined using a Zeiss Axioskop 2 mot light microscope equipped with a Zeiss Axiocam HRc camera. Cell morphology was evaluated using phase-contrast microscopy, and the proportion of non-viable cells was determined via fluorescence microscopy. Images were further analyzed and the percentage of dead cells calculated using ImageJ software (version 2.1.0/1.53c; Fiji, ImageJ; Wayne Rasband, National Institutes of Health).

RNA Isolation

Total RNA was isolated from untreated control *C. auris* cells and cultures treated with quorum sensing molecules in three independent biological replicates. Treatments involved 75 µM farnesol or 15 mM tyrosol, depending on the experimental setup. Cells were collected by centrifugation at 4 000 g for 5 minutes at 4 °C, 2 hours post-treatment. Cells were washed three times with phosphate-buffered saline (PBS) and stored at -70 °C until further processing. For all samples, biomass was freeze-dried (CHRIST Alpha 1-2 LDplus lyophilizer, Osterode, Germany). Total RNA was extracted using TRIzol/TRISOL reagent (Invitrogen, Thermo Fisher

Scientific). RNA quality and concentration were assessed on an Agilent BioAnalyzer using the Eukaryotic Total RNA Nano kit (Agilent Technologies, Santa Clara, CA, USA), following the manufacturer's instructions. Only samples with RNA Integrity Number (RIN) > 7 were used for library preparation.

Whole Transcriptome Analysis (RNA-Seq)

Transcriptome profiling was performed using high-throughput mRNA sequencing. RNA-Seq libraries were prepared from total RNA using the NEBNext Ultra II RNA Sample Preparation Kit (New England Biolabs, Ipswich, USA) according to the manufacturer's instructions. Library preparation and sequencing were carried out at the University of Debrecen Genomic Medicine and Bioinformatics Laboratory. Sequencing was performed on an Illumina NextSeq500 platform, generating 75 bp single-end reads. Approximately 18–22 million reads per sample were obtained. Reads were aligned to the *C. auris* reference genome (https://fungi.ensembl.org/candida_auris_gca_002759435/Info/Index; features: http://www.candidagenome.org/download/gff/C_auris_B8441/archive/C_auris_B8441_version_s01-m01-r11_features_with_chromosome_sequences.gff.gz). Alignment rates ranged from 90–95% per sample. Normalized gene expression values were calculated using the DESeq algorithm in StrandNGS software. Differential expression between treated (75 μ M farnesol or 15 mM tyrosol) and untreated control samples was assessed using moderated t-tests. Multiple testing corrections were performed using the Benjamini–Hochberg false discovery rate (FDR) method, with adjusted $p < 0.05$ considered significant. Genes exhibiting at least 1.5-fold change ($FC > 1.5$ for upregulation, $FC < -1.5$ for downregulation) were considered differentially expressed. Fold change values were calculated from normalized expression data. RNA-Seq analyses were conducted on three independent biological replicates for each treatment.

Reverse Transcription Quantitative PCR (RT-qPCR)

To validate RNA-Seq results, RT-qPCR assays were performed. For tyrosol treatment, six upregulated, five downregulated, and five non-significant genes were selected for further analysis. For farnesol treatment, five upregulated, five downregulated, and five non-significant genes were validated. RT-qPCR for tyrosol-treated samples was carried out using the Xceed qPCR SG 1-step 2 $\times$ Mix Lo-ROX kit (Institute of Applied Biotechnologies, Prague, Czech Republic), following the manufacturer's instructions, with 500 ng DNase-treated total RNA per reaction (Merck, Hungary). Farnesol-treated samples were analyzed using the Luna Universal

