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Toxicological and pharmacologic effects of farnesol ($C_{15}H_{26}O$): A descriptive systematic review

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ABSTRACT

The objective of the present study was to perform a systematic review (SR) composed of preclinical and clinical studies which investigated the toxicological and pharmacologic effects of farnesol [Molecular formula: $C_{15}H_{26}O$; IUPAC: (3,7,11-Trimethyl-2,6,10-dodecatrien-1-ol]. This SR was performed according to PRISMA guidelines. Literature research was performed using PubMed, MEDLINE, Scopus and Web of Science databases using the descriptor combinations: "farnesol and pharmacological effect" and "farnesol and toxicology". The inclusion criteria used were original articles from preclinical and clinical studies investigating the pharmacological and toxicological effects of farnesol, published between January 1960 and December 2017 which were written in English, Portuguese and Spanish. Primary research identified 414 articles, from which 76 articles were selected for final analysis following the inclusion criteria. After grouping, 51.32 and 22.37% of the articles investigated the antimicrobial and antitumor effect, respectively. Methodological biases have been observed both in preclinical studies with non-human animals and in clinical trials, mainly in group allocation and blinding. This SR is the first study developed to compile the studies concerning the pharmacological and toxicological effects of farnesol. This study concludes that farnesol possesses different pharmacological and toxicological features, which permit its use as an active or a coadjuvant drug.

1. Introduction

Farnesol [Molecular formula: $C_{15}H_{26}O$; IUPAC: 3,7,11-Trimethyl-2,6,10-dodecatrien-1-ol], an alcohol found in essential oils, is a natural terpene formed by 15 carbons made in plant cells by farnesyl pyrophosphate dephosphorylation (Khan and Sultana, 2011). The name Farnesol was given for being first identified in *Vachellia farnesiana* (L.) Wight & Arn flowers, known as "acacia farnese", the "ol" suffix was added because it is chemically an alcohol (Trimble, 1885). All four geometrical isomers of farnesol have been found in nature and are commercially available: *trans,trans*-Farnesol (CAS 106-28-5, Fig. 1A), 2-*trans*,6-*cis*-Farnesol (CAS 3879-60-5, Figure 1B), 2-*cis*,6-*trans*-Farnesol (CAS 3790-71-4, Fig. 1C) and *cis,cis*-Farnesol (CAS 16106-95-9, Fig. 1D). Farnesol is also commercially available as a mixture of isomers (CAS 4602-84-0).

Farnesol presents itself as an uncolored liquid oil with a sweet, soft and delicate smell. This substance has a wide application in the cosmetic and perfumery industries (Lapczynski et al., 2008), it is used to improve sweet flower-based perfume scents and as an antibacterial cosmetic (Buchbauer and Ilic, 2013). In the food industry, farnesol has been used as a flavoring agent, and has been identified in more than 30 essential oils and other flora products used in food production. Examples of these products include: apricot, citrus peel oils, grapefruit juice, strawberry jam, ginger, clove bud, hop oil, cardamom, ginger, thyme, beer, whiskey, basil, papaya, anise seed and German chamomile (Burdock, 2010; Oser, 1965).

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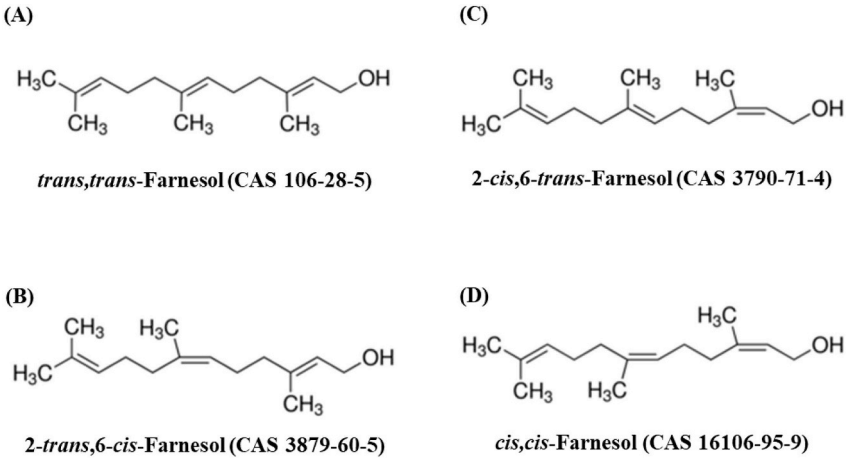

Fig. 1. Structural representation of the different farnesol geometric isomers.

Terpenes are compounds with natural occurrence, frequently found in essential oils, with monoterpenes and sesquiterpenes found at greater quantities (La Cruz et al., 2014; Lapczynski et al., 2008). Substances belonging to this secondary metabolite class are used as aromatizers, cosmetic fragrances and perfumes, alimentary adjuvant (de Siqueira et al., 2014) and as active principles or drug excipients (Oliveira et al., 2014).

The growing interest in studying terpenes is associated with their clinical application potential, thus terpenes show different biological properties, which can be useful in different disease treatments which affect organic systems, such as: anti-fungal, anti-bacterial, anti-viral, anti-tumor, anti-parasitic, hypoglycemic, anti-inflammatory and analgesic effects (Paduch et al., 2007).

In view of the terpenes therapeutic potential, especially sesquiterpene compounds, and the scarce existence of studies evaluating the therapeutic and toxic effects of farnesol, the objective of this study was to perform a SR comprised of pre-clinical and clinical studies which investigated the pharmacological and toxicological effects of this substance. The research was lead based on the following guiding question: What are the pharmacological and toxicological properties of farnesol?

2. Methods

2.1. Search strategy

This SR was executed according to PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Moher et al., 2009).

The article search was performed from September to December 2017 at PubMed (of the US National Library of Medicine National Institutes of Health), MEDLINE (of the Virtual Health Library), SciVerse Scopus and Web of Science electronic databases, using the descriptor combinations: “farnesol and pharmacological effect” and “farnesol and toxicology”. The descriptor combinations mentioned above led to the following searches: ("farnesol"[MeSH Terms] OR "farnesol"[All Fields]) AND ("pharmacology"[MeSH Terms] OR "pharmacology"[All Fields] OR "pharmacological"[All Fields]) AND effect[All Fields]; ("farnesol"[MeSH Terms] OR "farnesol"[All Fields]) AND toxicological[All Fields]; TW: (farnesol AND pharmacological effect) AND (instance:"regional"); TW: (farnesol AND toxicological) AND (instance:"regional").

