



Review

Farnesol as a Multifunctional Regulator of Fungal Biology: Mechanisms and Significance

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Abstract

Farnesol is a small isoprenoid metabolite that has emerged as a key regulator of fungal biology beyond its original identification as a quorum-sensing molecule in *Candida albicans*. This review examines farnesol across pathogenic and non-pathogenic fungi, emphasizing its roles in morphogenesis, biofilm development, stress adaptation, membrane-associated physiology, and ecological interaction. In pathogenic fungi, farnesol modulates virulence-related traits, antifungal susceptibility, and host interaction, while in non-pathogenic systems, it influences growth, differentiation, and metabolic balance. Evidence from *Saccharomyces cerevisiae*, *Trichoderma*, *Candidozyma auris* (formerly known as *Candida auris*), and other fungi highlights the context-dependent nature of its effects. We also discuss farnesol biosynthesis, secretion, and the apparent absence of canonical salvage pathways in fungi. Together, these findings support a broader view of farnesol as a multifunctional fungal metabolite that links signaling with metabolism. Understanding its diverse biological roles may clarify fungal evolution and inform future strategies targeting fungal persistence, adaptation, and antifungal tolerance.

Keywords: farnesol; fungal quorum sensing; morphogenesis; fungal metabolism; secondary metabolites



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1. Introduction

Farnesol is a small sesquiterpene alcohol and a biologically active fungal metabolite. It is generated by dephosphorylation of farnesyl diphosphate (FPP), whereas FPP, not free farnesol, is the central isoprenoid intermediate used for sterol biosynthesis and protein prenylation [1]. Farnesol was first identified as a quorum-sensing molecule in *Candida albicans*, where Hornby et al. demonstrated density-associated accumulation and inhibition of the yeast-to-hypha transition [2–4]. Subsequent studies have shown that exogenous farnesol can affect biofilm formation, growth, morphogenesis, stress adaptation, and interactions with other microorganisms across diverse fungi. Subsequent studies have

shown that exogenous farnesol can affect biofilm formation, growth, morphogenesis, stress adaptation, and interactions with other microorganisms across diverse fungi [5]. However, evidence that these responses constitute bona fide quorum sensing is strongest for *C. albicans*; in other species, the more cautious terms ‘response to exogenous farnesol’ or ‘farnesol-associated phenotype’ are preferable unless density-dependent production, signal specificity, and a reproducible response to purified farnesol have been demonstrated [6,7]. In pathogenic fungi, farnesol can modulate traits that shape colonization, persistence, and disease outcome, whereas in non-pathogenic fungi, it may participate in growth regulation, developmental transitions, and ecological interactions [8,9]. This dual relevance makes farnesol especially compelling from both mechanistic and evolutionary perspectives. Rather than functioning as a simple quorum-sensing signal, it is increasingly recognized as a multifunctional metabolite whose effects depend strongly on species context, concentration, developmental state, and environmental conditions [4,10]. The core features of farnesol biology in fungi are summarized in Table 1.

This review differs from earlier farnesol-focused reviews by critically comparing pathogenic, opportunistic pathogenic, and predominantly non-pathogenic fungi within a common metabolic and ecological framework. Rather than treating all reported effects as equivalent evidence of quorum sensing, we distinguish observations based on exogenous exposure from evidence for endogenous, density-dependent signaling. We also explicitly separate the metabolic roles of FPP from the signaling and stress-associated activities attributed to free farnesol, evaluate dose- and model-dependent discrepancies, and assess the translational maturity and limitations of proposed applications, particularly within the broader context of fungal secondary metabolism and chemical communication networks [11,12].

Table 1. Core features of farnesol biology in fungi.

Feature	Key Points	Evidence Level/Interpretation	Ref.
Chemical identity	Farnesol is a 15-carbon sesquiterpene alcohol produced by dephosphorylation of farnesyl diphosphate (FPP).	Biochemical interpretation based on fungal isoprenoid metabolism.	[10]
Formation of FPP	Isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) first generate geranyl diphosphate (GPP); addition of a further IPP produces FPP.	Established isoprenoid-pathway biochemistry.	[10]
Role of FPP	FPP, rather than free farnesol, is the branch-point metabolite used in sterol biosynthesis and protein prenylation.	Essential distinction required for accurate interpretation of farnesol biology.	[10]
Formation of GGPP	Geranylgeranyl diphosphate synthase adds IPP to FPP to form geranylgeranyl diphosphate (GGPP).	Established isoprenoid-pathway biochemistry.	[10]
Quorum sensing in <i>C. albicans</i>	Endogenously produced farnesol accumulates as cell density increases and inhibits the yeast-to-hyphal transition.	Strong direct evidence for a quorum-sensing role in <i>C. albicans</i> .	[2]
Condition dependence	Germ-tube inhibition requires approximately 1–2 μ M farnesol in defined medium but up to 250 μ M in serum-containing medium.	In vitro; demonstrates that medium composition substantially alters apparent farnesol potency.	[13]
Farnesol biosynthesis	The FPP phosphatase Cwh8 contributes to farnesol production in <i>C. albicans</i> .	Genetic and biochemical evidence in <i>C. albicans</i> ; conservation across fungal taxa remains uncertain.	[10]
Farnesol salvage	Exogenous farnesol can accumulate intracellularly, but fungal cells show no demonstrated canonical pathway that salvages it back to FPP.	Direct evidence in <i>C. albicans</i> and supportive evidence in other studied fungi; should not be generalized to all fungal lineages without qualification.	[10]

Table 1. Cont.

Feature	Key Points	Evidence Level/Interpretation	Ref.
Biofilm modulation	Farnesol inhibits biofilm formation and alters biofilm architecture in selected <i>C. albicans</i> models.	In vitro; outcome varies with concentration, strain, growth medium, and biofilm developmental stage.	[14,15]
Stress-associated activity	High exogenous concentrations can cause growth inhibition, oxidative stress, mitochondrial dysfunction, and apoptosis-like phenotypes in some fungi.	Mainly in vitro; high-dose toxicity should not be conflated with physiological quorum sensing.	[16,17]
Interpretation outside <i>C. albicans</i>	Farnesol production or a response to exogenous farnesol does not alone establish quorum sensing.	A quorum-sensing claim requires density-dependent accumulation, physiological signal concentrations, specificity, and a reproducible response to a purified compound.	[2,10]

A comparative review of farnesol across pathogenic, opportunistic pathogenic, and predominantly non-pathogenic fungi is therefore timely for several reasons. First, the literature remains dominated by studies in *Candida*, leaving broader fungal diversity relatively underexplored [6,18,19]. Second, recent work suggests that farnesol biology is more complex than earlier models implied, with roles that extend from signaling and stress modulation to possible links with membrane and mitochondrial function [4,9,20,21]. Third, understanding how different fungi produce, sense, and respond to farnesol may clarify how this molecule evolved and why it has been retained across fungal lineages [10].

In this review, farnesol is examined as a context-dependent fungal metabolite with relevance to signaling, pathogenesis, and fungal ecology. The discussion moves from its biochemical basis to its roles in pathogenic fungi, then to its functions in non-pathogenic species, and finally to its translational implications and unresolved questions. This framework is intended to clarify both what is known and what remains uncertain about one of the most intriguing small molecules in fungal biology.

Peer-reviewed primary studies were prioritized for mechanistic findings, concentrations, synergism, transcriptomics, and in vivo outcomes; reviews were used chiefly for contextual synthesis. Studies were assessed for fungal species and strain, farnesol exposure conditions, experimental model, and evidence level. Reports that did not distinguish free farnesol from FPP, or that lacked interpretable experimental conditions, were considered cautiously.