One-Step RT-qPCR kit (New England Biolabs, USA), also with 500 ng DNase-treated total RNA (Sigma, Budapest, Hungary) per reaction. Primers were designed using OligoExplorer (v1.1) and OligoAnalyzer (v1.0.2) software and synthesized by Integrated DNA Technologies. Tyrosol measurements were performed on a LightCycler® 480 II (Roche, Switzerland), and farnesol measurements on a LightCycler® 96 (Roche, Switzerland). Three technical replicates per sample and three independent biological replicates were analyzed. Relative gene expression ($\Delta\Delta CP$) was calculated as $\Delta\Delta CP = \Delta CP_{\text{treated}} - \Delta CP_{\text{untreated}}$, where $\Delta CP = CP_{\text{reference gene}} - CP_{\text{target gene}}$, and CP represents the PCR cycle at which fluorescence threshold is crossed. ACT1 (B9J08_000486) was used as the reference gene. Values are reported as mean $\pm$ standard deviation. Statistical significance was assessed using Student's t-test, with $p < 0.05$ considered significant. $\Delta\Delta CP$ values significantly different from zero were interpreted as indicative of differential expression.

Gene Ontology (GO) Analysis

Significant GO categories were identified using the Candida Genome Database Gene Ontology Term Finder (<http://www.candidagenome.org/cgi-bin/GO/goTermFinder>) for the “function”, “process”, and “component” categories. Only hits with $p < 0.05$ were considered. In addition, functionally related gene groups were curated using the Candida Genome Database (<http://www.candidagenome.org>) and literature sources. Enrichment of *C. auris* genes in up- and downregulated gene sets was assessed using Fisher's exact test ($p < 0.05$). Statistical analyses were performed using the R platform (www.R-project.org).

(i) Virulence-related genes

The virulence gene group was compiled based on genes involved in the genetic regulation of *C. albicans* virulence and previously published gene lists. The category included genes related to adhesion, biofilm formation, morphogenesis, and stress response.

(ii) Metabolic pathway-related genes

This group included genes associated with carbohydrate, ergosterol, and fatty acid metabolic pathways according to the Candida Pathway Database (<http://pathway.candidagenome.org/>).

(iii) Genes associated with oxidative stress and antioxidant defense

The category included functionally validated or predicted antioxidant enzyme genes, such as catalases (GOID: 4096), superoxide dismutases (GOID: 4784), glutathione and glutaredoxin systems (GOID: 6749), thioredoxins (GOID: 8379 and 51920), peroxidases (GOID: 4601), and genes involved in oxidative stress response regulation.

(iv) Iron metabolism-related genes

Genes involved in iron uptake and homeostasis were compiled based on previously published gene lists, including elements of reductive iron uptake, siderophore transport, and hemoglobin utilization.

(v) Zinc, manganese, and copper homeostasis-related genes

Genes involved in zinc, manganese, and copper uptake and homeostasis were collected including transporters, regulatory factors, and key metal-metabolizing enzymes.

Analysis of Intracellular Trace Elements After Farnesol and Tyrosol Exposure

C. auris pre-cultures were grown as described, then incubated for 2 hours under various conditions with tyrosol or farnesol exposure. Cells were collected by centrifugation (5 min, 4 000 g, 4 °C). Dry cell mass (DCM) was determined by freeze-drying according to Jakab et al. (2021). Intracellular iron, zinc, manganese, and copper contents were measured using inductively coupled plasma optical emission spectrometry (ICP-OES; 5110 Agilent Technologies, USA). Prior to measurement, samples were acid-digested at atmospheric pressure using 3 ml 65% HNO₃ and 1 ml 30% H₂O₂ in sterile glass containers. Analyses were performed in three independent biological replicates. Results are expressed as mg/kg DCM ± standard deviation. Metal content changes induced by treatments were evaluated using Student's t-test, with $p < 0.05$ considered significant.

Measurement of Oxidative Stress Parameters

Reactive oxygen species (ROS) production and antioxidant enzyme activities were assessed as follows: pre-cultures were diluted to OD₆₄₀ = 0.1 in YPD and incubated at 37 °C for 4 hours. Tyrosol was then added to a final concentration of 15 mM, and cells were collected after 2 hours by centrifugation (5 min, 4 000 g, 4 °C). ROS levels were quantified via conversion of 2',7'-dichlorofluorescein diacetate (Merck, Hungary) to 2',7'-dichlorofluorescein (DCF), with fluorescence proportional to ROS concentration. Reduced and oxidized glutathione (GSH and GSSG) levels were measured using 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB; GR assay) according to Jakab et al. (2015). Activities of superoxide dismutase (SOD), catalase, glutathione reductase (GR), and glutathione peroxidase (GPx) were also determined as previously described. All measurements were performed in three independent biological replicates, results expressed as mean ± standard deviation. Differences between tyrosol-treated

and control samples were analyzed using paired Student's t-test in GraphPad Prism 6.05 (GraphPad Software, LLC, USA), with $p < 0.05$ considered statistically significant.