The inclusion criteria used were original articles from preclinical and clinical studies investigating the pharmacological and toxicological effects of farnesol, published between January 1960 to December 2017, written in English, Portuguese and Spanish.

2.2. Study selection

Two independent researchers carried out the search and selection of articles (G.A.D. and D.S.B.). Article screening was performed evaluating the title and abstract using an eligibility criteria evaluation sheet. Afterwards, the selected publications underwent a complete reading, this being an essential step to confirm the inclusion criteria. Eventual disagreements were solved through consensus of both researchers. The resulting articles were carefully revised with the objective of identifying those studies within the inclusion criteria and to extract data.

2.3. Study methodologic quality/bias risk evaluation

The methodological quality and study bias risk were evaluated using the SYRCLE's RoB (Hooijmans et al., 2014) tool for preclinical studies – *in vivo* and ex-vivo – with non-human animals; while the criteria set out by the Cochrane Collaboration's (Higgins et al., 2011) were used to evaluate clinical studies. This analysis was not carried out for pre-clinical *in vitro* studies as a validated tool for this purpose does not exist.

The SYRCLE's RoB tool, made based on the Cochrane Collaboration's criteria, is adapted to evaluate the methodologic quality and bias risk of experimental studies with non-human animals. This tool is composed of 10 inputs based on six bias types: selection bias, performance bias, detection bias, friction bias, bias notification and other bias (Hooijmans et al., 2014). The Cochrane Collaboration's tool considers the follow study items: random sequence generation, allocation, blindness, incomplete outcome data and funding source bias (Higgins et al., 2011). The studies were classified as “low risk of bias”, “high risk of bias” and as “unclear risk of bias”.

2.4. Extraction and data analysis

Two independent researchers carried out the extraction and data analysis (G.A.D. and D.S.B.) using a selection criteria list, which had its accuracy verified and analyzed by both researchers.

The data extraction process and description synthesis obeyed the PICOT acronym (P-population, I-intervention, C-control, O-outcome, T-Type of study). Extracted items included information relating to the study type, specie, strain and/or cell lineage used, type and origin of geometric isomers study aims, dose and/or tested concentration, administering route, main results and conclusion, as described on literature. However, the statistical grouping (metanalysis) was not possible due to methodological heterogeneity between the studies.

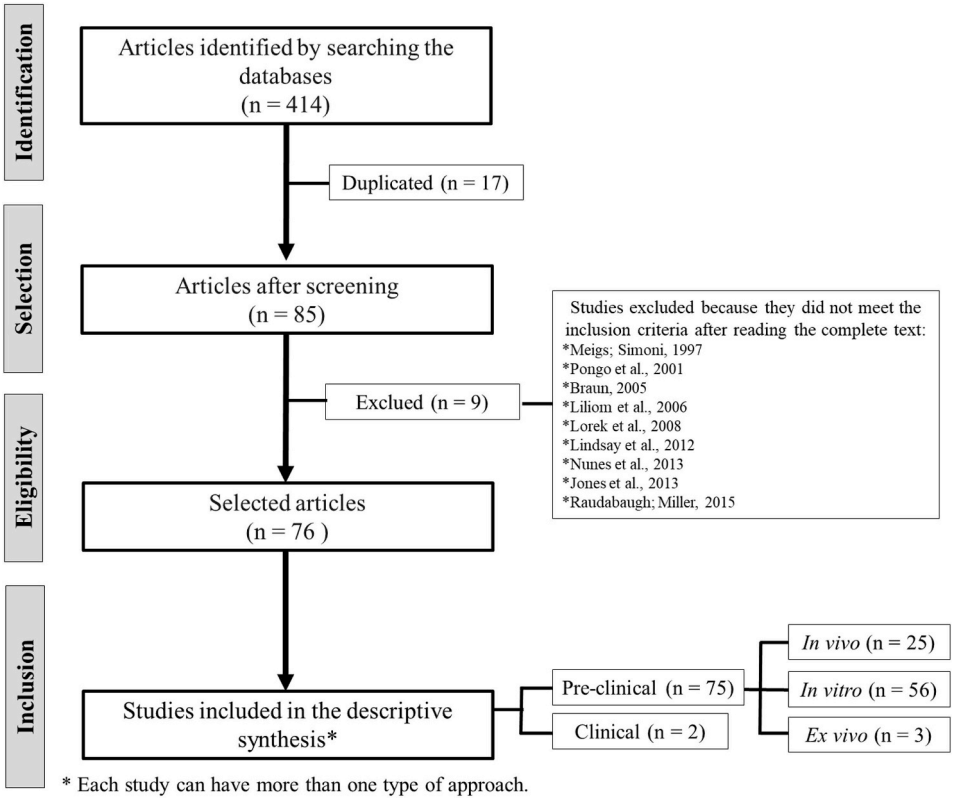

Fig. 2. Search parameters and selection results.

3. Results and discussion

This review searched for studies evaluating the pharmacological and toxicological effects of farnesol. A Primary research identified 414 articles: 390 with the descriptor "farnesol and pharmacological effect" and 24 with the descriptor "farnesol and toxicology". 27 articles were acquired from MEDLINE, 326 from PUBMED, 40 from SCOPUS and 21 from Web of Science. After screening, 102 articles fulfilled the inclusion criteria: 5 from MEDLINE, 83 from PUBMED, 8 from SCOPUS and 6 from Web of Science. From the total included by the inclusion criteria, articles indexed in two or more database were considered once, whereby 9 were excluded from the total, thus 76 articles were selected for the final analysis (Fig. 2). Regarding the study types, 75 were pre-clinical while 2 were of clinical nature, with some containing both approaches. Preclinical studies had more *in vitro* assays (n = 56) than *in vivo* (n = 25) and *ex vivo* (n = 3) assays (Fig. 2).