2. Biosynthesis, Regulation, and Cellular Context

Farnesol is a fungal isoprenoid alcohol produced from FPP. In the mevalonate pathway, isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) are first condensed to form geranyl diphosphate (GPP); a second IPP molecule is then added to GPP to generate FPP. FPP can be dephosphorylated to farnesol, whereas FPP itself is the branch-point precursor for sterol biosynthesis, including squalene formation, and for protein prenylation [22,23]. Addition of a further IPP unit to FPP by geranylgeranyl diphosphate synthase generates geranylgeranyl diphosphate (GGPP), as summarized in Figure 1 [21]. Thus, farnesol should not be described as the direct central intermediate of sterol biosynthesis or as a prenyl-group donor. Farnesol should therefore be viewed as a product of FPP dephosphorylation that can report or perturb isoprenoid-pathway status, rather than as a substitute for FPP in sterol synthesis or prenylation reactions [4,24].

In *C. albicans*, farnesol production and secretion are closely tied to physiological state, particularly growth phase, cell density, and environmental conditions [25]. Earlier studies showed that extracellular accumulation of farnesol contributes to the inoculum-size effect and helps regulate morphological transitions, especially the yeast-to-hypha

switch [4,26]. More recent work suggests that transcriptional regulators influence both synthesis and secretion, supporting the view that farnesol production is actively controlled rather than being a passive metabolic by-product [10]. The recent identification of Cwh8 as a farnesyl diphosphate phosphatase essential for farnesol biosynthesis has provided critical mechanistic insight, with *cwh8ΔΔ* mutants showing a >99% reduction in farnesol production and hyperfilamentous growth [27].

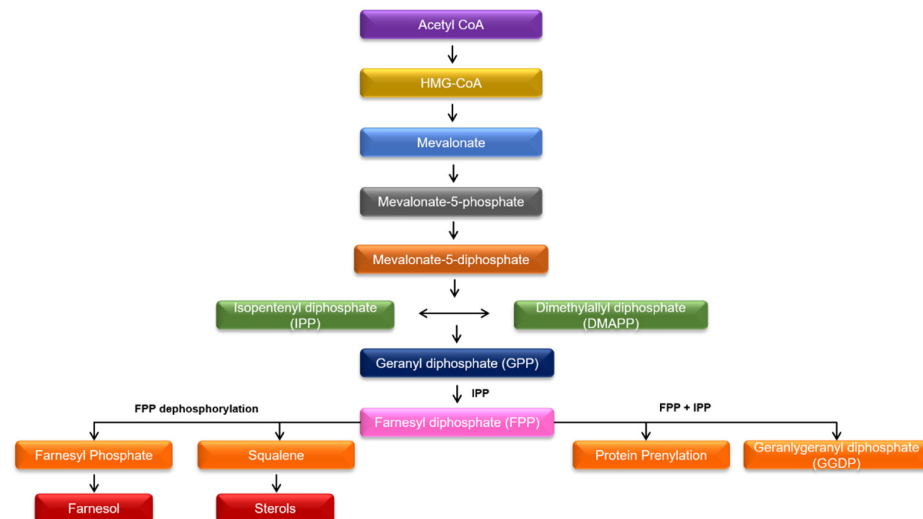


Figure 1. Farnesol formation from farnesyl diphosphate and major FPP-dependent isoprenoid branches in fungi. The fungal mevalonate pathway generates isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP), which are sequentially condensed to form geranyl diphosphate (GPP) and subsequently farnesyl diphosphate (FPP). FPP is a central branch-point metabolite that supports squalene and ergosterol biosynthesis, protein prenylation, and formation of geranylgeranyl diphosphate (GGPP). In contrast, free farnesol is generated through FPP dephosphorylation via farnesyl phosphate.

The distinction between intracellular and extracellular farnesol is important for interpreting its function. Extracellular farnesol can act as a signal sensed by neighboring cells, whereas intracellular farnesol may influence membrane-associated or metabolic processes within the producing cell [4]. Recent evidence in *C. albicans* indicates that exogenous farnesol increases intracellular farnesol levels but is not apparently metabolized through a detectable salvage route, suggesting that fungi can accumulate and respond to farnesol without efficiently converting it back into farnesyl diphosphate [10]. This supports the idea that farnesol biology depends on compartment-specific effects rather than simple metabolic recycling.

The question of salvage or recycling is particularly important because current evidence suggests that fungi may lack a canonical farnesol salvage pathway. In contrast to bacteria, plants, and animals, where farnesol can be converted back into prenylated intermediates, fungal studies so far support the absence of this pathway in both *Saccharomyces cerevisiae* and *C. albicans* [4,10]. This strengthens the interpretation that free farnesol is not routinely recycled to FPP for sterol biosynthesis in fungi. However, biological effects of exogenous farnesol should be interpreted in relation to the tested concentration, solvent, strain, growth phase, medium, and exposure duration, because these variables substantially influence the threshold between signaling-associated and stress-associated phenotypes.

From a methodological standpoint, farnesol is not always straightforward to study because it is a small, hydrophobic, and partly volatile molecule. Its detection and quantification depend on extraction conditions, analytical sensitivity, and careful separation from related isoprenoids [28], while studies using overlays or sealed systems show how loss dur-

ing culture can affect measured levels. Differences in strain background, culture medium, growth stage, and analytical platform can all influence apparent farnesol production or response. This methodological variability helps explain why apparent contradictions remain in the literature and why standardized measurement will be important for future work [4,28]. Furthermore, farnesol sensitivity has been shown to depend on mating type locus (MTL), with heterozygous MTL α / α diploids being more tolerant than haploids, and the mechanisms of farnesol tolerance encompassing a wide range of physiological functions, including ubiquinone type and energy availability [29]. Beyond its signaling-associated roles, exogenous farnesol can exert direct antifungal or stress-inducing activity by inducing or modulating reactive oxygen species production, disturbing mitochondrial and membrane-associated functions, and triggering apoptosis-like phenotypes in selected experimental systems [30]. Its interactions with conventional antifungal agents are variable rather than uniformly synergistic and must be interpreted according to the species, drug, concentration, and assay model used [9,31]. Its potential for clinical application is being explored through nanotechnology-based delivery systems to overcome its hydrophobicity and volatility [32,33].

3. Farnesol in Pathogenic Fungi

Among pathogenic fungi, farnesol has been studied most extensively in *C. albicans*, where it was first identified as a secreted quorum-sensing molecule that suppresses the yeast-to-hypha transition [2,4,6]. This discovery positioned farnesol as a key regulator of fungal morphogenesis and opened the broader field of density-dependent signaling in fungi [25,34]. Subsequent work, however, has shown that its biological significance extends well beyond morphogenetic control, encompassing biofilm development, stress adaptation [30], mitochondrial homeostasis [35], antifungal responsiveness, and virulence-associated behavior [4,19,32,36]. The major cellular outcomes associated with farnesol across fungal systems are shown in Figure 2.

