REVIEW

Comenius University in Bratislava, Faculty of Natural Sciences, Department of Microbiology and Virology, Bratislava, Slovakia

Properties and role of the quorum sensing molecule farnesol in relation to the yeast *Candida albicans*

S. Dižová, H. Bujdáková*

Received October 5, 2016, accepted January 6, 2017

**Corresponding author: Assoc. Prof. Helena Bujdáková, PhD.;Comenius University in Bratislava, Faculty of Natural Sciences, Department of Microbiology and Virology, Mlynská dolina, Ilkovičova 6, 842 15 Bratislava, Slovakia bujdakova@fns.uniba.sk*

Pharmazie 72: 307–312 (2017) *doi: 10.1691/ph.2017.6174*

Farnesol is a quorum sensing (QS) molecule synthesized by *Candida albicans* acting as a negative regulator of morphogenesis; it blocks the yeast-to-hyphae transformation. This molecule is currently studied in particular from the viewpoint of possible use as a substance with anticancer properties and with an antimicrobial, and anti-biofilm effect in yeasts resistant or tolerant to conventional therapeutic agents, for example fluconazole. Besides the aforementioned effect on morphological transformation through cyclic AMP (cAMP)/protein kinase A (cAMP-PKA) pathway, it also affects other biochemical pathways of yeasts, for example those ones for sterol biosynthesis or triggering of apoptosis via accumulation of ROS (reactive oxygen species) that damage essential cellular compartments. ROS activate intracellular caspases that are indicators of apoptotic response in *C. albicans*. However, an influence of farnesol on *C. albicans* yeasts is dependent on used concentrations; while higher concentrations (200 - 300 μM) are stressful for yeasts, lower concentrations (about 40 μM) protect them from stress. This QS molecule is also able to modulate efflux pumps in resistant yeasts. This review provides an overview of the current knowledge about production, role, and mode of action of farnesol in the clinically most important yeast *C. albicans*.

1. Introduction

Quorum sensing (QS) is a process of intercellular communication used by microorganisms to synchronize behaviour within a population. QS molecules, also named autoinducers, play a crucial role in this process. Their function is unique because during cell growth in a population, these molecules continuously accumulate and, after reaching threshold concentrations, they induce a coordinated expression of several key genes followed with the activation of relevant biochemical pathways (Miller and Bassler 2001; Katragkou et al. 2015). The QS system is involved in many processes. For example, in the bacterium *Burkholderia thailandensis*, the QS system BtaR2-BtaI2 is probably responsible for the production of polyketide or peptide antibiotics against Gram-positive bacteria (Duerkop et al. 2009). Another example - the QS molecule tyrosol - produced by some yeasts of the genus *Candida* stimulates hyphal formation and biofilm production. Besides biofilm production, QS molecules are also generally responsible for the adaptation of microorganisms to the environment in which they survive (Albuquerque and Casadevall 2012; Hennig et al. 2015). Farnesol is another QS molecule produced by the yeast of the genus *Candida*; but acting in the opposite way compared to tyrosol. It is able: i) to inhibit the yeast-to-hypha transformation in planktonic populations of yeasts; ii) to contribute to the control of biofilm development trough modulation of cell density and morphology; iii) to initiate programmed cell death – apoptosis. Because of all these effects, farnesol is assumed to play a role in fungal pathogenicity (Wongsuk et al. 2016). Besides yeasts, several plants are producing farnesol that can protect them against pests (Grace 2002). Considering the unique properties of the QS molecule farnesol, the aim of this study was to summarize the current knowledge about its production, role, and mode of action in the clinically most important yeast *C. albicans*.

2. Chemical signalling molecules produced by yeasts of the genus *Candida*

Farnesol was the first QS molecule identified in eukaryotic organisms and it was discovered in 2001 (Hornby et al. 2001). Chemically, it is a sesquiterpene alcohol (3,7,11-trimethyl-2,6,10-dodecatriene-1-ol) (Shchepin et al. 2003) which contains three isoprene units (Fig. 1 A). This alcohol is produced as a by-product of biosynthesis of ergosterol that plays a key role in the membrane integrity of microscopic fungi. Farnesol is a negative regulator of filamentous growth. Cell density is one of the main stimuli for

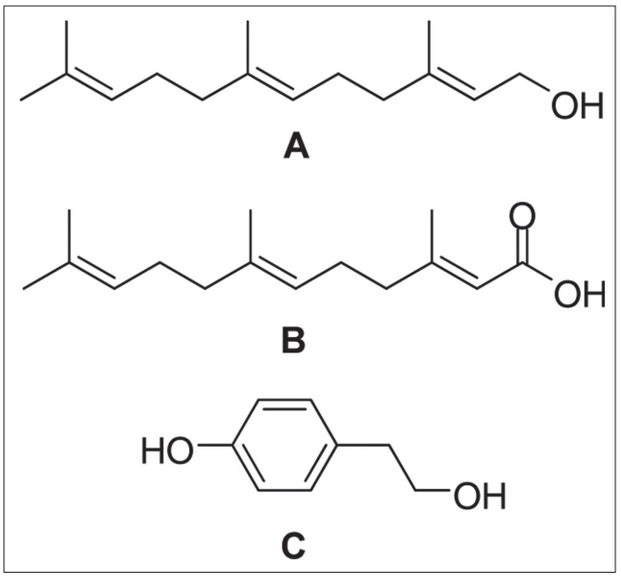

Fig. 1: Signalling molecules of *C. albicans* – A farnesol, B farnesoic acid, C tyrosol.

farnesol production (Madhani 2011). This molecule is not produced only in the planktonic culture of *C. albicans* but also in population colonizing solid surfaces during biofilm formation (Ramage et al. 2002). In the biofilm, this QS molecule inhibits the yeast-to-hyphae transformation resulting in decreased biofilm robustness (Martins et al. 2007; Yu et al. 2012). Weber et al. (2008) confirmed that not only *C. albicans* and *Candida dubliniensis* but also other representatives from the *Candida* genus, such as *Candida parapsilosis* or *Candida krusei,* can produce farnesol; but concentrations are so low that they do not probably play a role in biofilm formation (Weber et al. 2008). The main effects of farnesol to microorganisms and plants are summarized in the Table.