The selected studies were separated and gathered into five categories according to the farnesol effect: 1) Antimicrobial effect; 2) Antitumor effect; 3) Nervous and cardiovascular system effects; 4) Metabolic and hepatic effects and 5) Other pharmacological and toxicological effects. When grouped, 51.32% (n = 39) of publications investigated the antimicrobial effect of farnesol, 22.37% (n = 17) the antitumor effect, 13.16% (n = 10) the nervous and cardiovascular system effects, 5.26% (n = 4) the metabolic and hepatic system effects and 7.86% (n = 6) evaluated other pharmacological and toxicological effects such as anti-inflammatory and antioxidant activity. Among the studies included in this SR, 56 studies administered farnesol directly in the action site (*in situ*), 17 used the oral route (po.), 6 used the intraperitoneal route (i.p.) and 4 administered the product topically, using different doses and/or concentrations.

In the literature, farnesol is reported to be a safe substance and endowed with biological and pharmacological properties that may be useful in the treatment of various diseases. *In vitro* studies have demonstrated that farnesol shows a toxic potential inducing apoptotosis in different types of cell lines (Au-Yeung et al., 2008; Lee et al., 2015; Park et al., 2014; Wiseman et al., 2007). However, this substance has shown a selectivity in promoting cytotoxic effects in cells with malformations (Adany et al., 1994). Regarding the toxicity of farnesol *in vivo*, studies have shown that, when it is administered orally in rats or mice, it exhibited a mean lethal dose (LD50) ≥5000 mg/kg (Hoffmann-LaRoche, 1967; BASF, 1978, 1981; Moreno, 1974; Sterner and Stiglic, 1976).

In the study carried out by Oliveira-Júnior et al. (2013), evaluating the neurotoxic activity of farnesol in mice, the authors observed that at doses of 50 and 100 mg/kg this substance showed no toxic effects, since no lesions were found in the regions evaluated (hippocampus and striatum). On the other hand, studies have demonstrated the potential of farnesol protecting different vital organs that usually suffer from the damages caused by toxic subtances. There are important examples of the protective effects promoted by farnesol including: cardioprotection (Ferdinandy et al., 1998; Szücs et al., 2013), neuroprotection (Santhanasabapathy and Sudhandiran, 2015), hepatoprotection (Vinholes et al., 2014).

3.1. Antimicrobial effect

More than 50% of the articles included in this SR investigated the antimicrobial effect – antibacterial, antifungal and antiprotozoal activity – of farnesol in isolation and/or associated to commercially available antibacterial and antifungal drugs. It was observed that most of the studies included in this category do not specify the type of farnesol isomer used in the research (Table 1).

In the antiprotozoal evaluation, only the study carried out by Rodrigues Goulart et al. (2004) has investigated the farnesol (isomers unspecified) effect on parasites (*Plasmodium falciparum* clones). In this study, the authors observed the dolichol biosynthesis inhibitory action mediated by farnesol (isomers unspecified) in the trophozoite and schizont stages of these parasites with an mean inhibitory concentration (IC_{50}) of 60 μM, resulting in a decrease of isoprenyl precursor

incorporation into proteins (Rodrigues Goulart et al., 2004).

There is a predominance of studies regarding farnesol's antibacterial activity, which evaluate its effect against Gram-positive bacterial strains. *Staphylococcus* genus species was the most commonly used in the articles included in this SR. This predominance may be justified by farnesol's natural origin, since the literature cites Gram-negative bacteria as being more resistant to natural products (Veras et al., 2017). Holley and Patel (2005) and Oladimeji et al. (2004) affirmed that this resistance is due to the capacity of the membrane present in these bacteria to form a complex wrap capable of protecting them against natural antibacterial action. This information corroborates with the data obtained by Kaneko et al. (2011), where the authors evaluated the farnesol (isomers unspecified) effect against different Gram-positive bacterial strains (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus warneri*, *Staphylococcus xylosus*, *Enterococcus faecalis* and *Enterococcus faecium*) and Gram-negative strains (*Escherichia coli* and *Pseudomonas aeruginosa*), observing that farnesol was effective inhibiting the growth of Gram-positive bacteria, however, it was not effective against Gram-negative bacteria.

On the other hand, studies have also demonstrated that different isomers of farnesol (such as: *trans*-Farnesol and *trans,trans*-Farnesol) is capable of inhibiting Gram-negative bacterial growth (Castelo-Branco et al., 2016; Abdel-Rhman et al., 2015; Gonçalves et al., 2011) and that the *trans,trans*-Farnesol promotes a reduction of virulence factors (for example: hemosilin) (Abdel-Rhman et al., 2015). According to Castelo-Branco et al. (2016), in addition to farnesol (isomers unspecified) antibacterial activity against mature *Burkholderia pseudomallei* biofilms, farnesol also promoted a synergistic effect when associated to antibiotics commonly used to treat infections derived from these pathogens (amoxicillin, ceftazidime, doxycycline and sulfamethoxazole-trimethoprim). The authors suggest that this synergism may be due to the polymeric biofilm inhibition coused by farnesol, in the extracellular matrix.

As for the farnesol effect against Gram-positive bacteria, its different isomers has antibacterial action against many different bacteria and other forms included in this classification, as an example, biofilms (Fernandes et al., 2016; Horev et al., 2015; Mogen et al., 2015; Gomes et al., 2011a; Unnanuntana et al., 2009), planktonic forms (Horev et al., 2015), clinical isolates (Akiyama et al., 2002) and antibiotic-resistant bacteria (Bhattacharyya et al., 2014; Kuroda et al., 2007).

Studies have demonstrated that farnesol (isomers unspecified) causes damage to bacterial cell walls as part of the mechanism of action involved in its antibacterial activity against Gram-positive bacteria (Cerca et al., 2012; Gomes et al., 2011a; Kuroda et al., 2007). This action is due to lipid loss, which is essential for membrane biosynthesis. This damage is responsible to promote cellular content release and increasing bacterial susceptibility to antibiotic action (Kaneko et al., 2011; Kuroda et al., 2007). Kaneko et al. (2011) proposes that the lipid loss may be coused due to the mevalonate pathway inhibition induced by farnesol (isomers unspecified), through the HMG-CoA reductases (3-hidroxy-3-methyl-glutaryl-coenzyme A reductase, class I and II), using a mechanism different from statins. Additionally, farnesol (isomers unspecified) reduces some virulence factors associated with bacterial resistance, such as staphyloxanthin and protein A suppression as well as reduction in β-Lactamases enzymatic action (Kuroda et al., 2007).