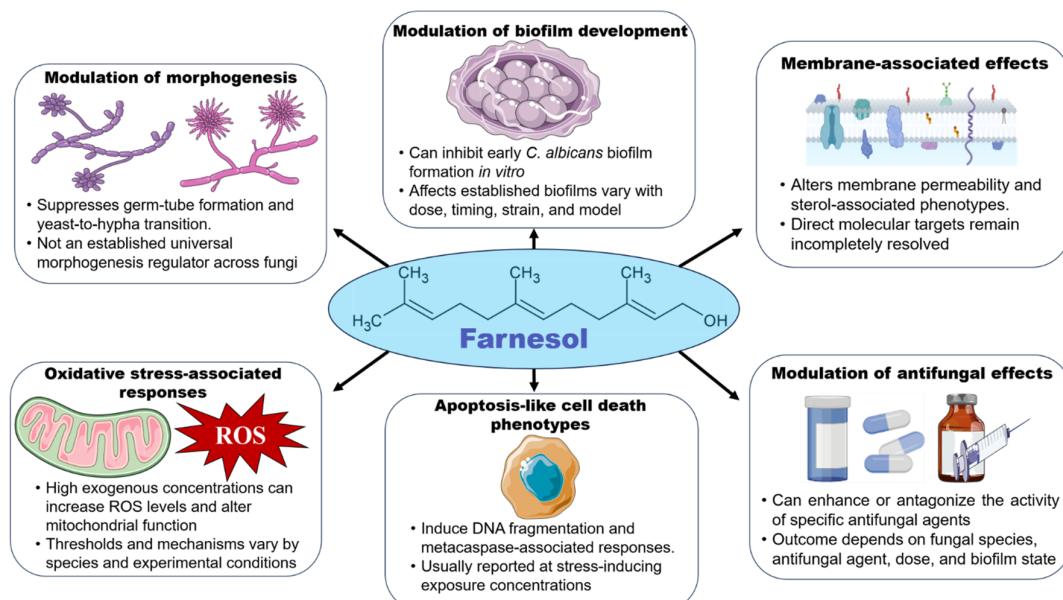


Figure 2. Reported cellular outcomes of exogenous farnesol exposure in fungi. In *C. albicans*, farnesol is an endogenous quorum-sensing molecule that suppresses germ-tube formation and the yeast-to-hypha transition under defined hypha-inducing conditions [2,13]. Exogenous farnesol can also inhibit early *C. albicans* biofilm development, although its effects on established biofilms depend on the concentration, timing of exposure, strain, growth medium, and assay model [14,15]. At stress-inducing concentrations, farnesol has been associated with reactive oxygen species accumulation, mitochondrial dysfunction, and

apoptosis-like phenotypes in selected fungal models [16]. Membrane-associated effects, including altered permeability and sterol-associated phenotypes, have been reported following farnesol exposure in *Coccidioides posadasii* [18]. Farnesol can also modify the activity of antifungal agents against *Candida* biofilms; however, both synergistic and antagonistic interactions have been reported, depending on the fungal isolate, antifungal agent, farnesol dose, and biofilm state [37,38]. Thus, the figure summarizes context-dependent responses to exogenous farnesol rather than universal fungal functions.

In *C. albicans*, the best-characterized effect of farnesol is inhibition of germ tube formation and hyphal development, processes closely tied to tissue invasion, immune evasion, and pathogenic fitness [21,34,39]. Because filamentation is a major determinant of pathogenicity in this species, the ability of farnesol to restrain this developmental switch initially suggested a predominantly anti-virulence role [4]. This interpretation was reinforced by studies showing that exogenous farnesol interferes with early biofilm formation, reduces biofilm maturation [40], and alters fungal behavior in multispecies communities [6,32,41]. In this context, farnesol functions as a negative regulator of developmental escalation, helping prevent uncontrolled filamentation as cell density rises [4,31,34]. Representative effects of farnesol in pathogenic fungi are listed in Table 2.

Table 2. Reported effects of farnesol in pathogenic fungi, in the context of experimental conditions.

Organism	Reported Effect	Farnesol Concentration	Exposure Duration	Experimental Model	Evidence Level	Interpretation	Ref.
<i>C. albicans</i>	Inhibition of germ-tube formation and yeast-to-hypha transition	1–2 μ M in defined medium; up to 250 μ M in serum-containing medium	3 h	In vitro hypha-induction/germ-tube assays	Strong evidence for endogenous quorum sensing	Apparent potency is strongly influenced by medium composition and hypha-inducing conditions.	[2,13]
<i>C. albicans</i>	Inhibition of initial biofilm formation	30 μ M	24 h	In vitro early biofilm assay	In vitro evidence	Farnesol addition at the initial attachment phase is more inhibitory than treatment of mature biofilms.	[14]
<i>C. albicans</i>	Altered mature-biofilm architecture and modulation of <i>ERG20</i> , <i>ERG9</i> , and <i>ERG11</i> expression during fluconazole treatment	200 μ M	48 h	In vitro mature biofilm; farnesol–fluconazole treatment	In vitro mechanistic association	Transcript changes do not establish direct molecular targets.	[15]
<i>C. albicans</i>	Interaction with fluconazole, amphotericin B, and micafungin against biofilms	75–300 μ M	24 h	In vitro biofilm checkerboard assay	In vitro combination-study evidence	Drug interactions vary by farnesol dose, antifungal agent, and biofilm maturity.	[37]
<i>C. albicans</i>	Modulation of susceptibility to fluconazole, 5-flucytosine, terbinafine, and itraconazole in resistant biofilms	30–300 μ M	24 h	In vitro resistant-biofilm assay	In vitro combination-study evidence	Both synergistic and antagonistic interactions have been reported; farnesol is not a universal antifungal adjuvant.	[38]
<i>C. auris</i>	Reduced planktonic growth and inhibition of biofilm formation	125–300 μ M	24 h	In vitro planktonic and biofilm assays using drug-resistant clinical isolates	In vitro evidence	<i>C. auris</i> is predominantly yeast-form; these observations do not support a generalized hyphal-inhibition claim.	[42]
<i>C. auris</i>	Reduced fungal burden in disseminated infection	75 μ M	Once daily for 5 days	Immunocompromised murine disseminated-candidiasis model	Limited in vivo preclinical evidence	One murine model does not establish clinical efficacy, safety, or pharmacokinetic feasibility.	[43]

Table 2. Cont.

Organism	Reported Effect	Farnesol Concentration	Exposure Duration	Experimental Model	Evidence Level	Interpretation	Ref.
<i>C. auris</i>	Increased echinocandin activity against developing and mature biofilms	125–300 μ M	24 h	In vitro biofilms treated with anidulafungin, caspofungin, or micafungin	In vitro combination-study evidence	Effects require validation across clades, isolates, and clinically relevant drug exposures.	[42]
<i>C. auris</i>	Enhanced fluconazole activity and altered <i>CDR1</i> and <i>ERG11</i> expression	125 μ M	24 h	Resistant clinical isolates; in vitro susceptibility and gene-expression analysis	In vitro mechanistic association	Expression changes are associative and do not prove direct molecular targeting.	[44]
<i>Cryptococcus neoformans</i> species complex	Growth inhibition with limited alteration of selected virulence-associated exoenzymes	25–150 μ M	48 h	In vitro growth and exoenzyme assays	In vitro evidence	Growth inhibition does not necessarily indicate reduced virulence in vivo.	[45]
<i>Paracoccidioides brasiliensis</i>	Reduced growth and altered morphogenesis	25–300 μ M	48 h	In vitro growth and dimorphic-transition assay	In vitro evidence	Supports a response to exogenous farnesol, not an established endogenous quorum-sensing system.	[46]
<i>Coccidioides posadasii</i>	Growth inhibition, reduced ergosterol content, increased permeability, and interaction with azoles	0.29–75 μ M	48 h	In vitro susceptibility, ergosterol, permeability, and drug-interaction assays	In vitro evidence	Effects may reflect membrane-active stress; direct targets and in vivo relevance are unresolved.	[18]
<i>Penicillium expansum</i>	Reactive oxygen species accumulation, mitochondrial dysfunction, metacaspase activation, and apoptosis-like cell death	25–100 μ M	24 h	In vitro filamentous-fungus stress and cell-death assays	In vitro, stress-associated phenotype	High-exposure stress phenotypes should not be interpreted as evidence of physiological quorum sensing.	[47]

Yet the role of farnesol in pathogenic fungi is not adequately captured by the idea of a simple quorum-sensing inhibitor. A more nuanced picture has emerged in which farnesol exerts highly context-dependent effects that may either limit or support fungal pathogenicity [4]. In addition to controlling morphogenesis, farnesol influences multiple physiological pathways linked to fungal fitness under host-relevant conditions, including oxidative stress responses, membrane-associated functions, energy metabolism, and cellular survival [30,34,39]. Recent syntheses of the field also emphasize that farnesol may act not only as an extracellular signaling molecule but also as an intracellular effector with consequences for mitochondrial function and broader cellular physiology [4,34].