Table: Effects of farnesol on microorganisms and plants

ORGANISM	EFFECT (concentration - dependent)
Candida albicans	Negative regulator of filamentation (Román et al. 2009; Lu et al. 2014)
	Reduction of biofilm formation (Ramage et al. 2002)
	Gene expression of ergosterol pathway (Yu et al. 2012)
	Protection against oxidative stress (Deveau et al. 2010)
	Induction of apoptosis (Léger et al. 2015)
Other microorganisms (bacteria, filamentous fungi)	Antimicrobial activity (Koo et al. 2002; Semighini et al. 2006; Wang et al. 2014; Bonikowski et al. 2015)
Plants	Protects against pests (Grace 2002)

Farnesoic acid [(2E,6E)-3,7,11-trimethyl-2,6,10-dodecatrien acid] (Oh et al. 2001), shown in Fig. 1 (B), is another QS molecule produced by *C. albicans* ATCC 10231. Its structure is very similar to that of farnesol, from which it is formed by oxidation via aldehyde (farnesal) to farnesoic acid. The particular steps in the synthesis of this substance are catalysed by one or two NAD^+-dependent dehydrogenases (Baker et al. 1983). Similarly to farnesol, this substance inhibits the yeast-to-hyphae transition of *C. albicans* (De Rossi et al. 2014) but its effectiveness is substantially lower than that to farnesol.

In 2004, another QS molecule - tyrosol (2-[4-hydroxyphenyl] ethanol) (Chen et al. 2004) shown in Fig. 1 (C), was identified in *C. albicans*. Tyrosol is derived from the amino acid tyrosine and it is a natural phenolic compound with antioxidant properties occurring also in olive oil (De La Torre-Robles et al. 2014). This aromatic alcohol acts in the opposite way to farnesol. Its production accelerates filamentous growth, i.e. the yeast-to-hyphae transition (Chen et al. 2004). Tyrosol is produced, especially by *C. albicans* and *C. tropicalis,* which is likely to be connected to their ability to form true hyphae that afterwards, allow the penetration of these yeasts into host tissues, compared to other yeasts of the *Candida* genus unable to perform filamentous growth (Cremer et al. 1999; Albuquerque and Casadevall 2012).

3. Farnesol as a part of essential oils and its antimicrobial, and anticancer properties

At present, it is generally known that essential oils produced as plant secondary metabolites are concentrated hydrophobic liquids containing volatile aromatic compounds (Hyldgaard et al. 2012). One of the best known essential oils is tea tree oil extracted from the Australian plant *Melaleuca alternifolia*. This essential oil consists of terpene hydrocarbons, especially monoterpenes, sequiterpenes and their associated alcohols (Carson et al. 2006). At present, the antimicrobial activity is one of the most important properties generally studied in essential oils and their components (Bassolé and Juliani 2012). Farnesol is a common molecule present in many essential oils manifesting antimicrobial properties. The essential oil from *Tetradenia riparia* was identified to be active against cariogenic bacteria (de Melo et al. 2015). The essential oils of plants such as *Cymbopogon martini*, *Mentha piperita*, *Pelargonium graveolens*, and *Rosmarinus officinalis* analyzed by GC – MS technique proved the best activity of four compounds, namely, geraniol, trans-geraniol, citral, and farnesol against *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Staphylococcus aureus*, and *Bacillus cereus in vitro* (Thanighaiarassu and Sivamani 2013). Similarly, the oil derived from the seeds of *Abelmoschus moschatus* containing farnesol acetate (51.45%) showed an antibacterial activity against bacteria *Bacillus subtilis*, *S. aureus*, and *Enterococcus faecalis* (Arokiyaraj et al. 2015). Additionally, volatile oils of *Pluchea dioscoridis*, with the major component farnesol (16.50 %) exhibited a cidal effect on *Culex pipiens* mosquito larvae (Grace 2002). Thus, one could hypothesize that farnesol can protect plants against pests. However, an evaluation of contribution of farnesol to an antimicrobial activity in essential oils should not be overestimated as oils are composed of many different molecules.

Antimicrobial properties of externally added purified farnesol have been tested as well. This alcohol contributes to the inhibition of several important human pathogens, including bacteria from the genus *Staphylococcus* (Bonikowski et al. 2015), *Streptococcus mutans* (Koo et al. 2002), or filamentous fungi from the genera *Aspergillus, Paracoccidioides*, or *Cryptococcus* (Semighini et al. 2006; Derengowski et al. 2009; Cordeiro Rde et al. 2012). Thus, farnesol seems to be a promising molecule potentially useful for the control of growth of several microorganisms (Derengowski et al. 2009).

In spite of the antimicrobial activity of farnesol proved *in vitro*, inconsistent results have been published about its effects in respect to the treatment of candidiasis and host immune system. Hisajima et al. (2008) described the effects of farnesol treatment against experimental oral candidiasis in mice. Results from histological examination indicated that farnesol suppressed the mycelial growth of *C. albicans* on the surface of tongues, but did not decrease detected CFU (colony forming units) of *C. albicans* not only on tongues, but also in faeces, kidneys, and livers. Another publication described the *in vivo* effect of the exogenous administration of a "cocktail solution" that contained alcohols including farnesol in a murine model of hematogenously disseminated candidiasis. The mice injected intraperitoneally proved an increased survival and histological observations suggested an inhibitory effect on *C. albicans* filamentation within the kidney (Martins et al. 2012). These observations are consistent with our preliminary results that showed an inhibitory effect of externally added farnesol to the yeast-to-hyphae transition *in vitro* and *ex vivo* on mouse tongues, but its administration did not prevent surviving *C. albicans* cell population (Dižová, unpublished results). In context of this information, it is questionable, whether farnesol could be effective enough in eradication of candidiasis. Moreover, recently, farnesol was described as a potent stimulator of macrophage chemokines (Hargarten et al. 2015). Authors suggested that secretion of farnesol in immunocompromised hosts could promote *C. albicans* dissemination though macrophages. A similar situation might be expected in patients with neutropenia treated with azoles as alike effect has already been described *in vitro* and *in vivo* (Hornby and Nickerson, 2004; Navarathna et al. 2005). Farnesol was also able to enhance inflammation via an activation of neutrophils and to damage differentiation of monocytes into mature dendritic cells (Leonhardt et al. 2015). In the light of this knowledge, farnesol acts rather as a virulence factor than as a molecule useful for direct treatment of generalized candidiasis. However, it is necessary to take into account that described effects were dependent upon tested concentrations of farnesol as well as on host status.