The studies included in this SR used more species from the Candida genus, predomintly *Candida albicans*, when evaluating the farnesol effect against fungal cells. Various authors demonstrated that farnesol in isolation and/or in association with antifungal drugs is capable of suppressing the growth of and deterring *C. albicans* infections (Fernandes et al., 2016; Katragkou et al., 2015; Décanis et al., 2009; Hisajima et al., 2008; Saidi et al., 2006; Jabra-Rizk et al., 2006a; Ramage et al., 2002). It is worth mentioning that regarding the farnesol action on *C. albicans* strains, only Fernandes et al. (2016) have specified the isomer type (*trans,trans*-Farnesol) used in their study.

In a study carried out by Fernandes et al. (2016), the authors demonstrated that *trans,trans*-Farnesol at concentrations greater than 12.5 mM have an antimicrobial effect similar to chlorhexidine gluconate. Katragkou et al. (2015) observed the farnesol (isomers unspecified) effect when combined with antifungals drugs as fluconazole, amphotericin B and micafungin demostrate a synergistic effect, which is more significant when associated with micafungin. Jabra-Rizk et al. (2006) demonstrated that concentrations at 30–50 μM farnesol (isomers unspecified) promote a synergistic effect when associated to fluconazole.

When evaluated in isolation at a concentration of 300 μM, farnesol (isomers unspecified) is capable of inhibiting the germination and adherence of *C. albicans* yeast resulting in scarce or inexistent biofilms (Saidi et al., 2006; Jabra-Rizk et al., 2006a; Ramage et al., 2002). Interestigly Ramage et al. (2002), proposed that this effect may be due to lower levels of HWP1 (hifal wall protein 1) and mRNA (messenger ribonucleic acid) in *C. albicans* cells caused by farnesol treatment.

Hisajima et al. (2008), when investigating farnesol (isomers unspecified) effects against oral candidiasis in mice, observed that in doses ranging from 1.125 to 9 μM farnesol was capable to protect against oral candidiasis, this being a dose-dependent effect. The histological results showed that this substance suppressed *C. albicans* mycelial growth at the tongue's surface. Décanis et al. (2009) when evaluating the synergistic interaction between epithelial cells and farnesol against *C. albicans,* observed that epithelial protection would be mediated by an increase in TLR-2, IL-6 and hBD2 promoted by farnesol (isomers unspecified). On the other hand, results from Navarathana et al. (2007a and 2007b) showed that *trans,trans*-Farnesol or farnesol mixed isomers increases susceptibility to systemic candidiasis in already infected mice, with farnesol potentially being a virulence factor for this fungus.

Brilhante et al. (2013) and Rossignol et al. (2007) stated that *trans,trans*-Farnesol or farnesol mixed isomers affects the steroidal distribution in *Coccidioides posadasii* and *Candida parapsilosis* strains, respectively. However, Rossignol et al. (2007), demonstrated that *trans,trans*-Farnesol affects the expression of several genes linked to the metabolism of phospholipids and amino acids such as GRP2 and ADH7.

Other pathways involved in the antifungal action of the different farnesol isomers are dependent of caspase (Liu et al., 2010) and of mitochondrial ROS (reactive oxygen species) generation (Semighini et al., 2006; Machida et al., 1998). As a result, from the oxidative stress, fungal cells increase the number of condensed nuclei and undergo an apoptotic process (Semighini et al., 2006) which can cause total cytoplasmic degeneration (Derengowski et al., 2009). Machida et al. (1998) evaluated the mechanism of action responsible for the farnesol (isomers unspecified) inhibitory effect, with concentrations ranging from 6.25 to 200 μM against *Saccharomyces cerevisiae* and demonstrated that the ROS level increase is dose-dependent.

3.2. Antitumor effect

From the 17 articles included in this category, 11 of them did not specify the type of farnesol isomer used. 5 of them investigated the antitumor effect of *trans,trans*-Farnesol and 1 investigated the effect of *trans*-Farnesol.

The results obtained has been shown that different isomers of farnesol are endowe with chemotherapeutic properities, effective against different tumor, such as leukemia, breast cancer, prostate cancer, different types of carcinomas, adenocarcinomas and tumor changes induced by different chemical agents (Table 2). This corroborates with data found by Rougereau and Rougereau-Person (2004) who filed a patent concerning the use of terpene compounds associated with pharmaceutical vehicles as useful agents in different cancer preventions and treatments, with farnesol being among them. Additionally, sesquiterpene compounds are cited because of their toxic action against cancerous human cells (Ghantous et al., 2010; Zhang et al., 2005; Lee et al., 1971, 1977).

In the literature, *trans,trans*-Farnesol has a selective toxicity that

induce apoptosis of defective cells. This selectivity was first verified in the study carried out by Adany et al. (1994), whose goal was to compare the *trans,trans*-Farnesol effect (at concentrations from 0 to 45 μM) against different neoplastic cell lines and cells from normal tissues. With the results obtained, the authors observed that this substance was more effective inhibiting the growth and inducing apoptosis in neoplastic cells when compared to non-tumor cells. It was also observed that concentrations ≥10 μM inhibited more significantly tumor cells. When tested at a concentration of 45 μM, farnesol provoked mortality in nearly all malignant cells after 48 h of incubation.