One major reason for this interpretive complexity is that farnesol can induce apoptosis-like death under some conditions while promoting adaptation or persistence under others. In *C. albicans*, exposure to farnesol has been associated with oxidative stress, mitochondrial dysfunction, and programmed cell death-like processes, indicating that elevated levels can be directly cytotoxic [4,39]. Similar effects have been documented in other fungal pathogens, including *P. expansum*, in which farnesol triggers reactive oxygen species accumulation, mitochondrial disorganization, metacaspase activation, and apoptotic hallmarks [47]. These observations support the interpretation that farnesol can act as a stress-active metabolite in specific exposure conditions. Because much of this evidence derives from in vitro experiments and, in several cases, single studies, it does not establish a universal mechanism across fungi or demonstrate that comparable effects occur during infection.

Its effects on biofilms further illustrate this duality. Biofilm-associated infections are among the most difficult fungal infections to treat because biofilm growth increases tolerance to environmental stress and antifungal therapy. Farnesol can inhibit biofilm

establishment and disrupt aspects of biofilm maturation in *C. albicans*, thereby reducing one of the major pathogenic strategies of this organism [6,32,48]. At the same time, the outcome depends on timing, concentration, and growth state, suggesting that farnesol is best understood as a modulator of biofilm dynamics rather than a universal biofilm suppressor [32,49]. This distinction is important in review writing because it avoids overstating farnesol as uniformly antifungal.

A similarly complex pattern is evident in studies of antifungal susceptibility. Farnesol has frequently been investigated as an experimental adjuvant that may alter the activity of conventional antifungal drugs, particularly in in vitro biofilm models. The evidence base remains heterogeneous, with outcomes shaped by the fungal species and strain, biofilm maturation stage, farnesol dose, antifungal concentration, and method used to define synergy [32]. However, its interaction with antifungal agents is not uniformly synergistic, and reported outcomes vary depending on organism, compound, and experimental setting [25]. This variability likely reflects the fact that farnesol influences several interrelated processes, including membrane physiology, stress signaling, and mitochondrial status, all of which can shape drug response in distinct ways. Accordingly, farnesol should be discussed not as a predictable sensitizer, but as a biologically active modifier of susceptibility whose effects must be interpreted in context.

Although *C. albicans* remains the principal model, evidence from other pathogenic fungi indicates that farnesol activity is not confined to a single species. In *C. auris*, an emerging multidrug-resistant opportunistic pathogen, exogenous farnesol has shown inhibitory activity in vitro and reduced fungal burden in a limited immunocompromised murine model [43]. These findings are promising but remain preclinical; they do not yet establish safety, pharmacokinetic feasibility, or clinical efficacy in difficult-to-treat candidiasis [50]. In the *Cryptococcus neoformans* species complex, farnesol inhibits growth but does not appear to markedly alter certain virulence-related exoenzymes [45], suggesting that growth suppression and virulence modulation may be partially separable in this genus. In *P. brasiliensis*, farnesol interferes with growth and morphogenesis [46], extending its relevance to dimorphic fungal pathogens beyond *Candida*. Together, these observations support the idea that farnesol acts across phylogenetically diverse pathogens, although the exact cellular outcomes differ between taxa. Species-specific responses to farnesol in representative pathogenic fungi are illustrated in Figure 3.

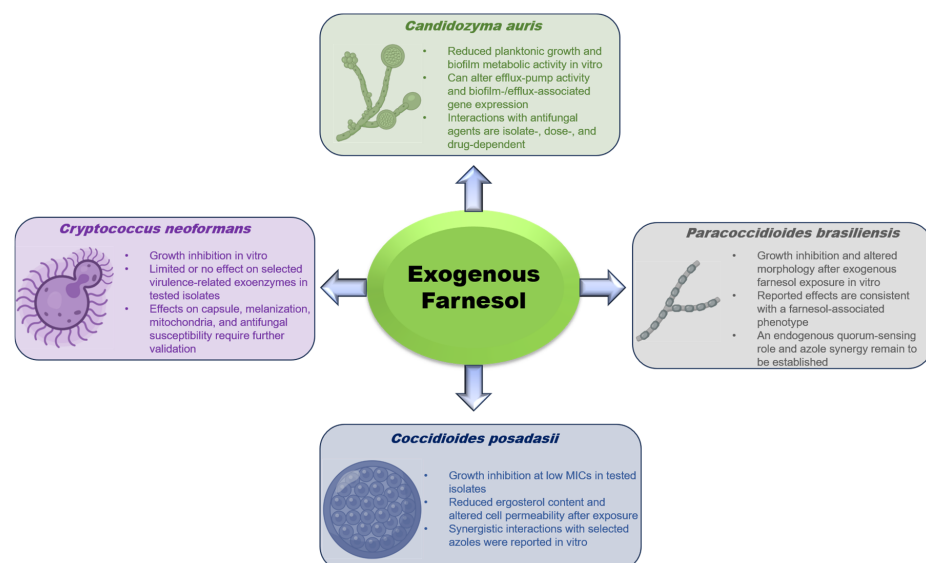


Figure 3. Reported responses to exogenous farnesol in selected pathogenic and opportunistic pathogenic fungi. In *C. auris*, exogenous farnesol has been associated with reduced planktonic growth and biofilm

metabolic activity, as well as changes in efflux-associated and biofilm-associated gene expression; interactions with antifungal agents depend on the isolate and experimental conditions [42,43,51]. In *Cryptococcus neoformans*, farnesol inhibits growth in vitro but has limited effects on selected virulence-related exoenzymes in the tested isolates [45]. In *P. brasiliensis*, farnesol exposure affects growth and morphology in vitro [46]. In *C. posadasii*, farnesol inhibits growth and is associated with reduced ergosterol content, altered cell permeability, and in vitro interactions with selected azoles [18]. The figure summarizes species- and context-dependent experimental responses; it does not imply that farnesol acts as an endogenous quorum-sensing signal in every fungus.

Overall, the literature supports a balanced interpretation of farnesol in pathogenic fungi. On one hand, it can suppress filamentation, interfere with biofilm development, and enhance antifungal control under certain conditions, all of which argue for an anti-virulence or antifungal-like role [6,7,29]. On the other hand, it is also integrated into fungal physiology in ways that may promote adaptation, survival, or infection-related fitness depending on dose, localization, developmental state, and species background [31,34,39]. Farnesol is therefore best regarded not as a unidirectional virulence inhibitor, but as a multifunctional and context-dependent pathogenicity modulator. That conceptual shift is essential for understanding why farnesol remains both biologically intriguing and therapeutically ambiguous in fungal pathogenesis [23].

4. Farnesol in Non-Pathogenic Fungi and Ecological Interactions

Although the literature on farnesol is dominated by pathogenic fungi, studies in non-pathogenic systems have become increasingly important for determining whether its functions are evolutionarily conserved or specialized for host-associated lifestyles [52]. In these fungi, the emphasis shifts away from virulence and toward physiology, development, metabolic coordination, and environmental interaction [34,52]. This broader perspective is essential because it places farnesol within general fungal biology rather than treating it solely as a pathogenicity-related molecule.

A particularly informative model in this regard is *S. cerevisiae*, which has provided insight into how farnesol affects growth and cellular homeostasis outside the context of mammalian infection [53]. Experimental studies in *S. cerevisiae* have shown that farnesol can inhibit growth, promote reactive oxygen species generation, and indirectly disrupt mitochondrial electron transport, thereby linking this metabolite to oxidative stress and energy metabolism [20,54,55]. Additional work indicates that farnesol can inhibit translation and restrict growth in both *S. cerevisiae* and *C. albicans* [29,56], suggesting that at least part of its cellular action is conserved across pathogenic and non-pathogenic yeasts. The identification of ubiquinone side-chain length as a determinant of farnesol resistance has further shown that *S. cerevisiae* engineered to produce longer ubiquinone side chains (UQ9 instead of UQ6) was 4–5 times more resistant to exogenous farnesol, with greatly reduced reactive oxygen species production [55]. These findings support the view that farnesol is not simply a quorum-sensing molecule of pathogenic fungi, but a metabolically active compound capable of influencing core eukaryotic processes. The broader roles of farnesol in non-pathogenic fungi and ecological interactions are summarized in Figure 4.