Farnesol is also produced in humans. It is a metabolite of the mevalonate/cholesterol pathway located in the position similar to that in the yeast ergosterol synthesis. Additionally, it is the last common intermediate for the synthesis of coenzyme Q and dolichol, and the substrate for protein isoprenylation (Parmryd and Dallner 1996). It has been already proved that isoprenoids including farnesol play a critical role in the negative regulation of cell proliferation and differentiation, promote apoptosis, and are effective in tumor

suppression using different experimental models. Participation in those processes suggests a great anticancer potential of isoprenoids (Ong et al. 2012; Chen et al. 2014; Joo et al. 2015; Lee et al. 2015). These actions are mediated via a variety of signalling pathways like the phosphatidylinositol-3-kinase (PI3K)/serine/threonine kinase (Akt) signalling pathway (Park et al., 2014), CDP-choline pathway (Clement and Kent 1999), or MAP- (*Mitogen Activated Protein*) kinase pathways (McCubrey et al. 2006). Farnesol also activates the nuclear receptor farnesoid X (Forman et al. 1995), induces the expression of thyroid hormone receptor-β1 mRNA (Duncan and Archer 2006), and facilitates the activities of peroxisome proliferator-activated receptor-α and -γ (Takahashi et al. 2002). Additionally, farnesol manifested *in vitro* effects on 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, an enzyme converting HMG-CoA to mevalonate, but in dose and cell line selection-dependent manner (Meigs and Simoni 1997). Yeasts use HMG-CoA reductase for the same enzymatic step as humans, but while HMG-CoA represents a possible target in treatment or prevention of cancer diseases in humans, an inhibition of HMG-CoA in *Candida*, for example by pravastatin, can prevent farnesol production resulting in decreased virulence of *C. albicans* (Tashiro et al. 2012). Farnesol has also been reported to increase ROS (Reactive Oxygen Species) production in mammalian cells. However, while generation of ROS resulting from farnesol activity can inhibit growth and promote apoptosis in fungi (Semighini et al. 2006; Fairn et al. 2007; Wang et al. 2014), it seems that it is not a major factor contributing to the death of mammalian cells (Joo and Jetten 2010).

4. Farnesol production and its impact on metabolic pathways of yeasts

Farnesol in yeasts is formed as a by-product from the ergosterol biosynthesis pathway by enzymatic dephosphorylation of farnesyl pyrophosphate (farnesyl diphosphate) (Hornby et al. 2003; Han et al. 2011; Rodriguez et al. 2014). Important enzymes for this pathway are encoded by *ERG* genes. Farnesyl diphosphate synthase, encoded by the *ERG20* gene, synthesizes trans trans farnesyl diphosphate – a precursor of farnesol from isopentenyl diphosphate (Piłsyk et al. 2014) (Fig. 2).

After the administration of antifungals, especially in the case of long-term therapy or in immunocompromised patients, the yeasts become resistant to therapeutic agents (Loeffler and Stevens 2003). The resistance to azole antimycotics, particularly the drug fluconazole used in the treatment of many mycotic diseases is very common (Senevirante et al. 2016). The target for the azoles is the enzyme cytochrome P450 lanosterol-14α-demethylase, which is encoded by the *ERG11* gene (Borecká-Melkusová et al. 2009) (Fig. 2). The most common resistance to fluconazole is due to mutation or increased expression of the *ERG11* gene (Borecká-Melkusová et al. 2009; Lee et al. 2014) or expression of genes encoding of efflux pumps *CDR (Candida Drug Resistance)* and *MDR (Multiple Drug Resistance)*, responsible for the efflux of drug out of the cell. Another mechanism is a change in an expression of various *ERG* genes in the ergosterol pathway resulting in the increased production of sterols other than ergosterol. These sterols ensure the partial functionality of yeast membranes (Loeffler and Stevens 2003). In 2012, Yu et al. (2012) tested the hypothesis that externally added farnesol could affect resistance to fluconazole of the biofilm produced by *C. albicans*. They studied the change in expression of potential target genes in the ergosterol pathway in the presence of farnesol using molecular methods: reverse transcription PCR (RT-PCR) and quantitative PCR (qPCR). The results showed that the expression of certain genes in the ergosterol pathway, i.e. *ERG3, ERG1, ERG6, ERG25*, and *ERG11* significantly decreased in the group treated with 300 μM farnesol (Yu et al. 2012). Besides the genes of the ergosterol pathway, the reduced expression of the aforementioned *MDR1* gene was recorded as well. At the same time, the concentration of fluconazole required for a 50% reduction in yeast biofilm decreased after 24 h from more than 1024 μg/ml of the drug to 4 μg/ml in the group affected by farnesol and the yeasts formed a three-times thinner biofilm compared to the biofilm not affected by farnesol (Yu et al. 2012). Additionally, *in vitro* synergic interactions between farnesol and other antifungals (micafungin, amphotericin B) were described (Katragkou et al. 2015).

It has already been mentioned that certain QS molecules affect morphological transition with an impact on the *C. albicans* life cycle. Hyphae can better adhere to the host skin and mucosa as well as penetrate deeper into the tissues or vessels resulting in significant injury (Chevalier et al. 2012; Wibawa et al. 2015). Additionally, if the yeast is able to form hyphae, the biofilm is more robust (Paramonova et al. 2009; Wibawa et al. 2015). In *C. albicans*, hyphae production is regulated via the activation of the cyclic AMP/protein kinase A (cAMP-PKA) signalling pathway, which regulates decreasing the *NRG1* gene expression. The *NRG1* gene is a repressor of filamentous growth. Farnesol can block the yeast-to-hyphae transition by affecting the cAMP signalling via blocking the activity of adenylate cyclase Cyr1 (Hogan and Muhlschlegel 2011; Albuquerque and Casadevall 2012; Lu et al. 2014) and Tpk2, the catalytic subunit of PKA in cAMP-PKA pathway, when *NRG1* gene expression is not decreased and the repressor of filamentous growth remains active. Farnesol can affect the *NRG1* repressor also via stabilization of Cup9, a transcriptional repressor, which