The mechanism of action through which farnesol promotes its antitumor effect is due to different signaling pathways. Lee et al. (2015) observed that in multiple human myeloma cells (U266), farnesol (isomers unspecified) promotes a genotoxic effect blocking the activation of the induced and constitutive signal transducer and transcription activator 3 (STAT3), response mediated by the inhibition of Janus-like kinase (JAK1 and JAK2) and c-Src kinases activation. STAT proteins, especially STAT3, possess important roles on the survival and proliferation of many tumor types, such as leukemia, lymphoma, solid tumours and multiple myelomas (Ahn et al., 2008; Buettner et al., 2002). This pathway may be activated by interleukins (e.g. IL-6) and growth factors (e.g. EGF). After activation, STAT3 undergoes a homodimerization process and induced phosphorylation, this phosphorylation is mediated by the activation of JAK and c-Src kinases (Ren and Schaefer, 2002; Schreiner et al., 2002). As a consequence, nuclear translocation, DNA binding and subsequent gene transcription occurs (Ihle, 1996). STAT3 activation may result in the expression of numerous gene products required for tumor cell survival (eg, survivin, Bcl-x1, Bcl-2), proliferation, metastasis and angiogenesis (Aggarwal et al., 2006). Therefore, substances which act by inhibiting STAT3 activation have the potential to act as preventative agents and in the treatment of cancers (Yu and Jove, 2004).

In addition to the mechanisms described, farnesol (isomers unspecified) induces U266 cell apoptosis through caspase-3 activation (Lee et al., 2015). This data corroborates with Lee et al. (2015) study, which evaluated the anti-carcinogenic effect of farnesol in human colon cancer cells. In this study the authors showed that farnesol can induce cancerous cell apoptosis (HT-29 and HCT-116) through caspase-3 activation, which leads to the cleavage of the PARP [Poly (ADP-ribose) polymerase cleavage] enzyme and reduction of BclxL and survivin protein expression.

When it comes to leukemic cell lines, one of the action mechanisms mediating the cytotoxic effect is induced by the *trans,trans*-Farnesol action on phospholipase C (PLC) dependent signal transduction (Voziyan et al., 1995), since CEM-C1 acute leukemic cells treated with 20 μM of farnesol causes a reduction in the incorporation rate of radioactively labeled diacylglycerol – DAG (a physiological activator of PKC - protein kinase C) and cellular phosphocholine - both products generated by phosphatidylcholine (PC) degradation - which indicates PLC inhibition.

Voziyan et al. (1993), when investigating the mechanism of action of PC biosynthesis inhibition caused by farnesol (20 μM) using the same leukemic cells line as the one mentioned above, the authors observed that *trans,trans*-Farnesol did not promote CTP (choline-phosphate cytidylyltransferase) and DAG enzymatic activity alteration. However, farnesol was capable of inhibiting [3H]choline incorporation into cell lipid membrane, reducing radioactive label incorporation in PC and promoting a reduction in CPT enzyme activity, thus inhibiting PC biosynthesis. As a consequence of the aforementioned mechanisms of action, leukemic cells suffer from decreased cell viability and apoptotic DNA fragmentation in the internucleosome ligand regions (Voziyan et al., 1995; Haug et al., 1994). Joo et al. (2015) demonstrated another pathway involved in leukemic cell apoptosis induction by *trans,trans*-Farnesol involving the activation of the apoptosome through the PERK-eIF2αATF3/4 cascade intrinsic pathway, in a manner independent of MAPKs-induced activation.

Farnesol (isomers unspecified) has shown to be efficient protecting against genotoxic damages induced by different chemical agents [$CdCl_2$, benzo(a)pyrene, DMBA, TPA, Fe-NTA and azoxymethane] due to its antioxidant action (Chaudhary et al., 2009; Jahangir and Sultana, 2008; Jahangir et al., 2005, 2006), its interference in gene transcriptional signal transduction (Chaudhary et al., 2009), and by modifying the metabolism of some compounds as decreasing NADPH-cytochrome P450 reductase and mycosomic epoxide hydrolase enzyme activities (Qamar et al., 2012) as well as by the increase in glutathione S-transferase enzyme activity (Qamar et al., 2012; Jahangir and Sultana, 2008; Jahangir et al., 2006).

3.3. Nervous and cardiovascular system effects

There are few studies investigating farnesol action on the nervous system. From the articles included in this SR, three studies evaluating the effect of farnesol on the nervous system demonstrated that farnesol (isomers unspecified) possesses analgesic due to possible interactions with K^{+}_{ATP} channels and 5-hydroxytryptamine receptors (5-HT3) (Silva et al., 2017), anxiolytic, sedative, depressant (Shahnouri et al., 2016) and neuroprotective properties (Santhanasabapathy and Sudhandiran, 2015) (Table 3). From the studies investigating the action of farnesol in the CNS, only Santhanasabapathy and Sudhandiran (2015) specifies the type of isomer used (*trans*-Farnesol).

Shahnouri et al. (2016) associated the anxiolytic effect promoted by farnesol (isomers unspecified) to a reduction in cortisol plasmatic levels due to the administration of farnesol (isomers unspecified). As for the neuroprotective effect, Santhanasabapathy and Sudhandiran (2015) claimed that *trans*-Farnesol regulates the intrinsic apoptotic cascade leading to the protection against oxidative damage promoted by lipopolysaccharides.

The effects observed by Silva et al. (2017) and Santhanasabapathy and Sudhandiran (2015) corroborate with the study carried out by Oliveira-Júnior et al. (2013), which aimed to evaluate farnesol antinociceptive and neurotoxic activity in mice, where the authors observed that farnesol (50, 100 and 200 mg/kg doses, i.p.) effectively reduced the pain stimulus and that farnesol at 50 and 100 mg/kg concentrations did not cause brain injury in the evaluated brain regions (hippocampus and striatum).

In the cardiovascular system, farnesol (isomers unspecified) and *trans,trans*-Farnesol possesses cardioprotective effect and promotes cardiovascular actions leading to a decrease in blood pressure, such as: negative inotropism in the left atrium, change in Ca^{+2} conductance in the vascular cell membrane and vasodilation (Table 3).

Regarding the mechanisms of action responsible for farnesol cardiovascular effects, when evaluating its cardioprotective effect in rats with ischemic heart lesions Szücs et al. (2013) observed that farnesol (isomers unspecified) decreases the size of the infarcted area, probably by its interaction with the mevalonate pathway which promotes an increase in proteins by geranylgeranylation. However, in Ferdinandy et al. (1998) study, the authors noted that farnesol (isomers unspecified) restores cardiac preconditioning in rats with hypercholesterolemia and does not affect the severity of heart ischemia in rats with a high cholesterol diet. With regards to the vasoactive effects of farnesol (isomers unspecified) and *trans,trans*-Farnesol, studies have shown that this substance acts blocking L-type Ca^{+2} channels (Luft et al., 1999; Roullet et al., 1996, 1997), with this inhibitory action being independent of Ca^{+2} channel G proteins and being present only in cells expressing the α_1 subunit (Luft et al., 1999).