Predominantly non-pathogenic filamentous fungi add an important ecological dimension. In *T. harzianum*, overexpression of *dpp1* increased farnesol production and altered squalene and ergosterol levels, linking FPP dephosphorylation to isoprenoid homeostasis. However, the available study did not demonstrate improved antifungal activity, biomass accumulation, conidiation, or stress tolerance; instead, increased *dpp1* expression reduced tomato-root colonization to approximately 52% of the control level. These findings support a role in metabolic regulation and fungus–plant interaction, but they do not justify claims

that elevated farnesol promotes ecological fitness or root colonization [52]. Notably, in *Trichoderma*, increased farnesol production does not simply translate into enhanced antifungal activity [52], indicating that its role in non-pathogenic fungi may be more closely related to internal metabolic regulation and environmental responsiveness than to direct antagonism alone [19].

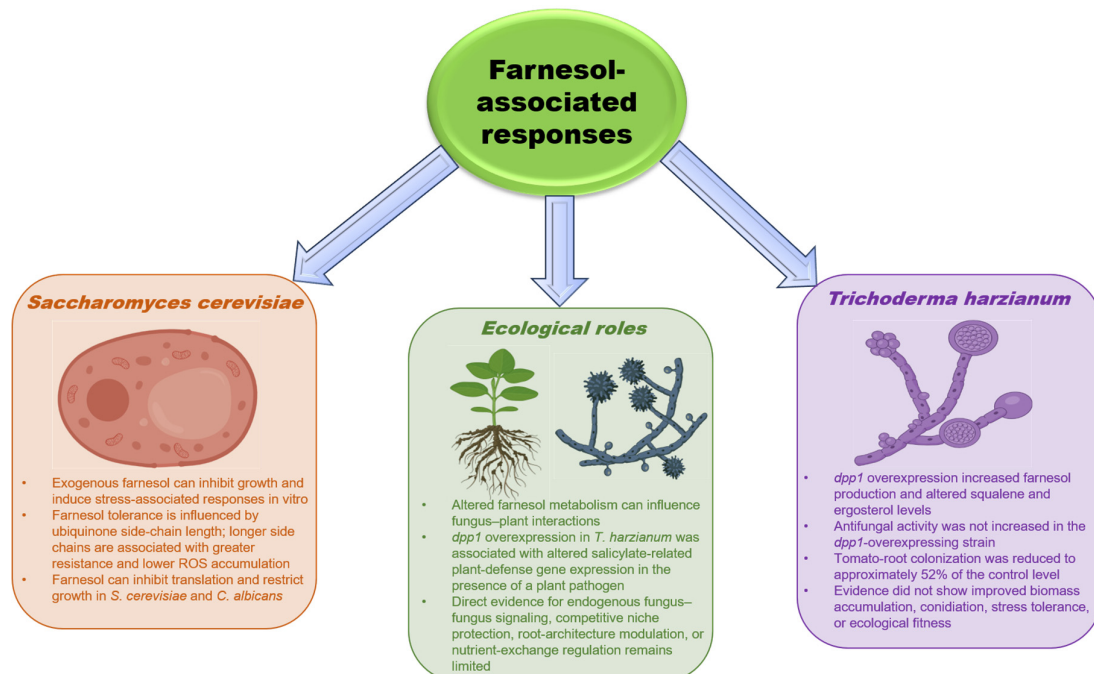


Figure 4. Reported farnesol-associated phenotypes in predominantly non-pathogenic fungi and fungus–plant models. In *S. cerevisiae*, exogenous farnesol can inhibit growth and induce stress-associated responses; farnesol tolerance is influenced by ubiquinone side-chain length, and farnesol can inhibit translation in both *S. cerevisiae* and *C. albicans* [55,56]. In *T. harzianum*, *dpp1* overexpression increased farnesol production and altered squalene and ergosterol levels, but did not improve anti-fungal activity and reduced tomato-root colonization to approximately 52% of the control level [52]. Altered farnesol metabolism was also associated with changes in plant defense-related responses, but direct evidence that farnesol mediates endogenous fungus–fungus communication or broad ecological signaling remains limited [52].

The ecological relevance of farnesol becomes even clearer in fungus–environment interactions. In *Trichoderma*–plant systems, altered *dpp1* expression and farnesol production were associated with altered plant defense-related responses and reduced root colonization. These observations suggest that fungal farnesol metabolism can influence fungus–plant interactions, although the causal contribution of farnesol relative to concurrent changes in other isoprenoid metabolites requires further experimental resolution [52]. These findings raise the possibility that altered farnesol metabolism may influence ecological interactions beyond the fungal cell; however, direct evidence that free farnesol functions as an endogenous ecological signal remains limited [57]. In this setting, farnesol can be understood as part of a broader metabolic language linking physiology to habitat-level interaction [52,58]. Representative effects of farnesol in non-pathogenic fungi and ecological settings are summarized in Table 3.

Table 3. Farnesol in non-pathogenic fungi and ecological settings.

Organism or System	Main Reported Effect	Concentration and Exposure	Experimental Model	Evidence Level	Interpretation	Ref.
<i>S. cerevisiae</i>	Growth inhibition and oxidative-stress-associated responses to exogenous farnesol	100 μ M farnesol for 24 h	In vitro growth and oxidative-stress assays	In vitro	A response to externally added farnesol does not establish an endogenous quorum-sensing mechanism.	[16,17]
<i>S. cerevisiae</i>	Increased tolerance to farnesol associated with altered ubiquinone side-chain length	50 μ M farnesol for 24 h	Engineered yeast strains; ROS and growth assays	In vitro; mechanistic genetic evidence	Identifies a possible determinant of farnesol tolerance under laboratory exposure, not necessarily an ecological signaling role.	[4,55]
<i>S. cerevisiae</i> and <i>C. albicans</i>	Translation inhibition and reduced growth after farnesol exposure	100 μ M farnesol for 2 h for translation-related analyses	In vitro translation and growth assays	In vitro	Direct targets and relevance at physiological extracellular farnesol concentrations remain unclear.	[56]
<i>T. harzianum</i>	<i>dpp1</i> overexpression increased farnesol production and altered squalene and ergosterol levels	No exogenous farnesol was added	Metabolite, gene-expression, and physiological assays	In vitro/ fungal–plant model	Demonstrates linkage between FPP dephosphorylation and isoprenoid homeostasis; free farnesol is not a direct ergosterol precursor.	[52]
<i>T. harzianum</i>	Increased <i>dpp1</i> expression reduced tomato-root colonization to approximately 52% of the control	No exogenous farnesol was added.	Tomato root-colonization assay	Plant-associated model	Contradicts any claim that increased farnesol improves plant-root colonization or ecological fitness.	[52]
<i>T. harzianum</i> -plant interaction	Altered fungal isoprenoid metabolism was associated with changes in plant defense-related responses	No exogenous farnesol was added.	Plant–fungus interaction model	Plant-associated model	Concurrent changes in FPP flux, squalene, ergosterol, and other metabolites prevent attribution solely to free farnesol.	[52]
<i>Saccharomycopsis fibuligera</i>	Changes in morphogenesis and squalene biosynthesis after farnesol exposure	50 μ M farnesol for 24 h before phenotypic, transcriptomic, and metabolomic analyses.	In vitro phenotyping, transcriptomics, and metabolomics	In vitro; multi-omics association	Omics associations require functional validation of causal targets.	[59]
Mixed fungal or polymicrobial communities	Altered biofilm architecture, fungal growth, or interspecies outcomes after farnesol addition	30–300 μ M farnesol for 24–48 h, depending on the species composition and the biofilm or co-culture model used.	In vitro mixed-culture systems	In vitro	Exogenous-addition experiments do not prove endogenous interspecies signaling.	[14]

Evidence also suggests that farnesol-associated phenotypes occur in fungi not traditionally central to quorum-sensing research. Reports that *S. cerevisiae* produces farnesol under defined culture conditions, together with its response to exogenous farnesol, indicate that production and responsiveness are not confined to *Candida* [60–62]. Nevertheless, these observations alone do not establish a quorum-sensing system; this would require evidence of density-dependent accumulation, physiological concentrations, signal specificity, and reproducible responses to purified endogenous compound [29]. Even where direct signaling roles remain incompletely established, the ability of non-pathogenic fungi to produce or respond to farnesol strengthens the argument that this molecule has broader evolutionary roots in fungal metabolism [4,10,29].