Results

Effect of quorum sensing molecules on *Candida auris* growth

The growth and pathogenic properties of *Candida auris* cells were assessed in the presence of different quorum sensing molecules, specifically farnesol and tyrosol. In experiments with farnesol (75 μ M, YPD medium), a marked growth inhibition was observed following addition to pre-incubated cells, which became evident as early as 2 hours post-treatment. This effect was confirmed by both optical density measurements (OD_{640}) and colony-forming unit (CFU) counts. Growth inhibition was significant within 2 hours, as indicated by the reduction in CFU counts (control: $5.8 \times 10^7 \pm 1.1 \times 10^7$ CFU/ml; farnesol-treated: $1.1 \times 10^7 \pm 0.3 \times 10^7$ CFU/ml; $p < 0.001$) and measurable differences in optical density (control: 1.28 ± 0.04 ; treated: 0.72 ± 0.04 OD_{640} ; $p < 0.001$) (Figure 7A and B). Decreased growth was also reflected in dry cell mass measurements. After 12 hours of incubation, dry biomass reached 5.5 ± 0.2 g/l in control samples, compared with only 1.3 ± 0.1 g/l in farnesol-treated cells ($p < 0.001$). The proportion of non-viable cells was $3.3\% \pm 1.2\%$, $1\% \pm 0\%$, $1.7\% \pm 0.6\%$, and $3.6\% \pm 0.6\%$ at 0 h, 4 h, and 6 h in untreated cells, and at 6 h in farnesol-treated cells following 2 hours of exposure.

Tyrosol treatment (15 mM, YPD medium) also induced a significant growth reduction within 2 hours, as evidenced by CFU counts (control: $5.6 \times 10^7 \pm 1.2 \times 10^7$ CFU/ml; treated: $2.5 \times 10^7 \pm 0.6 \times 10^7$ CFU/ml; $p < 0.001$) and OD_{640} values (control: 1.25 ± 0.09 ; treated: 1.06 ± 0.04 ; $p < 0.001$). However, tyrosol did not produce a notable effect on cell morphology. The ratio of yeast to pseudohyphal forms was similar in control ($84\% \pm 4\%$ and $16\% \pm 3\%$) and treated cells ($88\% \pm 4\%$ and $12\% \pm 2\%$) ($p > 0.05$).

In summary, while both farnesol and tyrosol inhibited *C. auris* growth within a short time frame, tyrosol had minimal impact on cell morphology or extracellular enzyme activity. In contrast, farnesol exerted a more pronounced effect on biomass reduction, suggesting potential antifungal relevance.

Transcriptomic analysis following farnesol and tyrosol treatment

The transcriptional response of *C. auris* to farnesol and tyrosol was examined via transcriptomic analysis, complemented by principal component analysis (PCA) to visualize similarities between samples. Farnesol- and tyrosol-treated cells were clearly separated from untreated controls, while biological replicates under identical conditions clustered tightly, indicating high correlation among replicates. Farnesol exposure induced substantial transcriptomic changes.

RNA-Seq analysis identified 1766 differentially expressed genes (DEGs) following farnesol treatment, including 447 upregulated and 304 downregulated genes compared to control. Tyrosol treatment yielded 615 DEGs, with 142 upregulated and 108 downregulated. Functional grouping of farnesol-sensitive genes by GO analysis revealed downregulation of virulence-associated genes involved in biofilm maturation (*RBT1*, *HWP1*, *BCR1*, *EFG1*, *DSE1*, *BRG1*, *UME6*, *ZAP1*, *RLM1*) and biofilm dispersion (*NRG1*, *UME6*), as well as genes related to morphogenesis (*EFG1*, *HWP1*, *HGC1*, *WAL1*, *VRP1*). RT-qPCR confirmed downregulation of *RBT1* and *NRG1*. Upregulated oxidative stress-related genes included *CCP1*, *SOD1*, *SOD2*, *SOD6*, *GPX1*, *DOT5*, *PRX1*, *AHP1*, as well as *HSP21*, *YPD1*, and *HOG1*. Increased transcription of catalase (*CAT1*) was also validated by RT-qPCR.