3.4. Metabolic and hepatic effects

From the 4 articles included in this classification, 2 evaluated the effect of farnesol on the hepatic system and 2 evaluated its metabolic effects (Table 4). Regarding the type of farnesol isomer investigated, only the Špičáková et al. (2017) study does not specify the type of

Table 1
Descriptive summary of the studies investigating the antimicrobial effect of farnesol.

Reference	Type of study (species, cell strain and/or cell line)	Farnesol geometric isomers/origin (as described in the literature)	Aims	Dose/Concentration (route of administration)	Main results and conclusion (as described in the literature)
Castelo-Branco et al. (2016)	*In vitro* preclinical study (clinical isolates of *B. pseudomallei*)	IU (Sigma-Aldrich)	To analyse the susceptibility of *B. pseudomallei* biofilms to farnesol alone and in combination with antimicrobials conventionally used in the treatment of melioidosis	0.58–600 mMl^{-1} (*in situ*)	Farnesol has presented antimacrobial activity against mature biofilms of *B. pseudomallei*. This substance has increased the bacteria's susceptibility to routinely utilized antibiotics to treat melioidosis (amoxicillin, ceftazidime, doxycycline e sulfamethoxazole-trimethoprim), thereby, this effect may be due to polymeric extracellular matrix interuptions of the biofilm coused by farnesol.
Fernandes et al. (2016)	*In vitro* preclinical study (cell strains of *Candida albicans* and *Streptococcus mutans*)	*trans,trans*-Farnesol (Sigma Aldrich)	To evaluate the effects of different concentrations of *trans,trans*-Farnesol on single and mixed species biofilms of *C. albicans* and *S. mutans*	1.56–300 mM (*in situ*)	Evaluating its Minimum Inhibitory Concentration (MIC), the strains of *S. mutans* were more susceptible to *trans,trans*-Farnesol action than the strais of *C. albicans*. This effect may be related with structural differences in the cell of the tested microorganisms, giving that, the thicker cell wall finded in *C. albicans* may have impaired *trans,trans*-Farnesol's action. Evaluating *trans,trans*-Farnesol's inhibitory effect in biofilms of isolated and mixted species, the concentrations tested have produced significant reductions in the biomass total, in the number of feasible cells and in the metabolic activity against the bacterial strains tested, except for the metabolic activity of *S. mutans* in biofilms of isolated species. Using concentrations above 12.5 mM the *trans,trans*-Farnesol's effect was similar to that of chlorhexidine gluconate (positive control).
Kovács et al. (2016)	*In vitro* preclinical study (clinical isolates of *C. parapsilosis*)	IU (Sigma-Aldrich)	To examine the *in vitro* interactions between two echinocandins (caspofungin and micafungin) and farnesol against *C. parapsilosis* biofilms	1.17–300 μM (*in situ*)	Farnesol has promoted a synergistic effect when associated with caspofungin e micafungin against the biofilms of *C. parapsilosis*. The association of caspofungin + farnesol has promoted a significant reduction on fungal cells metabolic activity in three combinations tested (4 mg/L+75 μM, 8 mg/L+75 μM e 16 mg/L+75 μM) between 3 and 24 h when compared with the control groupe. On the other hand, the combination of micafungin + farnesol utilizing the same three concentration, has promoted a significant inhibition only between 3 and 12 h, but not to 24 h when compared with the control groupe.
Katragkou et al. (2015)	*In vitro* preclinical study (cell strains of *C. albicans*)	IU (Sigma-Aldrich)	To investigate the *in vitro* effects of farnesol in combination with different classes of different antifungal agents (triazoles – fluconazole, polyenes – amphotericin B, chinocandins – micafungin) against *C. albicans* biofilms	0.58–300 μM (*in situ*).	Farnesol has developed a synergistic interaction when combined with antifungals (fluconazole, amphotericin B e micafungin), presenting a greater synergistic effect when associated with micafungin. The farnesol's association with antifungal agents also leads to structural changes in *C. albicans* biofilms.
		IU (Sigma Chemical Co.)		0.0009 a 0.5 μM (*in situ*)	

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Table 1 (*continued*)