Comparison with pathogenic fungi is particularly informative here. In both pathogenic and non-pathogenic fungi, farnesol is tied to growth control, stress responses, membrane-associated metabolism, and developmental regulation [6,34]. What differs is the biological framing: in pathogens, these effects are often interpreted through their consequences for virulence, whereas in non-pathogenic fungi, they are more naturally understood in terms of environmental adaptation, competitive fitness, and metabolic coordination. This distinction

suggests that at least some pathogenic roles of farnesol may represent ecological functions that were later co-opted into host-associated biology [10,27].

Taken together, the available evidence is consistent with, but does not prove, an evolutionary model in which farnesol-associated metabolic and stress responses preceded specialized quorum-sensing functions in pathogenic contexts. Comparative phylogenetic, chemical-ecological, and density-dependent signaling studies are required to resolve the evolutionary origin of fungal farnesol signaling [4,23]. From this perspective, quorum sensing in *C. albicans* may represent one prominent expression of a more general fungal capacity to use isoprenoid metabolites as internal and external regulatory cues [4,27]. This comparative view strengthens the rationale for studying pathogenic and non-pathogenic fungi together, because only such a framework can reveal which aspects of farnesol biology are deeply conserved and which are lineage- or lifestyle-specific.

5. Biological and Translational Implications of Farnesol in Fungal Control

The relevance of farnesol to fungal control is best understood as a direct extension of its biological effects on fungal development, metabolism, and stress adaptation. Rather than functioning as a detached therapeutic concept, this topic follows naturally from the observation that farnesol modulates filamentation, biofilm architecture, ergosterol-associated pathways, and cellular responses to environmental stress. In this sense, the translational value of farnesol lies not only in fungistatic activity, but also in its ability to perturb regulatory states that underpin fungal persistence and pathogenic fitness [7,9,63].

One of the clearest preclinical implications concerns biofilm control. Because farnesol can suppress the yeast-to-hypha transition and interfere with biofilm maturation in *Candida* species under selected conditions, it has attracted attention as a possible means of weakening fungal communities that are otherwise highly tolerant to antifungal treatment. However, its activity is strongly influenced by dose, timing of exposure, strain background, biofilm stage, and the experimental model [6,7]. Studies of *C. albicans* biofilms show that higher concentrations of farnesol reduce biofilm robustness, inhibit hyphal development, and alter the expression of ergosterol-pathway genes such as *ERG20*, *ERG9*, and *ERG11*, indicating that its anti-biofilm action is mechanistically linked to fungal developmental and metabolic regulation [15,48]. This is conceptually important because it shows that farnesol-based control strategies do not merely damage fungal cells; they destabilize the physiological programs that sustain biofilm-associated growth.

The same principle extends to antifungal susceptibility. In multiple experimental systems, farnesol has modified the activity of conventional antifungal agents, including fluconazole, amphotericin B, micafungin, and related compounds, although the outcome is strongly context-dependent [7,9,64]. In resistant *C. albicans* biofilms, synergistic effects have been reported with fluconazole and 5-fluorocytosine, whereas antagonism has been observed with terbinafine and itraconazole [7,31], underscoring that farnesol does not function as a universally beneficial adjuvant. A study investigating in vitro interactions between farnesol and fluconazole, amphotericin B, or micafungin against *C. albicans* biofilms found significant synergy between each of the three antifungal agents and farnesol, with the greatest synergistic effect observed for the farnesol/micafungin combination (observed effects 39–52% higher than expected if acting independently) [37]. These variable outcomes are best interpreted in light of its broader biological actions on membrane organization, ergosterol homeostasis, and biofilm state, all of which can reshape fungal sensitivity in ways that are mechanistically meaningful but pharmacologically unpredictable [41].

Drug-resistant fungi provide an especially informative test case. In *C. auris*, exogenous farnesol inhibits planktonic growth, alters biofilm metabolic activity, and can modify

triazole susceptibility in experimental systems [44]; a reduction in fungal burden has been reported in an immunocompromised murine model [43]. These data constitute early pre-clinical evidence rather than a validated therapeutic strategy [7,65]. Recent transcriptomic analyses further show that farnesol exposure in *C. auris* biofilms affects pathways associated with morphogenesis, ergosterol biosynthesis, glycolysis, fatty acid oxidation, iron metabolism, autophagy, and stress adaptation [65]. These findings support a broader interpretation in which farnesol is valuable because it reprograms fungal physiology at multiple levels, thereby shifting the state of the cell toward one that may be less robust, less biofilm-competent, or more drug-responsive.

The biological and translational relevance of farnesol is not restricted to *Candida*. In *C. posadasii*, exogenous farnesol inhibits growth, alters ergosterol biosynthesis, and increases cell permeability, again linking its practical significance to membrane- and sterol-related physiology [18]. Such observations are consistent with the idea that the translational promise of farnesol emerges from conserved aspects of fungal biology rather than from a narrow, species-specific pharmacological effect. This broader framing is particularly useful in a review centered on fungi and metabolites, because it allows antifungal relevance to be discussed as a consequence of metabolite biology instead of as an isolated clinical add-on. The translational implications and key limitations of farnesol-based control strategies are summarized in Table 4.

Table 4. Translational relevance, evidence maturity, and limitations of farnesol-based approaches to fungal control.

Proposed Application	Rationale/Reported Effect	Representative Evidence	Evidence Maturity	Limitations	Ref.
Modulation of <i>C. albicans</i> morphogenesis	Farnesol inhibits germ-tube formation and the yeast-to-hypha transition under selected conditions.	1–2 μM in defined media and up to 250 μM in serum-containing media.	In vitro; strong biological evidence for <i>C. albicans</i> quorum sensing	No evidence that inhibiting morphogenesis alone produces safe or durable therapeutic benefit in humans.	[2,13]
Biofilm control	Farnesol can inhibit early biofilm development and alter biofilm structure in <i>C. albicans</i> .	In vitro biofilm studies; one 48 h model tested 200 μM farnesol.	In vitro	Effects depend on dose, strain, medium, timing, and biofilm maturation stage; in vivo validation is limited.	[14,15]
Antifungal adjuvant	Farnesol can alter antifungal activity in <i>Candida</i> biofilms.	Synergy with fluconazole, amphotericin B, micafungin, or 5-flucytosine in some experiments; antagonism with terbinafine or itraconazole in others.	In vitro	No universal synergistic effect; dose ratio, fungal isolate, drug class, and assay design strongly influence results.	[37,38]
Activity against <i>C. auris</i>	Farnesol reduced growth and biofilm metabolic activity and showed limited in vivo activity in one murine model.	100–300 μM in vitro; daily 75 μM treatment in the cited animal study.	In vitro plus limited in vivo evidence	No clinical studies; safety, pharmacokinetics, optimal formulation, and reproducibility across <i>C. auris</i> clades are unresolved.	[43,51]
Echinocandin enhancement against <i>C. auris</i> biofilms	Farnesol increased echinocandin activity in biofilm combination assays.	Anidulafungin, caspofungin, and micafungin combinations tested in vitro.	In vitro	Requires validation in animal infection models and under pharmacologically achievable exposure conditions.	[51]
Fluconazole enhancement against <i>C. auris</i>	Farnesol enhanced fluconazole activity and was associated with altered <i>CDR1</i> and <i>ERG11</i> expression.	Resistant clinical isolates tested in vitro.	In vitro	Expression changes are associative; clinical relevance and drug-exposure compatibility are unknown.	[44]
Direct antifungal stress induction	High exogenous farnesol levels can trigger ROS accumulation, mitochondrial dysfunction, and apoptosis-like cell death.	In vitro fungal cultures.	In vitro	Host-cell toxicity, poor solubility, volatility, and uncertain selectivity limit systemic therapeutic use.	[16,47]

Table 4. Cont.