Metabolic pathway analysis showed that farnesol inhibited transcription of gluconeogenesis key enzymes (*PCK1*, *FBP1*) but did not affect glycolysis or TCA cycle genes. Genes involved in the glyoxylate cycle (*ACO2*, *ICL1*, *MDH1–3*) and fatty acid β -oxidation (*POX1*, *ECI1*, *FAT1*, *FAA21*, *POT1*) were upregulated, whereas inositol-1-phosphate synthase (*INO1*) expression was decreased.

Genes associated with ion homeostasis, including reductive iron uptake (*FRE10*, *FET31*, *SMF12*, *FTR1*), siderophore transport (*SIT1*), hemoglobin utilization (*RBT5*), and manganese (*SMF1*), copper (*CRP1*), and zinc metabolism (*CSR1*), were downregulated. Upregulation of *POT1* was confirmed by RT-qPCR. Farnesol treatment also increased transcription of 60 genes related to transmembrane transport, including putative drug transporters (*MDR1*, *CDR1*, *CDR4*, *HOL3*, *YOR1*), several carbohydrate transporters (*HGT2*, *HGT17*, *HGT19*, *HXT5*), amino acid transporters, and phosphate/sulfate transporters (*PHO84*, *PHO89*, *GIT1*, *SUL2*). Upregulation of *CDR1*, *MDR1*, and *HGT2* was confirmed by RT-qPCR.

Tyrosol treatment upregulated virulence-associated genes involved in adhesion (*ALS4*, *ALS9*, *IFF4*), lipase secretion (*LIP4*), biofilm maturation (*RBT1*, *XOG1*), and morphogenesis (*HYR1*).

Stress response genes (*HSF1*, *HSP21*, *HSP78*, *HSP104*) were also upregulated, while *BCR1*, *NRG1*, *WAL1*, and *VRP1* were downregulated.

Metabolically, tyrosol reduced transcription of genes involved in reductive iron uptake (*CFL4*, *FRE9*, *FRE10*, *FTR1*, *FTR2*), hemoglobin utilization (*RBT5*, *HMX1*, *CSA2*), and fatty acid biosynthesis (*FAS1*, *FAS2*), but did not affect carbohydrate or ergosterol metabolism genes. DNA replication genes, including MCM complex subunits, were downregulated. Oxidative stress-related genes, such as *CAT1*, *SOD1*, *GPX1*, *YCP4*, *CAP1*, and *CIP1*, were upregulated, whereas *SOD4* transcription decreased. These changes were confirmed by RT-qPCR.

Comparative analysis indicated that farnesol induced more pronounced transcriptomic changes than tyrosol. Farnesol upregulated 381 genes and downregulated 258, whereas tyrosol upregulated 76 genes and downregulated 62. Notably, 66 genes were commonly upregulated and 46 commonly downregulated by both treatments. Several DNA replication genes were specifically downregulated by tyrosol, whereas farnesol predominantly enhanced transcription of genes involved in transmembrane transport, fatty acid metabolism, β -oxidation, and sulfate assimilation.

Effects of farnesol and tyrosol on oxidative stress processes and intracellular metal ion content in *C. auris*

Farnesol and tyrosol exposure significantly affected the intracellular metal ion content of *C. auris* cells, though the magnitude and direction of change differed. Farnesol treatment significantly reduced intracellular iron, manganese, and zinc levels compared to untreated controls (–24%, –73%, and –69%), while copper content increased dramatically by 302%, indicating a fundamental reorganization of metal ion homeostasis (iron: 152.2 ± 21.1 mg/kg vs. 116.0 ± 10.0 mg/kg; manganese: 67.9 ± 5.1 mg/kg vs. 18.6 ± 1.8 mg/kg; zinc: 787.8 ± 22.2 mg/kg vs. 245.8 ± 34.4 mg/kg; copper: 274.6 ± 15.7 mg/kg vs. 828.8 ± 106.4 mg/kg; $p < 0.05$ –0.001).