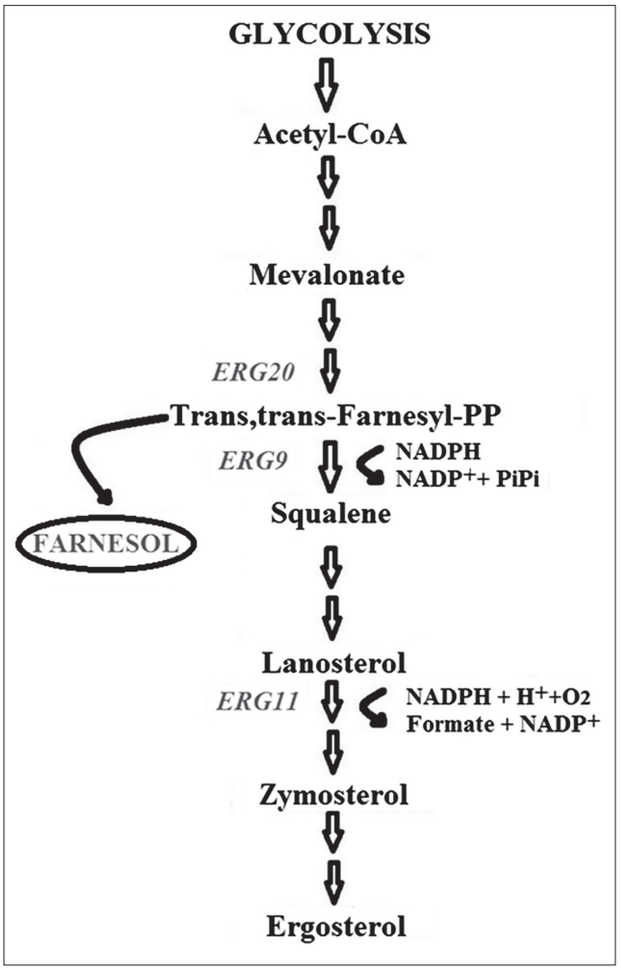

Fig. 2: Scheme of ergosterol pathway and indication of the site of synthesis of farnesol from trans-farnesyl-pyrophosphate. The pathway is illustrated schematically (two consecutive arrows show an association of chemical reactions involving several products - multiple steps). The localization of the *ERG20* gene encoding farnesyl-diphosphate synthase, which is important for farnesol synthesis, is indicated. The *ERG9* gene encoding squalene synthase is located after the farnesol synthesis. The target site of azole derivatives, including fluconazole, is the enzyme lanosterol-14α-demethylase, which is encoded by the *ERG11* gene.

blocks *SOK1* gene expression participating in Nrg1 protein degradation. In the absence of farnesol, the Cup9 repressor is degraded by ubiquitin protein ligase Ubr1 (Lu et al. 2014). In this case, the *SOK1* gene is expressed and induces Nrg1 protein degradation. The described process is shown in Fig. 3.

Farnesol also acts on the MAP kinase pathway, which responds to extracellular stimuli and stress, and regulates multiple processes, including proliferation in eukaryotic cells (Román et al. 2009). Cek1 is the protein MAP kinase in *C. albicans*, which is involved in hyphae formation (Román et al. 2005). QS molecule farnesol represses the phosphorylation Cek1, encoded by the gene *CEK1*, resulting in inhibition of filamentation. Damage of this gene reduces the virulence of yeasts. Cek1 is independent of Chk1 (Román et al. 2009), the *Candida* histidine kinase that is the QS molecule receptor, but mutations in Chk1 causes insensitivity to farnesol (Kruppa et al. 2004; Kruppa and Calderone 2006).

Farnesol plays an important role in protection against oxidative stress in which ROS are crucial. These include either free radicals, such as hydroxyl radicals (OH) and superoxide anions (O_2^-), or non-radical molecules, for example, hydrogen peroxide (H_2O_2) (Powers et al. 2011). ROS effectively interact with nucleic acids, lipids or proteins causing a serious or even lethal destruction of cell structures of microorganisms leading to programmed cell death – apoptosis (Fan et al. 2005). However, yeasts developed defence mechanisms – they produce enzymes (catalases, superoxide dismutases and others) which convert ROS to less dangerous forms (Martchenko et al. 2004). Several studies showed that ROS production does not necessarily lead to cell death (Pan 2011; Cáp et al. 2012) and for example, certain bacteria can take advantage from them as a form of protection against other microorganisms. It seems that low level stress activates defence mechanisms and increases an adaptability of microorganisms to external environmental conditions (Cáp et al. 2012). Farnesol at a concentration of 40 μM that is considered to be physiological, i.e. naturally produced in a yeast population, is able to activate response of yeasts to oxidative stress induced by ROS production (Shirtliff et al. 2009) and, thus, protect cells against apoptosis. The possible mechanism is the induction of a catalase encoded by the *CAT1* gene during negative regulation of morphological transition via inhibition of the Ras-cAMP-PKA pathway. Farnesol also triggers Hog1 phosphorylation where Hog1 acts as a regulator of resistance to oxidative stress (Deveau et al. 2010).

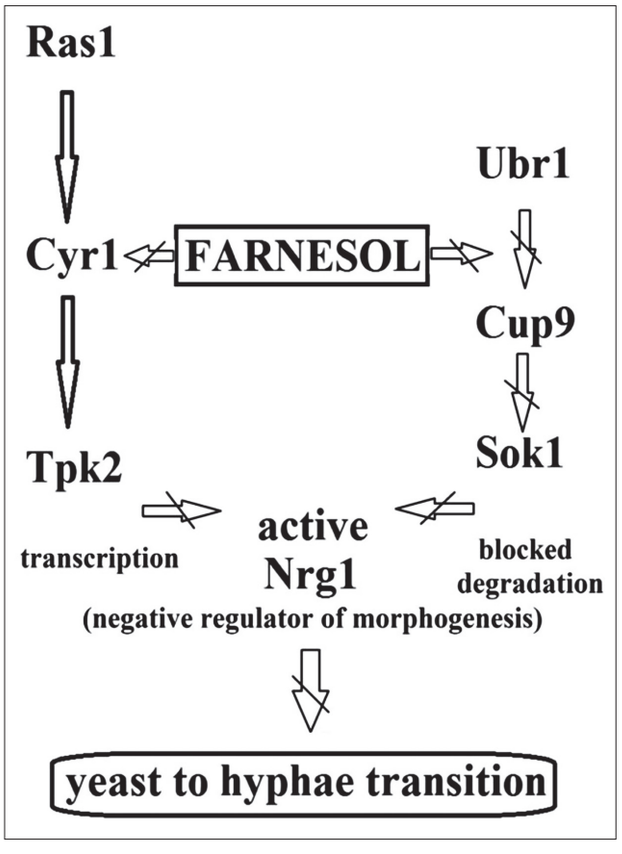

Fig. 3: Effect of farnesol on the inhibition of *C. albicans* filamentous growth by two pathways affecting the *NRG1* negative regulator of filamentous growth (designed according to Lu et al. 2014). The first pathway is the cAMP-PKA signalling pathway where farnesol blocks the activity of adenylate cyclase Cyr and, subsequently, the catalytic subunit PKA Tpk2, which results in no reduction of the *NRG1* gene expression. Farnesol also blocks the degradation of the protein Cup9 leading to the derepression of gene encoding *SOK1* that does not degrade the protein Nrg1 which remains stable. In both cases, the repressor encoded by the *NRG1* gene remains active and, thus, it blocks the yeast-to-hyphae transformation of *C. albicans.*