Proposed Application	Rationale/Reported Effect	Representative Evidence	Evidence Maturity	Limitations	Ref.
Topical, local, or device-associated delivery	Hydrophobicity makes encapsulation, coatings, emulsions, and local delivery conceptually attractive.	Mostly formulation-oriented or laboratory-stage studies.	Conceptual/early preclinical	Controlled release, chemical stability, host compatibility, toxicology, and in vivo efficacy remain to be established.	[51]
Biological probe	Farnesol perturbs morphogenesis, stress responses, mitochondrial function, and biofilm physiology.	Diverse in vitro systems across fungi.	Strong research-tool rationale; not a treatment indication	Molecular targets and the distinction between primary signaling and secondary stress responses remain unresolved.	[10,16]

Host interaction adds a further layer of complexity and significance. Farnesol can influence epithelial and immune responses, including the induction of TLR2 expression, IL-6 production, and human beta-defensin 2 in epithelial cells [66,67]. These findings indicate that farnesol operates not only within fungal cells or fungal communities, but also at the fungal-host interface [68]. Accordingly, any discussion of fungal control must recognize that the effects of farnesol may arise from combined modulation of fungal physiology and host response [68], rather than from a single direct antifungal mechanism [69].

At the same time, this complexity explains why direct therapeutic translation remains challenging. Farnesol is hydrophobic and partly volatile, has dose-dependent and context-dependent effects, and may affect both fungal and host cells. Major translational barriers include limited aqueous solubility, uncertain pharmacokinetics and tissue exposure, potential host toxicity, formulation instability, incomplete target definition, and the scarcity of rigorous in vivo and clinical studies. Nanocarrier, topical, surface-coating, and combination-treatment strategies are plausible approaches, but they require pharmacokinetic, toxicological, and efficacy validation before clinical claims can be made [7,9,33]. In a murine vulvovaginitis model, for example, farnesol alone was not protective and showed only limited benefit in combination with fluconazole [70], despite favorable in vitro anti-biofilm results. Such discrepancies highlight the need for caution and suggest that farnesol is unlikely to become a straightforward standalone antifungal agent without substantial advances in formulation, delivery, and mechanistic targeting [71].

Taken together, the most coherent view is that farnesol has biological and translational significance because it exposes vulnerable connections among fungal morphogenesis, sterol metabolism, biofilm biology, stress adaptation, and host interaction. Its greatest value may therefore lie not in direct therapeutic deployment alone, but in serving as a biological probe, an adjuvant scaffold, or a guide for designing strategies that interfere with fungal state transitions essential for persistence and pathogenicity [7,9,65].

6. Future Perspectives

Farnesol is increasingly viewed not only as a quorum-sensing molecule in *C. albicans* but also as a metabolite that intersects with isoprenoid homeostasis, redox balance, and fungal developmental programs. Outside *C. albicans*, the available evidence more conservatively supports farnesol-associated responses or effects of exogenous farnesol unless quorum-sensing criteria have been directly tested [4,34]. In this sense, one of the most important future directions is to consider farnesol as a regulator of fungal metabolism rather than as a molecule confined to morphogenesis alone [19,69]. This perspective is supported by studies in *C. albicans* showing that farnesol exposure alters metabolic responses under hypha-inducing conditions [27,28,72], and by work in *T. harzianum* linking farnesol production to changes in ergosterol, squalene, and growth-related physiology [52]. Multi-omics investigations in *S. fibuligera* have further revealed that farnesol regulates morphogenesis and squalene biosynthesis, reinforcing the connection between this molecule and sterol

metabolism across fungal lineages [59]. This broader conceptual framework is depicted in Figure 5.

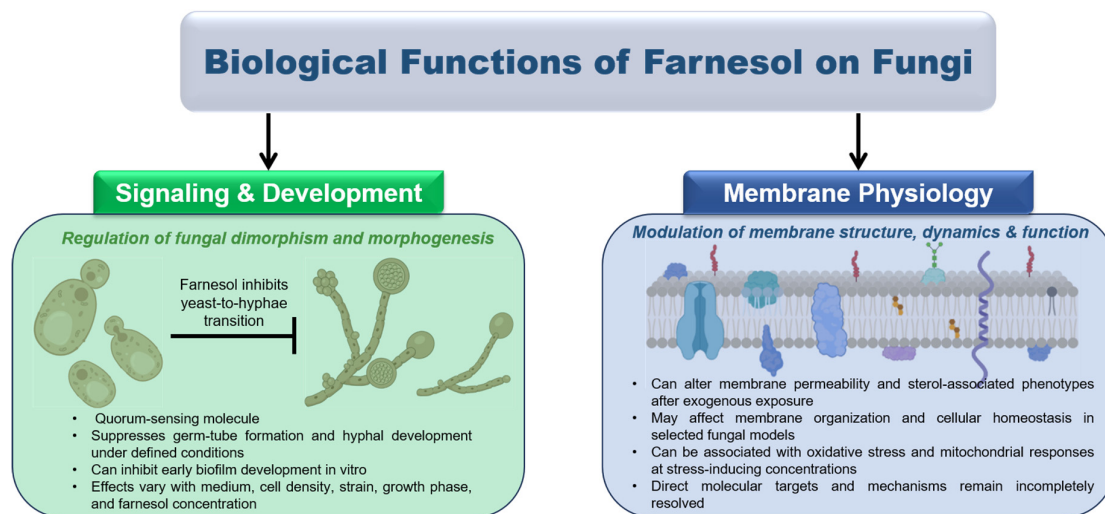


Figure 5. Reported biological effects of farnesol in fungi. In *C. albicans*, farnesol is an endogenous quorum-sensing molecule that suppresses the yeast-to-hypha transition and can inhibit early biofilm development under defined experimental conditions [2,13,14]. In diverse fungal models, exogenous farnesol has also been associated with membrane permeability changes, sterol-associated phenotypes, oxidative-stress responses, mitochondrial effects, and apoptosis-like cell-death phenotypes; these outcomes are strongly dependent on species, strain, concentration, growth conditions, and exposure duration [16,18]. Free farnesol should be distinguished from farnesyl diphosphate (FPP), which is the branch-point metabolite used in sterol biosynthesis and protein prenylation.

A broader metabolic perspective is also justified by the fact that fungal secondary metabolism is deeply integrated with ecological adaptation and chemical communication. In fungi, secondary metabolite production is not merely a specialized chemical output, but part of a larger system that helps organisms compete, colonize, and respond to environmental change [6]. Farnesol may therefore be considered alongside other biologically active fungal metabolites as a candidate regulator of such adaptive programs, particularly in contexts where growth state, nutrient availability, and interspecies interactions shape metabolite flux [28].