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Brilhante et al. (2015)	*In vitro* preclinical study (clinical isolates of *Histoplasma capsulatum* var. *capsulatum*)		To evaluate the *in vitro* susceptibility of *Histoplasma capsulatum* var. *capsulatum* to the antifungals itraconazole and amphotericin B and the compound farnesol, alone and combined, as well as to determine the *in vitro* antifungal activity of these compounds against *H. capsulatum* var. *capsulatum* biofilms		The farnesol has presented antifungal activity against *H. capsulatum* in its yeast and filamentous phases, with MIC values varying from 0.78 to 0.312 μM. It was observed a synergistic effect when itraconazole + farnesol (100% e 83.30% from its isolated forms of yeast and mycellium, respectively) and anphoterecin B + farnesol (37.50% e 44.40% from its isolated forms of yeast and filamentous, respectively) were combined.
Horev et al. (2015)	*In vivo* and *in vitro* preclinical study (*Sprague-Dawley* rats and biofilms and planktonic forms of *Streptococcus mutans*)	IU	To evaluate the effect of free and nanoparticulate farnesol on the virulence of oral biofilms	1.5 mg/mL free nanoparticles and 0.3 mg/ml nanoparticles + farnesol (topical use in *in vivo* and *in situ* assays for *in vitro* assays)	Farnesol when carried by nanoparticles, was 4-fold more effective in interrupting formation of *S. mutans* biofilms than free farnesol, and it has also reduced the severity and the number of carious lesion in rats.
Mogen et al. (2015)	*In vitro* preclinical study (cell strains of *S. mutans*)	IU	Understand the morphological changes and degree of cell death in *S. mutans* biofilms when co-cultured with NBMs (non-binding micelles) containing hydrophobic antimicrobial compounds	50 μg/mL (*in situ*)	In each cell strains of *S. mutans* tested, the biomass was significantly decreased in those biofilms tested with farnesol olone and NBMs with farnesol, compared with those untreated biofilms. The farnesol formulated with pluronics induce changes in the biofilm architecture, Presumably through its interaction with a sucrose-dependent biofilm matrix. The farnesol formulated with pluronics was also effective in promoting death of the *S. mutans* strains, however, this effect ar not related with tower formation, which occurs in sucrose-dependent biofilms.
Abdel-Rhman et al. (2015)	*In vitro* preclinical study (clinical isolates of de *P. aeruginosa*)	*trans,trans*-Farnesol (Sigma-Aldrich)	To investigate the effect of *C. albicans* quorum sensing compounds, tyrosol and *trans,trans*-Farnesol, on the antibiotic resistance and some of the virulence factors of Egyptian isolates of *P. aeruginosa*	10–200 μM (*in situ*)	*trans,trans*-Farnesol has inhibited the growth of *P. aeruginosa* in 10% and 30% using concentrations of 50 and 200 μM, respectively. Regarding virulence factors, farnesol has reduced the hemolysins produced by *P. aeruginosa*, but it has not significantly reduced the proteases reduction.
Bhattacharyya et al. (2014)	*In vitro* preclinical study [(cell strains of *S. aureus* and Methicillin-resistant *S. aureus* (MRSA)]	IU	To evaluate the effect f the incorporation of vancomycin and farnesol in silica sol-gel as a therapeutic strategy for the simultaneous delivery of antibiotic and adjuvant in the treatment of infections by MRSA	10%, 20% and 30% (% by weight - weight % is percentual of the weight of the drug for the weight of SiO_2 – silicon dioxide) (*in situ*)	This study has demonstrated that films of sol-gel may be administered in titinium implants for controlled release of antibiotics and adjuvantes. Farnesol also has shown to be a powerful adjuvante, increasing the vancomycin's antibiotic action efficiency.
Wang et al. (2014)	*In vitro* preclinical study (cell strains of *Aspergillus flavus*)	IU (Sigma-Aldrich)	To evaluate the apoptotic effect of farnesol against strains of *A. flavus*	50–400 μM (*in situ*)	Farnesol has inhibited the germination and growth of *A. flavus*, being effective inducing apoptosis through a mechanism of caspases activation and ROS production.
Brilhante et al. (2013)	*In vitro* preclinical study (clinical and environmental cell strains of *C. posadasii*)	Mixture of isomers (Sigma-Aldrich)	To evaluate the *in vitro* antifungal activity of farnesol (mixture of isomers) alone and in combination with antifungal agents against clinical and environmental strains of *C. posadasii*, as well as to determine its effect on	0.00000667–0.0137 mg/L (*in situ*)	Farnesol (mixture of isomers) has shown a MIC varying from 0.00171 to 0.01369 mg/L against all strains tested. When combined with antifungals (amphotericina B, itraconazole, voriconazole and caspofungin),

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			the synthesis of ergosterol and on cell permeability		farnesol (mixture of isomers) has presented synergistic effects. Regarding ergosterol quantification, it was observed that the exposure to the farnesol (mixture of isomers) is subinhibitory concentrations have diminished the quantity of ergosterol extracted from fungal cells. Furthermore, farnesol (mixture of isomers) has also shown lower MIC values when the strains were submitted to osmotic stress.
Cordeiro et al. (2012)	*In vitro* preclinical study (cell strains of *Cryptococcus neoformans* and *Cryptococcus gattii*)	IU	To evaluate the antifungal potential of farnesol against *C. neoformans* and *C. gattii*, as well as to investigate the effect of farnesol on phospholipase and protease activities	0.29–150 μM (*in situ*)	Farnesol has ihibitory activity against *C. neoformans* and *C. gattii* with MIC range of 0.29–75.0 μM, showing no significant interference on production of the virulence factors analised (phospholipase and protease activity).
Cerca et al. (2012)	*In vitro* preclinical study (clinical isolates of biofilm-producing *S. epidermidis* strain)	IU (Sigma-Aldrich)	To analyse of structure, viability and biomass changes of *S. epidermidis* biofilms exposed to farnesol, as well as to compare it with biofilms exposed to vancomycin or rifampicin	300 μM (*in situ*)	Farnesol has not significantly diminished the cell viability of *S. epimermidis* biofilms, however, it has efficiently diminished the biomass in these biofilms. Farnesol has also caused vancomycin-similar damages in cell membrane. Moreover, farnesol may induce the biofilm detachment, as determined by the biomass reduction.
Gomes et al. (2011)	*In vitro* preclinical study (clinical isolates of biofilm-producing *S. epidermidis* strain)	IU (Sigma-Aldrich)	To evaluate the effect of farnesol on the structure and composition of *S. epidermidis* biofilm matrix	30 and 300 μM (*in situ*)	The biofilms of *S. epidermidis*, in the presence of farnesol (300 μM), has shown less biomass presence and composition changes in its matrix. It has also been observed, changes in its biofilms spatial structure, when analyzed with confocal laser scanning microscope. Obtained results from extracellula polymers quatification and fluorescent detection of agglutinin in wheat germ, sugests that farnesol causes interuption of the cytoplasmic membrane and, consequently, intracelular contente release.
Gonçalves et al. (2011)	*In vitro* preclinical study (cell strains of *Staphylococcus aureus* and *E. coli*)	*trans*-Farnesol (Aldrich Cemical)	To evaluate the antibacterial effect of a wide range of antibiotic structures when combined with *trans*-Farnesol or other eight sesquiterpene compounds against strains of *S. aureus* and *E. coli*	14–222 μg/plate (*in situ*)	*trans*-Farnesol has developed an antibacterial effect in all concentrations tested against *S. aureus* e *E. coli* strains, being devoid of mutagenic effect at these concentrations. Moreover, it was observed that sesquiterpene compounds have increased the antibacterial activity in antibiotics tested against *S. aureus*. However when it was tested against *E. coli*, an antagonistic effect was observed for several combinations of sesquiterpenes with antibiotics on its growth.
Gomes et al. (2011b)	*In vitro* preclinical study (cell strains of *S. epidermidis*)	IU (Sigma-Aldrich)	To investigate the post-antimicrobial effect of farnesol against *S. epidermidis* and to evaluate the antimicrobial action of farnesol alone and combined with antibiotics (vancomycin, tetracycline and rifampicin) against planktonic and biofilm strains of *S. epidermidis*	100, 200 and 300 μM (*in situ*)	Farnesol has shown to be a potential therapeutic agent used as an antibiotic adjuvant for the treatment of planktonic cells of *S. epidermidis*. Furthermore, farnesol alone and combined with antibiotics were effective in preventing biofilm formation.