On the other hand, higher concentrations of farnesol (200 - 300 μM) cause in *C. albicans* the disruption of the mitochondrial electron transport chain and it is accompanied by ROS release resulting in apoptosis (Fan et al. 2005). Besides this yeast, farnesol can trigger apoptosis also in other microorganisms, such as *Saccharomyces cerevisiae* (Fairn et al. 2007) used in the food industry, or in the filamentous micromycete *Aspergillus nidulans* (Semighini et al. 2006; Wang et al. 2014). The process of apoptosis is induced by extracellular and intracellular stimuli, which activate cysteine proteases, caspases responsible for the mediation of the apoptotic signal in proteolytic cascade (McStay and Green 2014). Farnesol participation in apoptosis was revealed by studies in which an increased number of caspases, depending on the tested higher farnesol concentrations, was detected in *C. albicans* (Shirtliff et al. 2009; Léger et al. 2015). At present, metacaspase Mca1p encoded by the *MCA1* gene is considered to be one of the most important proteases inducing cell death. Although this metacaspase has not been sufficiently examined, it probably plays an important role in the degradation of "heat shock" proteins that weaken cell defence leading to subsequent cell death. Probably, this caspase is involved in the process of mitochondrial biogenesis control and mitochondrial degradation (Léger et al. 2015). It can be assumed that the association between apoptosis induced by farnesol in *C. albicans* and metacaspase Mca1p exists because regulation of the gene for this protein is affected by various farnesol concentrations (Léger et al. 2015). The most new publication of Léger et al. (2016) supported previous observations; they proved that metacaspase Mca1p plays a critical role in the early phase of apoptosis through alteration of the protein glycosylation machinery generated by farnesol stress (250 μM). In *C. albicans*, the apoptosis might be associated also with glutathione elimination. Glutathione acts as an antioxidant and plays an important role during cell detoxification from harmful substances and contaminants, or ROS. Glutathione, which is mainly present in its reduced form (GSH), is an omnipresent thiol compound which contains a tripeptide consisting of cysteine, glutamic acid, and glycine. Glutathione is synthesized in the cell via six enzyme-catalysed reactions, called the γ-glutamyl cycle. Farnesol (300 μM) conjugates with glutathione, while the expression of the *CDR1* gene encoding efflux pumps increases. Glutathione conjugates are effluxed out of the cell by efflux pumps and, subsequently, the viability of yeasts decreases (Zhu et al. 2011).

Understanding of the QS molecule farnesol and its mode of action, can result in the development of new, alternative antifungals. In spite of the fact that farnesol itself proved antimicrobial effects only in high concentrations, it has a great potential to be used as a supporting substance in combination with another drugs (azole antifungal agents). Its ability to interact with efflux pumps that most frequently mediate resistance to azoles in *C. albicans*, might be an option for the treatment of infections caused by resistant fungi.

5. Conclusion

In recent years, the number of clinical isolates of microorganisms resistant to conventional therapeutic agents has increased. The situation is even worse in the treatment of biofilm-associated

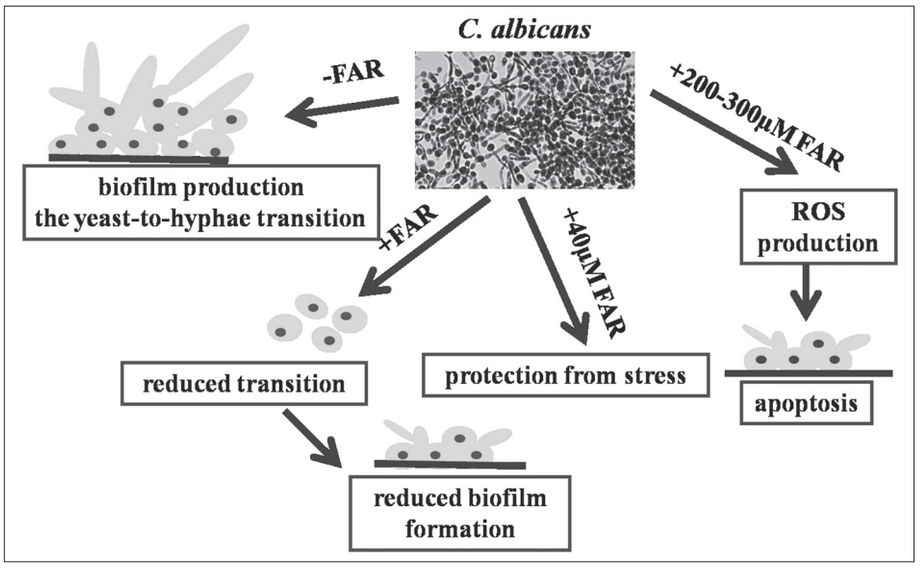

Fig. 4: Summary of effects of farnesol on filamentation and biofilm formed by *C. albicans*, and response of this yeast to different concentrations of externally added farnesol.

infections. The mentioned limitations have stimulated scientists for searching new therapeutic options. Use of signalling molecules which help microorganisms to adapt to the environment is one possibility. Farnesol, which is produced by *C. albicans* and participates in the regulation of biofilm and filamentous growth in this yeast, could be an interesting choice. The effects of farnesol on *C. albicans* are summarized in Fig. 4. At present, this sesquiterpene alcohol is studied not only in relation to yeasts, in which it modulates the above mentioned processes, but also in relation to various bacteria, filamentous fungi, or cancer cells. Although the effect of farnesol on the physiology of microorganisms has been partially examined, especially in relation to the generation and accumulation of ROS, not all of its effects on prokaryotic or eukaryotic cells of microorganisms are known. Also, mammalian cells should not be overlooked because the toxicity and other effects of farnesol represent a necessary parameter of any substance applicability in practice. In conclusion, it can be summarized that farnesol is a compound with a high potency. However, there is still not enough information about all of its possible effects in order to be able to, unequivocally, identify farnesol as a substance suitable for clinical use.

Acknowledgments: This publication was supported by the Slovak Research and Development Agency under the contract No. APVV-15-0347 and by the project VEGA 1/0628/15 granted by the Ministry of Education, Science, Research, and Sport of the Slovak Republic. Authors thank MSc. Róbert Mišicák from the Comenius University in Bratislava, Faculty of Natural Sciences, Department of Organic Chemistry, for his help in the preparation of Fig. 1.