Evidence from non-pathogenic and filamentous fungi supports this interpretation. In *Trichoderma*, manipulating farnesol biosynthesis affects downstream sterol-related metabolites and can influence plant-fungal interactions, indicating that farnesol may help coordinate physiological outputs beyond simple self-signaling [52]. In *S. cerevisiae*, farnesol exposure produces stress-related and translational effects [55,56], reinforcing the idea that its influence extends to conserved cellular processes relevant to both ecology and metabolism. Together, these findings argue that farnesol can function as a metabolic cue that links isoprenoid pathway status to broader cellular behavior.

One possible future research direction is the use of farnesol or carefully designed analogs to modulate biologically important fungal metabolites. This remains a hypothesis rather than an established application because direct evidence that farnesol reliably redirects secondary-metabolite output across multiple fungal species is limited. This idea is attractive because fungal metabolite biosynthesis is often coupled to developmental state, membrane composition, and stress responses [4,27]. However, this should be framed cautiously: the current literature supports the concept that farnesol influences fungal physiology and metabolite balance, but direct evidence that it reliably redirects secondary-metabolite production across multiple fungi remains limited [52]. For that reason, a strong review

should present this as an evidence-based research direction rather than as an established biotechnological application.

Another useful perspective is ecological. Farnesol may contribute to fungus-fungus and fungus-environment interactions by modulating growth and responses to host- or plant-associated niches. However, direct evidence for an endogenous ecological signaling role remains limited; future studies should quantify endogenous farnesol across population densities, test the purified compound at physiological concentrations, and distinguish farnesol-specific effects from generalized hydrophobic or stress responses [6,52]. Because dimorphism, biofilm formation, and metabolic state are deeply tied to ecological success in fungi, the ability of farnesol to influence these features suggests that it may have been conserved as a broad adaptive signal before being co-opted into pathogen-associated functions [4]. This helps explain why farnesol biology appears across both pathogenic and non-pathogenic fungi [73], even though the downstream outcomes differ by lifestyle. For instance, in *Cryptococcus neoformans*, farnesol inhibits growth but does not markedly alter virulence-related exoenzymes [45], suggesting that growth suppression and virulence modulation are partially separable in this genus. In *Aspergillus fumigatus*, coating hydrophobic surfaces with farnesol transforms them into hydrophilic surfaces, altering conidium-surface interactions and potentially preventing biofilm formation [74]. These observations indicate that farnesol's ecological roles extend beyond *Candida* and may involve species-specific mechanisms.

The translational potential of farnesol in polymicrobial and drug-resistant contexts remains preliminary. While selected in vitro studies report antibiofilm or combination-treatment effects, these findings require replication with standardized dosing, clinically relevant isolates, pharmacokinetic measurements, host-toxicity assessment, and appropriately powered animal models before therapeutic development can be justified. In mixed biofilms of *C. albicans* and *Staphylococcus aureus*, farnesol combined with oxacillin achieves 80% inhibition, with scanning electron microscopy confirming patchy biofilm and lack of candidal hyphae [75]. In *C. auris*, transcriptomic analysis following farnesol treatment reveals an 89.9% reduction in intracellular calcium and a 73.8% reduction in magnesium, with genes involved in biofilm formation, glycolysis, ergosterol biosynthesis, fatty acid oxidation, iron metabolism, and autophagy primarily affected [65]. These findings highlight farnesol's potential in combination therapy against challenging fungal infections. Additionally, farnesol inhibits growth rate and biofilm formation mostly in non-*albicans* *Candida* species, while tyrosol exerts inconsistent responses; farnesol also upregulates *ALS3* and *HSP70* expression in *C. albicans*, confirming its role in regulating virulence mechanisms in a species- and concentration-dependent manner [29,50].

Priority research questions include: (i) defining the enzymes, transport processes, and compartment-specific pools that regulate farnesol production and secretion; (ii) establishing which fungi fulfill rigorous quorum-sensing criteria; (iii) mapping concentration-response relationships under physiologically relevant conditions; (iv) identifying direct molecular targets and separating primary mechanisms from downstream stress responses; (v) testing whether farnesol-associated phenotypes are conserved across strains and species; and (vi) determining pharmacokinetics, safety, formulation performance, and therapeutic efficacy in validated infection models. Addressing these gaps will be essential before clinical or industrial applications can be credibly advanced.

Overall, the most defensible perspective is that farnesol should be treated as a multifunctional fungal metabolite whose biological significance extends from signaling to metabolism and ecological adaptation. The strongest claims are those already supported by published work: farnesol affects sterol-related metabolism, growth, differentiation, stress responses, and interactions with other organisms [4,52,56]. Future work can build on

this foundation by determining when farnesol acts primarily as an intracellular metabolic cue, when it functions as an extracellular signal, and whether these roles can be exploited to manipulate fungal metabolite production in a controlled and biologically meaningful way [27,55].

7. Conclusions

Farnesol has emerged as more than the first recognized fungal quorum-sensing molecule in *C. albicans*. Evidence from pathogenic, opportunistic pathogenic, and predominantly non-pathogenic fungi indicates that exogenous or endogenously produced farnesol can be associated with morphogenesis, biofilm behavior, stress adaptation, and membrane-associated physiology. Nevertheless, the strength of evidence differs substantially among species, and reported farnesol responses should not automatically be interpreted as evidence of quorum sensing [4,34]. This expanded interpretation moves the field beyond a narrowly *Candida*-centered signaling model and places farnesol within the larger framework of fungal metabolic regulation and environmental responsiveness [6,52].

The comparative perspective is especially revealing. In pathogenic fungi, farnesol is closely tied to morphogenetic control, biofilm development, virulence-associated behavior, and altered responses to antifungal stress [4,9,65]. In non-pathogenic fungi, its roles are more naturally interpreted in terms of growth control, differentiation, redox balance, sterol-related physiology, and ecological fitness [52,55,56]. Taken together, these findings suggest that the apparent diversity of farnesol functions reflects differences in biological context rather than unrelated phenomena.

A central message of this review is therefore that farnesol should not be treated as a single-purpose signaling molecule. Its effects are highly context-dependent, shaped by species background, physiological state, growth environment, and cellular localization [4,34], and these variables help explain why farnesol can appear protective, inhibitory, adaptive, or even virulence-associated under different conditions [7,75]. Farnesol exposure in *C. auris* biofilms, for instance, affects genes involved in glycolysis, ergosterol biosynthesis, fatty acid oxidation, iron metabolism, and autophagy, while in *Cryptococcus neoformans*, it inhibits growth without significantly altering virulence-related exoenzymes [45,65]. Recognizing this complexity is essential for interpreting published data and for integrating mechanistic, ecological, and translational observations into a coherent framework.

Overall, farnesol occupies a distinctive position at the interface of metabolism and signaling. FPP is the central metabolic intermediate that supports sterol biosynthesis and protein prenylation, whereas free farnesol is a dephosphorylation product that can influence fungal state transitions and cellular stress responses. Maintaining this biochemical distinction is essential for interpreting farnesol biology and for evaluating its therapeutic or ecological significance [4,27]. A review that treats pathogenic and non-pathogenic fungi together therefore provides the clearest picture of its biological significance and underscores why farnesol remains one of the most informative small molecules in contemporary fungal research.

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Abbreviations

The following abbreviations are used in this manuscript:

ALS3	Agglutinin-Like Sequence 3
ATP	Adenosine Triphosphate
Cwh8	Cell Wall Biogenesis Protein 8
ERG9	Squalene Synthase Gene
ERG11	Lanosterol 14 α -Demethylase Gene
ERG20	Farnesyl Diphosphate Synthase Gene
FPP	Farnesyl Diphosphate
HOG	High Osmolarity Glycerol
HSP70	Heat Shock Protein 70
IL-6	Interleukin-6
IPP	Isopentenyl diphosphate
MTL	Mating Type Locus
QS	Quorum Sensing
ROS	Reactive Oxygen Species
TLR2	Toll-Like Receptor 2
UQ6	Ubiquinone-6
UQ9	Ubiquinone-9

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