Tyrosol treatment produced more moderate yet significant changes: intracellular iron, manganese, zinc, and copper decreased by 25%, 37%, 34%, and 55%, respectively, relative to controls (iron: 155.7 ± 17.9 mg/kg vs. 114.3 ± 16.2 mg/kg; manganese: 69.3 ± 4.2 mg/kg vs. 42.6 ± 1.14 mg/kg; zinc: 735.4 ± 18.5 mg/kg vs. 516.5 ± 22.1 mg/kg; copper: 259.9 ± 16.1 mg/kg vs. 123.5 ± 9.8 mg/kg; $p < 0.05$ –0.001).

Overall, both treatments substantially altered cellular metal ion homeostasis, potentially impacting metabolic processes and oxidative stress responses.

Discussion

Alternative therapeutic strategies targeting quorum sensing have recently become increasingly attractive, particularly against difficult-to-treat, multidrug-resistant pathogens such as *C. auris*. Previous studies reported that fungal-derived quorum sensing molecules exhibit pronounced antifungal activity and, when combined with conventional antifungals, can act as strong adjuvants, especially at supra-physiological concentrations. Nagy et al. (2020) demonstrated that supra-physiological farnesol exposure significantly reduces the growth rate of planktonic *C. auris* cells and the metabolic activity of biofilms. Furthermore, treatment with 75 μ M farnesol significantly decreased the number of viable fungal cells recovered from the kidneys in immunosuppressed, systemically infected mouse models.

RNA-Seq-based transcriptomic analysis represents an important tool for comprehensively understanding the mechanisms underlying the antifungal effects of these molecules. In *C. albicans*, it has been shown that farnesol at supra-physiological concentrations modulates the transcription of multiple genes. Cao et al. (2005) reported that farnesol exposure increased the expression of *TUP1* (morphogenesis-related), *FCR1* (drug resistance-related), *FTR2* (iron transport-related), and *CHT2/CHT3* (chitinases), whereas *CSH1* (cell surface hydrophobicity-related), *HSP70*, *HSP90*, *SSA2* (heat shock proteins), *PDR16* (drug resistance), and *CRK1/PDE2* (morphogenesis-related) genes were downregulated.

Previous studies have also demonstrated that farnesol induces reactive oxygen species (ROS) production in a dose-dependent manner in *C. albicans*. Farnesol further affects the transcription of *CAT1*, *SOD1*, and *SOD2*, key genes in oxidative stress response in *C. albicans*. These findings are consistent with observations in *C. auris* by Nagy et al. (2020), where several putative oxidative stress-responsive genes (*CAT1*, *GPX1*, *SOD1*, *SOD2*, *SOD6*) were upregulated following farnesol exposure. Notably, farnesol enhanced *HOG1* transcription, a key regulator of fungal oxidative stress response, further supporting the role of farnesol-induced oxidative stress in *C. auris*. This is corroborated by increased DCF levels and superoxide dismutase activity in farnesol-treated cultures.

Recent transcriptomic data showed that farnesol treatment affects transcription of genes involved in iron homeostasis and alters *C. auris* intracellular iron, zinc, manganese, and copper levels. Downregulation of iron uptake genes correlated with significantly reduced intracellular iron in farnesol-exposed cells. Similarly, oxidative stress induced by menadione sodium bisulfite affected transcription of iron homeostasis genes and iron content in *C. albicans* cells.

It is plausible that responses linked to reduced iron constitute a general defense mechanism aimed at minimizing damage induced by farnesol and menadione via divalent iron-mediated oxidative reactions. Prior studies indicate that elevated free intracellular iron promotes ROS formation and mediates iron-dependent cell death in *S. cerevisiae*.