Conflicts of interest: None declared.

References

Albuquerque P, Casadevall A (2012) Quorum sensing in fungi –a review. Med Mycol 50: 337 - 345.

Arokiyaraj S, Seong HCH, Lee Y, Bharanidharan R, Hairul-Islam VI, Vijayakumar B, Oh YK, Dinesh-Kumar V, Vincent S7, Kim KH (2015) Characterization of ambrette seed oil and its mode of action in bacteria. Molecules 20: 384-395.

Baker FC, Mauchamp B, Tsai LW, Schooley DA (1983) Farnesol and farnesal dehydrogenase(s) incorporate allata of the tobacco hornworm moth, *Manduca sexta*. J Lipid Res 24: 1586–1594.

Bassolé IH, Juliani HR (2012) Essential oils in combination and their antimicrobial properties. Molecules 17: 3989-4006.

Bonikowski R, Świtakowska P, Sienkiewicz M, Zakłos-Szyda M (2015) Selected compounds structurally related to acyclic sesquiterpenoids and their antibacterial and cytotoxic activity. Molecules 20: 11272-11296.

Borecká-Melkusová S, Moran GP, Sullivan DJ, Kucharíková S, Chorvát DJr, Bujdáková H (2009) The expression of genes involved in the ergosterol biosynthesis pathway in *Candida albicans* and *Candida dubliniensis* biofilms exposed to fluconazole. Mycoses 52: 118-128.

Cáp M, Váchová L, Palková Z (2012) Reactive oxygen species in the signaling and adaptation of multicellular microbial communities. Oxid Med Cell Longev 2012: 976753.

Carson CF, Hammer KA, Riley TV (2006) *Melaleuca alternifolia* (Tea tree) oil: a review of antimicrobial and other medicinal properties. Clin Microbil Rev 19: 50-62.

Clement JM, Kent C (1999) CTP:phosphocholine cytidylyltransferase: insights into regulatory mechanisms and novel functions. Biochem Biophys Res Commun 257: 643-650.

Cordeiro Rde A, Nogueira GC, Brilhante RS, Teixeira CE, Mourão CI, Castelo-Branco DdeS, Paiva Mde A, Ribeiro JF, Monteiro AJ, Sidrim JJ, Rocha MF (2012) Farnesol inhibits *in vitro* growth of the *Cryptococcus neoformans* species complex with no significant changes in virulence-related exoenzymes. Vet Microbiol 159: 375-380.

Cremer J, Vatou V, Braveny I (1999) 2,4-(hydroxyphenyl)-ethanol, an antioxidative agent produced by *Candida* spp., impairs neutrophilic yeast killing *in vitro*. FEMS Microbiol Lett 170: 319-325.

De La Torre-Roble A, Rivas A, Lorenzo-Tovar ML, Monteagudo C, Mariscal-Arcas M, Olea-Serrano F (2014) Estimation of the intake of phenol compounds from virgin olive oil of a population from southern Spain. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 31: 1460-1469.

de Melo NI, de Carvalho CE, Fracarolli L, Cunha WR, Veneziani RCS, Martins CHG, Miller Crotti AE (2015) Antimicrobial activity of the essential oil of *Tetradenia riparia* (Hochst.) Codd. (*Lamiaceae*) against cariogenic bacteria. Braz J Microbiol 46, 519-525.

De Rossi BP, García C, Alcaraz E, Franco M (2014) *Stenotrophomonas maltophilia* interferes via the DSF-mediated quorum sensing system with *Candida albicans* filamentation and its planktonic and biofilm modes of growth. Rev Argent Microbiol 46: 288-297.

Derengowski LS, De-Souza-Silva C, Braz SV, Mello-De-Sousa TM, Báo SN, Kyaw CM, Silva-Pereira I (2009) Antimicrobial effect of farnesol, a *Candida albicans* quorum sensing molecule, on *Paracoccidioides brasiliensis* growth and morphogenesis. Ann Clin Microbiol Antimicro 8: 13.

Deveau A, Piispanen AE, Jackson AA, Hogan DA (2010) Farnesol induces hydrogen peroxide resistance in *Candida albicans* yeast by inhibiting the Ras-cyclic AMP signaling pathway. Eukaryot Cell 9: 569-577.

Duerkop BA, Varga J, Chandler JR, Peterson SB, Herman JP, Churchill ME, Parsek MR, Nierman WC, Greenberg EP (2009) Quorum-sensing control of antibiotic synthesis in *Burkholderia thailandensis.* J Bacteriol 191: 3909-3918.

Duncan RE, Archer MC (2006) Farnesol induces thyroid hormone receptor (THR) beta1 but inhibits THR-mediated signaling in MCF-7 human breast cancer cells. Biochem Biophys Res Commun 343: 239-243.

Fairn GD, MacDonald K, McMaster CR (2007) A chemogenomic screen in *Saccharomyces cerevisiae* uncovers a primary role for the mitochondria in farnesol toxicity and its regulation by the Pkc1 pathway. J Biol Chem 282: 4868-4874.

Fan TJ, Han LH, Cong RS, Liang J (2005) Caspase family proteases and apoptosis. Acta Biochim Biophys Sin (Shanghai) 37: 719-727.

Forman BM, Goode E, Chen J, Oro AE, Bradley DJ, Perlmann T, Noonan DJ, Burka LT, McMorris T, Lamph WW, Evans RM, Weinberger C (1995) Identification of a nuclear receptor that is activated by farnesol metabolites. Cell 81: 687–693.