The *CSR1* gene, encoding a major transcription factor stabilizing zinc homeostasis and providing zinc-dependent protection against farnesol-induced oxidative stress, was downregulated, corresponding to the observed decrease in intracellular zinc. Zinc is essential for oxidative stress defense as a structural component of superoxide dismutase, a key enzyme for neutralizing superoxide radicals. In contrast, manganese at high concentrations acts predominantly as an antioxidant rather than promoting ROS generation. Farnesol inhibited transcription of *SMF1*, responsible for maintaining intracellular manganese levels for antioxidant defense, and also downregulated *PMR1*, leading to reduced fungal virulence (Bates et al., 2005). These findings align with our previous results showing that daily farnesol treatment significantly reduced *C. auris* virulence. Downregulation of *CRP1* and *CCC2* may be linked to the significantly elevated copper content and marked growth inhibition observed in farnesol-treated cells. Copper participates in numerous cellular processes in pathogenic fungi, and excess copper can generate ROS via the Fenton reaction and disrupt iron-sulfur clusters, further compromising cell viability. Elevated free copper in farnesol-exposed cells may contribute to increased redox imbalance as measured by DCF, accompanied by increased superoxide dismutase activity.

Farnesol exposure also significantly upregulated multiple fatty acid β -oxidation genes (*POX1*, *ECI1*, *FAT1*, *FAA21*, *POT1*). Enhanced removal of excess membrane lipids and increased fatty acid utilization may provide greater metabolic flux required to maintain membrane fluidity. Jabra-Rizk et al. (2006) and Rossignol et al. (2007) demonstrated that farnesol affects membrane permeability in non-*albicans* species, such as *C. dubliniensis* and *C. parapsilosis*. The elevated β -oxidation activity may explain the membrane-associated farnesol effects and is consistent with previously observed antifungal activity. Another potential explanation is the decreased transcription of ergosterol biosynthesis genes, altering membrane permeability and fluidity. For example, Dižová et al. (2018) reported that 200 μ M farnesol reduced *ERG20*, *ERG11*, and *ERG9* transcription in *C. albicans*. In our study, *ERG6* expression decreased after farnesol exposure, potentially enhancing farnesol passive diffusion across membranes and increasing *C. auris* sensitivity to oxidative stress. *ERG6* mutants in *Cryptococcus neoformans* exhibited reduced heat tolerance, heightened oxidative stress sensitivity, and increased

antifungal susceptibility, explaining previously observed azole synergy. *ERG6* mutants were completely avirulent in invertebrate models, potentially explaining the reduced *C. auris* virulence after daily farnesol treatment.

Additionally, *INO1*, encoding inositol-1-phosphate synthase, a key enzyme in inositol and phosphatidylinositol synthesis, was downregulated after farnesol exposure, which may explain the synergistic effects between farnesol and azoles in *C. auris*, since *INO1* is highly upregulated in resistant *Candida* isolates.

Farnesol exposure also significantly increased transcription of efflux pump-related genes (*CDR1*, *CDR4*, *MDR1*, *HOL3*, *YOR1*), while *SNQ2* was downregulated. These transporters contribute to *C. auris* drug resistance. Srivastava and Ahmad observed downregulation of *CDR1*, *CDR2*, *MDR1*, *MDR2*, and *SNQ2* in the presence of farnesol. It is important to note that the concentration used to induce transcriptional upregulation in their study differed approximately 1,000-fold from that used here. Our results support the hypothesis that lower concentrations of farnesol may act as substrates for upregulated transport proteins, providing cellular protection against farnesol-induced oxidative stress.

In the second part of our study, the effects of tyrosol were investigated and compared to those observed with farnesol. After 2 hours of exposure, tyrosol significantly inhibited *C. auris* growth. A similar pattern was observed in *C. parapsilosis*, where inhibition correlated with downregulation of ribosome biosynthesis genes. Interestingly, 15 mM tyrosol exposure in *C. auris* did not significantly alter ribosome biosynthesis gene transcription; however, several DNA replication-related genes were downregulated, providing a molecular explanation for the observed growth inhibition. Similar growth-inhibitory effects were reported by Cordeiro et al. (2015) at 2.5–5.0 mM in other non-albicans species, including *C. tropicalis* and *C. glabrata*. Adampour et al. (2022) showed that tyrosol-treated planktonic *C. glabrata* cells suffered significant damage in the cell wall, membrane, cytoplasm, nucleus, and mitochondria. In other fungi (*Coccidioides posadasii*, *Histoplasma capsulatum*), tyrosol reduced membrane ergosterol content and increased membrane permeability. Similar inhibitory effects were observed in *Sporothrix* species in both filamentous and yeast forms.