Grace MH (2002) Chemical composition and biological activity of the volatiles of *Anthemis melampodina* and *Pluchea dioscoridis*. Phytother Res 16: 183–185.
Han TL, Cannon RD, Villas-Boas SG (2011) The metabolic basis of *Candida albicans* morphogenesis and quorum sensing. Fungal Genet Biol 48: 747-763.
Hargarten JC, Moore TC, Petro TM, Nickerson KW, Atkin AL (2015) *Candida albicans* quorum sensing molecules stimulate mouse macrophage migration. Infect Immun 83: 3857-3864. Hennig S, Rödel G, Ostermann K (2015) Artificial cell-cell communication as an emerging tool in synthetic biology applications. J Biol Eng 9: 13.
Hisajima T, Maruyama N, Tanabe Y, Ishibashi H, Yamada T, Makimura K, Nishiyama Y, Funakoshi K, Oshima H, Abe S (2008) Protective effects of farnesol against oral candidiasis in mice. Microbiol Immunol 52: 327-333.
Hogan DA, Muhlschlegel FA (2011) *Candida albicans* developmental regulation: adenylyl cyclase as a coincidence detector of parallel signals. Curr Opin microbiol 14: 682-686.
Hornby JM, Jensen EC, Lisec AD, Tasto JJ, Jahnke B, Shoemaker R, Dussault P, Nickerson KW (2001) Quorum sensing in the dimorphic fungus *Candida albicans* is mediated by farnesol. Appl Environ Microbiol 67: 2982-2992.
Hornby JM, Kebaara BW, Nickerson KW (2003) Farnesol biosynthesis in *Candida albicans*: cellular response to sterol inhibition by zaragozic acid B. Antimicrob Agents Chemother 47: 2366-2369.
Hornby JM, Nickerson KW (2004) Enhanced production of farnesol by *Candida albicans* treated with four azoles. Antimicrob Agents Chemother 48: 2305–2307.
Hyldgaard M, Mygind T, Meyer RL (2012) Essential oils in food preservation: mode of action, synergies, and interactions with food matrix components. Front Microbiol 3: 12
Chen H, Fujita M, Feng Q, Clardy J, Fink GR (2004) Tyrosol is a quorum-sensing molecule in *Candida albicans.* Proc Natl Acad Sci U S A 101: 5048-5052.
Chen M, Knifley T, Subramanian T, Spielmann HP, O'Connor KL (2014) Use of synthetic isoprenoids to target protein prenylation and Rho GTPases in breast cancer invasion. PLoS One 9: e89892.
Chevalier M, Medioni E, Prêcheur I (2012) Inhibition of *Candida albicans* yeast-hyphal transition and biofilm formation by *Solidago virgaurea* water extracts. J Med Microbiol 61: 1016-1022.
Joo JH, Jetten AM (2010) Molecular mechanisms involved in farnesol-induced apoptosis. Cancer Lett 287: 123-135.
Joo JH, Ueda E, Bortner CD, Yang XP, Liao G, Jetten AM (2015) Farnesol activates the intrinsic pathway of apoptosis and the ATF4-ATF3-CHOP cascade of ER stress in human T lymphoblastic leukemia Molt4 cells. Biochem Pharmacol 97: 256-268.
Katragkou A, McCarthy M, Alexander EL, Antachopoulos C, Meletiadis J, Jabra-Rizk MA, Petraitis V, Roilides E, Walsh TJ (2015) *In vitro* interactions between farnesol and fluconazole, amphotericin B or micafungin against *Candida albicans* biofilms. J Antimicrob Chemother 70: 470-478.
Koo H, Rosalen PL, Cury JA, Park YK, Bowen WH (2002) Effects of compounds found in propolis on *Streptococcus mutans* growth and on glucosyltransferase activity. Antimicrob Agents Chemother 46: 1302-1309.
Kruppa M, Calderone R (2006) Two-component signal transduction in human fungal pathogens. FEMS Yeast Res 6: 149-159.
Kruppa M, Krom BP, Chauhan N, Bambach AV, Cihlar RL, Calderone RA (2004) The two-component signal transduction protein Chk1p regulates quorum sensing in *Candida albicans.* Eukaryot Cell 3: 1062-1065.
Lee JH, Kim C, Kim SH, Sethi G, Ahn KS (2015) Farnesol inhibits tumor growth and enhances the anticancer effects of bortezomib in multiple myeloma xenograft mouse model through the modulation of STAT3 signaling pathway. Cancer Lett 360: 280-293.
Lee PY, Yong VC, Rosli R, Gam LH, Chong PP (2014) Cloning, expression and purification of squalene synthase from *Candida tropicalis* in *Pichia pastoris.* Protein Expr Purif 94: 15-21.
Léger T, Garcia C, Camadro JM (2016) The metacaspase Mca1p restricts O-glycosylation during farnesol-induced apoptosis in *Candida albicans.* Mol Cell Proteomics, in press.
Léger T, Garcia C, Ounissi M, Lelandais G, Camadro JM (2015) The metacaspase (Mca1p) has a dual role in farnesol-induced apoptosis in *Candida albicans.* Mol Cell Proteomics 14: 93-108.
Leonhardt I, Spielberg S, Weber M, Albrecht-Eckardt D, Bläss M, Claus R, Barz D, Scherlach K, Hertweck C, Löffler J, Hünniger K, Kurzai O (2015) The fungal quorum-sensing molecule farnesol activates innate immune cells but suppresses cellular adaptive immunity. MBio 6: e00143.
Loeffler J, Stevens DA (2003) Antifungal drug resistance. Clin Infect Dis 36: 31-41.
Lu Y, Su C, Unoje O, Liu H (2014) Quorum sensing controls hyphal initiation in *Candida albicans* through Ubr1-mediated protein degradation. Proc Natl Acad Sci U S A 111: 1975-1980.
Madhani HD (2011) Quorum sensing in fungi: Q&A. PLoS Pathog 7: e1002301.
Martchenko M, Alarco AM, Harcus D, Whiteway M (2004) Superoxide dismutases in *Candida albicans*: transcriptional regulation and functional characterization of the hyphal-induced *SOD5* gene. Mol Biol Cell 15: 456-467.
Martins M, Henriques M, Azeredo J, Rocha SM, Coimbra MA, Oliveira R (2007) Morphogenesis control in *Candida albicans* and *Candida dubliniensis* through signaling molecules produced by planktonic and biofilm cells. Eukaryot Cell 6: 2429-2436.
Martins M, Lazzell AL, Lopez-Ribot JL, Henriques M, Oliveira R (2012) Effect of exogenous administration of *Candida albicans* autoregulatory alcohols in a murine model of hematogenously disseminated candidiasis. J Basic Microbiol. 52: 487-491.
McCubrey JA, Lahair MM, Franklin RA (2006) Reactive oxygen species-induced activation of the MAP kinase signaling pathways. Antioxid Redox Signal 8: 1775-1789.