The reduced growth rate may also be partly explained by elevated ROS levels in the presence of tyrosol. Previous studies have shown that fungal quorum sensing molecules generate oxidative stress at supra-physiological concentrations. Differences exist between the effects of farnesol and tyrosol on oxidative stress in various *Candida* species. *C. auris* possesses a unique stress-resistance profile compared with other *Candida* species. In our study, increased oxidative

stress was accompanied by elevated catalase, superoxide dismutase, and glutathione peroxidase activity. However, the number of upregulated antioxidant genes was considerably lower than in *C. parapsilosis* after tyrosol treatment (6 vs. 18 genes). Notably, *SOD4* was significantly downregulated, a gene critical for detoxification in *C. albicans*, potentially explaining the reduced virulence observed in vivo under daily tyrosol treatment. *CAT1* was upregulated in *C. auris* following tyrosol exposure, similar to observations in *C. parapsilosis*. In *C. albicans*, *CAT1* transcription correlates with hydrogen peroxide resistance after farnesol exposure, suggesting that catalase induction enhances oxidative stress resistance and is a reliable marker of oxidative stress resilience. Tyrosol-induced *CAT1* upregulation likely indicates activation of preventive mechanisms against oxidative stress.

The role of oxidative stress in antifungal activity is further supported by significant decreases in intracellular iron, manganese, copper, and zinc, which are essential for oxidative stress defense. Downregulation of iron uptake genes (*CFL4*, *FRE9*, *FRE10*, *FTR1*, *FTR2*) reduced intracellular iron, constituting a general defense strategy against divalent iron-mediated oxidative damage, similar to the effect of farnesol. Manganese is a key antioxidant in *Candida* species, whereas reduced zinc and copper levels impair superoxide dismutase function. Moreover, *Candida* adaptive responses depend heavily on zinc and copper concentrations, especially during transitions between commensal, environmental, and infectious states.

Regarding virulence, a general downregulation of genes encoding various virulence factors was observed. Monteiro et al. (2015) reported that tyrosol negatively affects adhesion. Metabolic activity profiling showed that tyrosol treatment reduced overall metabolic activity by 22–51% in *C. albicans*. Surprisingly, in our study, adhesion-related genes (*ALS4*, *ALS9*, *IFF4*) were significantly upregulated. In *C. albicans*, *IFF4* contributes to adhesion both in vitro and in vivo, with increased expression during late biofilm formation. *Iff4Δ* null mutants exhibit reduced adhesion during early biofilm formation. Tyrosol plays a key role in *C. albicans* morphogenesis and biofilm formation; its role in *C. auris* biofilm formation remains to be elucidated. In our study, tyrosol treatment induced only minor changes in biofilm-related gene expression, suggesting effects primarily on later biofilm events. The biofilm-promoting gene *RBT1* was upregulated by tyrosol, whereas its regulator *BCR1* ortholog was significantly downregulated, differing from responses observed in *C. parapsilosis*. Additionally, *NRG1* (a hyphal development repressor) was downregulated, potentially promoting filamentous elements, concurrent with *ALS4* upregulation, which showed increased expression in pseudohyphal *C. auris* cells.

RNA-Seq analysis revealed downregulation of two key fatty acid biosynthesis genes (*FAS1*, *FAS2*), associated with reduced pathogenicity and virulence. In prior work, tyrosol treatment decreased expression of delta12-fatty acid desaturase (*FAD2*) and omega-3 fatty acid desaturase (*FAD3*) in *C. parapsilosis*, reducing overall fitness. Collectively, tyrosol exerts broad effects on fatty acid metabolism, which may be exploited for novel antifungal strategies targeting these pathways.

The experimental work forming the basis of this dissertation represents the first comprehensive study analyzing global transcriptional changes in *C. auris* following quorum sensing molecule exposure (farnesol and tyrosol), providing new insights into their antifungal mechanisms. Transcriptomic analysis indicates that both molecules significantly enhance oxidative stress response at supra-physiological concentrations, accompanied by decreased intracellular microelement levels (especially iron, zinc, and manganese) and redox imbalance. Substantial transcriptional changes were also observed in fatty acid metabolism (particularly β -oxidation), ergosterol and fatty acid biosynthesis, nucleic acid synthesis, adhesion, and drug efflux pumps. Collectively, these findings provide a molecular explanation for observed growth-inhibitory and virulence-reducing effects, highlighting that quorum sensing molecules exert antifungal activity through complex, multi-target mechanisms. The elucidated molecular relationships contribute not only to a deeper understanding of *C. auris* stress adaptation and pathogenicity but also lay the groundwork for innovative therapeutic strategies to more effectively treat this multidrug-resistant pathogen.

New findings

- Farnesol significantly inhibited the growth of *Candida auris*, an effect that was detectable even after short exposure times and was associated with a reduction in the metabolic activity of the fungal cells.
- Based on transcriptomic analysis, farnesol treatment reduced the transcription of genes associated with biofilm formation, morphogenesis, and virulence, indicating an attenuation of pathogenicity.
- Farnesol induced a significant oxidative stress response in *Candida auris*, which was accompanied by increased transcription of genes associated with antioxidant enzymes and stress adaptation, as well as elevated activity of antioxidant enzymes.
- Farnesol exposure significantly altered intracellular metal ion homeostasis in *Candida auris*, as evidenced by decreased levels of iron, manganese, and zinc, along with an increased copper concentration.
- Tyrosol also inhibited the growth of *C. auris*; however, its effect was primarily associated with reduced transcription of genes involved in the cell cycle and DNA replication.
- Quorum sensing molecules induced substantial changes in lipid metabolism: farnesol increased the transcription of genes involved in fatty acid β -oxidation, whereas tyrosol decreased the transcription of genes associated with fatty acid biosynthesis, suggesting a reorganization of cell membrane structure and function.

Summary

Candida auris has emerged over the past decade as one of the most significant multidrug-resistant opportunistic fungal pathogens, responsible for severe nosocomial outbreaks worldwide. Its outstanding clinical relevance is attributed to its multidrug resistance, environmental persistence, biofilm-forming capacity, and invasive infections associated with high mortality rates. Current therapeutic options remain limited; therefore, there is an urgent need to explore novel and alternative antifungal strategies. In recent years, quorum sensing molecules—particularly farnesol and tyrosol—have gained increasing attention as promising virulence-modulating compounds with potential antifungal activity.

The aim of the present study was to investigate the global changes in gene transcription in *C. auris* following exposure to farnesol and tyrosol. Our results demonstrated that both molecules significantly enhanced the oxidative stress response, as evidenced by increased activities of antioxidant enzymes (such as catalase, superoxide dismutase, and glutathione peroxidase) and the upregulation of several oxidative stress-related genes. This was accompanied by a disruption of redox homeostasis and a decrease in the intracellular concentrations of certain microelements—particularly iron, zinc, and manganese—which may contribute to increased cellular vulnerability. Significant alterations were also observed in lipid metabolism. Farnesol exposure upregulated genes associated with β -oxidation, while both molecules affected pathways related to ergosterol and fatty acid biosynthesis. These changes may lead to modifications in cell membrane composition and fluidity, potentially explaining the observed growth inhibition and altered susceptibility to antifungal agents. In addition, tyrosol treatment resulted in the downregulation of genes involved in DNA replication and nucleic acid synthesis, providing a molecular explanation for the reduced proliferative capacity.

The transcription of genes involved in adhesion and biofilm formation was also modulated, suggesting that quorum sensing molecules influence *C. auris* pathogenicity in a complex manner. The reduced expression of certain virulence factors is consistent with previously reported in vivo decreases in virulence. Overall, our findings indicate that farnesol and tyrosol exert their effects in *C. auris* through multiple interconnected molecular mechanisms. The induction of oxidative stress, alterations in microelement homeostasis, modulation of lipid and nucleic acid metabolism, and regulation of virulence-associated genes collectively contribute to their antifungal and virulence-attenuating effects.

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