McStay GP, Green DR (2014) Measuring apoptosis: caspase inhibitors and activity assays. Cold Spring Harb Protoc 2014: 799-806.
Meigs TE, Simoni RD (1997) Farnesol as a regulator of HMG-CoA reductase degradation: characterization and role of farnesyl pyrophosphatase. Arch Biochem Biophys 345: 1–9.
Miller MB, Bassler BL (2001) Quorum sensing in bacteria. Annu Rev Microbiol. 55: 165-199.
Navarathna DH, Hornby JM, Hoerrmann N, Parkhurst AM, Duhamel GE, Nickerson KW (2005) Enhanced pathogenicity of *Candida albicans* pretreated with subinhibitory concentrations of fluconazole in a mouse model of disseminated candidiasis. J Antimicrob Chemother 56: 1156–1159.
Oh KB, Miyazawa H, Naito T, Matsuoka H (2001) Purification and characterization of an autoregulatory substance capable of regulating the morphological transition in *Candida albicans.* Proc Natl Acad Sci U S A 98: 4664-4668.
Ong TP, Cardozo MT, de Conti A, Moreno FS (2012) Chemoprevention of hepatocarcinogenesis with dietary isoprenic derivatives: cellular and molecular aspects. Curr Cancer Drug Targets 12: 1173-1190.
Pan Y (2011) Mitochondria, reactive oxygen species, and chronological aging: a message from yeast. Exp Gerontol 46: 847-852.
Paramonova E, Krom BP, Van Der Mei HC, Busscher HJ, Sharma PK (2009) Hyphal content determines the compression strength of *Candida albicans* biofilms. Microbiology 155: 1997-2003.
Park JS, Kwon JK, Kim HR, Kim HJ, Kim BS, Jung JY (2014) Farnesol induces apoptosis of DU145 prostate cancer cells through the PI3K/Akt and MAPK pathways. Int J Mol Med 33: 1169-1176.
Parmryd I, Dallner G (1996) Organization of isoprenoid biosynthesis. Biochem Soc Trans 24: 677-682.
Piłsyk S, Perlińska-Lenart U, Górka-Nieć W, Graczyk S, Antosiewicz B, Zembek P, Palamarczyk G, Kruszewska JS (2014) Overexpression of *erg20* gene encoding farnesyl pyrophosphate synthase has contrasting effects on activity of enzymes of the dolichyl and sterol branches of mevalonate pathway in *Trichoderma reesei.* Gene 544: 114-122.
Powers SK, Ji LL, Kavazis AN, Jackson MJ (2011) Reactive oxygen species: impact on skeletal muscle. Compr Physiol 1: 941-969.
Ramage G, Saville SP, Wickes BL, López-Ribot JL (2002) Inhibition of *Candida albicans* biofilm formation by farnesol, a quorum-sensing molecule. Appl Environ Microbiol 68: 5459-5463.
Rodriguez S, Kirby J, Denby CM, Keasling JD (2014) Production and quantification of sesquiterpenes in *Saccharomyces cerevisiae,* including extraction, detection and quantification of terpene products and key related metabolites. Nat Protoc 9: 1980-1996.
Román E, Alonso-Monge R, Gong Q, Li D, Calderone R, Pla J (2009) The Cek1 MAPK is a short-lived protein regulated by quorum sensing in the fungal pathogen *Candida albicans*. FEMS Yeast Res 9: 942-955.
Román E, Nombela C, Pla J (2005) The Sho1 adaptor protein links oxidative stress to morphogenesis and cell wall biosynthesis in the fungal pathogen *Candida albicans.* Mol Cell Biol 25: 10611-10627.
Semighini CP, Hornby JM, Dumitru R, Nickerson KW, Harris SD (2006) Farnesol-induced apoptosis in *Aspergillus nidulans* reveals a possible mechanism for antagonistic interactions between fungi. Mol Microbiol 59: 753-764.
Seneviratne CJ, Rajan S, Wong SS, Tsang DN, Lai CK, Samaranayake LP, Jin L (2016) Antifungal susceptibility in serum and virulence determinants of *Candida* bloodstream isolates from Hong Kong. Front Microbiol 7: 216.
Shirtliff ME, Krom BP, Meijering RA, Peters BM, Zhu J, Scheper MA, Harris ML, Jabra-Rizk MA (2009) Farnesol-induced apoptosis in *Candida albicans.* Antimicrob Agents Chemother 53: 2392-2401.
Shchepin R, Hornby JM, Burger E, Niessen T, Dussault P, Nickerson KW (2003) Quorum sensing in *Candida albicans:* probing farnesol's mode of action with 40 natural and synthetic farnesol analogs. Chem Biol 10: 743-750.
Takahashi N, Kawada T, Goto T, Yamamoto T, Taimatsu A, Matsui N, Kimura K, Saito M, Hosokawa M, Miyashita K, Fushiki T (2002) Dual action of isoprenols from herbal medicines on both PPARgamma and PPARalpha in 3T3-L1 adipocytes and HepG2 hepatocytes. FEBS Lett 514: 315-322.
Thanighaiarassu R R Sivamani P (2013) Analysis of chemical composition of four essential oils by GC-MS and its antibacterial activity against human pathogenic bacteria. Inter J Pharm Biol Arch. 4: 195-200.
Tashiro M, Kimura S, Tateda K, Saga T, Ohno A, Ishii Y, Izumikawa K, Tashiro T, Kohno S, Yamaguchi K (2012) Pravastatin inhibits farnesol production in *Candida albicans* and improves survival in a mouse model of systemic candidiasis. Med Mycol. 50:353-360.
Wang X, Wang Y, Zhou Y, Wei X (2014) Farnesol induces apoptosis-like cell death in the pathogenic fungus *Aspergillus flavus.* Mycologia 106: 881-888.
Weber K, Sohr R, Schulz B, Fleischhacker M, Ruhnke M (2008) Secretion of E,E-farnesol and biofilm formation in eight different *Candida* species. Antimicrob Agents Chemother 52: 1859-1861.
Wibawa T, Praseno, Aman AT (2015) Virulence of *Candida albicans* isolated from HIV infected and non infected individuals. Springerplus 4: 408.
Wongsuk T, Pumeesat P, Luplertlop N (2016) Fungal quorum sensing molecules: Role in fungal morphogenesis and pathogenicity. J Basic Microbiol 56: 440-447.
Yu LH, Wei X, Ma M, Chen XJ, Xu SB (2012) Possible inhibitory molecular mechanism of farnesol on the development of fluconazole resistance in *Candida albicans* biofilm. Antimicrob Agents Chemother 56: 770-775.
Zhu J, Krom BP, Sanglard D, Intapa C, Dawson CC, Peters BM, Shirtliff ME, Jabra-Rizk MA (2011) Farnesol-induced apoptosis in *Candida albicans* is mediated by Cdr1-p extrusion and depletion of intracellular glutathione. PLoS One 6: e28830.