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Kaneko et al. (2011)	*In vitro* preclinical study (cell strains of *S. aureus, S. epidermidis*, *S. warneri*, *S. xylosus*, *E. faecalis*, *E. faecium*, *Escherichia coli* and *Pseudomonas aeruginosa*)	IU (Sigma Chemical)	To investigate the mechanism of action by which farnesol exerts its antibacterial effect and inhibits the growth of *S. aureus*	80 mg/mL^{-1} (*in situ*)	Farnesol has developed antibacterial activity against Gram positive bacteria, especially against *S. aureus*, but it has not shown efficacy inhibiting the growth of Gram negative bactirias. Regarding the farnesol's mechanism of action, it can effect the classes of HMG-CoA reductase – classes I and II - by a mechanism that differs from statin. Another pathway involved in the antibacterial action of farnesol is by the inhibition of mevalonate rout.
Liu et al. (2010)	*In vitro* preclinical study (cell strains of *Penicillium expansum*)	IU (Sigma Chemical)	To evaluate the effect of farnesol on the growth of *P. expansum*	25–200 μM (*in situ*)	Farnesol has inhibited the growth of *P. expansum* with approximately Minimum Fungal Concentration (MFC) of 100 μM, this effect is due to the appoptotic action of farnesol by the caspase dependent pathway.
Décanis et al. (2009)	*In vitro* preclinical study (cell strains of *C. albicans*)	IU (Sigma Chemical)	To evaluate the possible synergistic interaction between farnesol and epithelial cells against *C. albicans* infections	10, 100 and 300 μM (*in situ*)	Farnesol induces epithelial cell defence against *C. albicans* infections, this effect is mediated by the increasing TLR-2 (toll-lile receptor 2), IL-6 (interleukin 6) and e hBD2 (human β-defensin-2) expressions.
Gomes et al. (2009)	*In vitro* preclinical study (planktonic and biofilm strains of *S. epidermidis*)	IU (Sigma Chemical)	To investigate the effect of farnesol on planktonic and biofilm cells of *S. epidermidis*	30–300 μM (*in situ*)	Farnesol was effective against planktonic cells, this inhibitory effect is present in small concentrations (100 μM) of this substance. In biofilm cells, farnesol's effect was not as noticeable, once this effect demostrates to be dependent of the methabolic activity and the amount of matrix. The effect of farnesol at the concentration of 200 μM was similar to the effect of vancomycin on the peak serum concentration of planktonic and biofilm cells. Despite this, the loss of cell viability and, consequently, the loss of biofilm formation capacity, induced by farnesol, suggest the potential use of this substance in preventing *S. epidermidis* infections.
Derengowski et al. (2009)	*In vitro* preclinical study (yeast strains of the virulent isolate of *Paracoccidioides brasiliensis*)	Mixture of stereoisomers (Sigma-Aldrich)	To evaluate the effect of farnesol (mixture of stereoisomers) on the growth and morphogenesis of *P. brasiliensis*	2.5–300 μM (*in situ*)	Farnesol (mixture of stereoisomers) concentrations from 2.5 μM (MIC) to 300 μM were effective in inhibiting *P. brasiliensis* growth. When it was tested using concentrations which do not compromise cell (5 a 15 μM), it was observed an effect on fungal morphogenesis coused by farnesol (mixture of stereoisomers), leading to a delay in the germ-tube formation of this microorganism. On the other hand, at concentration of 25 μM, farnesol (mixture of stereoisomers) has shown total cytoplasmic degradation.
Unnanuntana et al. (2009)	*In vitro* preclinical study (*S. aureus* biofilms strains and pre-osteoblastic MC3T3-E1 cells grown on titanium alloy discs)	*trans,trans*-Farnesol (Sigma-Aldrich)	To investigate the effects of *trans,trans*-Farnesol on the formation of *S. aureus* biofilms on orthopedic biomaterials as well as its effects on osteoblasts	0–30 mM (*in situ*)	*trans,trans*-Farnesol (30 mM) has reduced in 104-fold the number of viable bacteria and has completely inhibited biofilm formation, which has lasted at least three days. When tested at low concentrations (0.03 a

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					3 mM), the *trans,trans*-Farnesol has not inhibited biofilm formation, neither it has potentialized the effect of gentamicin sub-maximal concentration. The effect of *trans,trans*-Farnesol was tested in already grown biofilms; this substance has reduced in 56-fold the final bacterial number. When farnesol has been tested on pre-osteoblastic MC3T3-E1 cells, the trans, trans-farnesol (3 mM e 30 mM) has inhibited this cell's propagation.
Hisajima et al. (2008)	*In vivo* and *in vitro* preclinical study (female mice and clinical isolates strains of *C. albicans*)	IU (NacalaiTesque, Inc.)	To investigate the effects of farnesol against oral candidiasis in mice	1.125, 2.25 e 9 μM/mice (po.) in the *in vivo* assays and 50–300 μM (*in situ*) in the *in vitro* assays	Treatment with farnesol using doses varying from 1.125 e 9 μM were effective in protecting from oral candidiasis, characterising this effect as a dose dependent type, as determined by the scores of tongue symptoms. Besides this, the results from histological tests have shown that farnesol suppressed the mycelial growth of *C. albicans* on the surface of the tongues. The group of animals trated with 9 μM had a derease in biomass loss, when compared with the other groups (control and farnesol at doses of 1.125 e 2.25 μM).
Kuroda et al. (2007)	*In vitro* preclinical study [cell strains of Methicillin-susceptible *S. aureus* (MSSA) and MRSA]	IU (Wako Pure Chemical Industries)	To investigate farnesol's synergistic effects on commonly used antimicrobials, b-lactams in particular, and to explore its potential inhibitory effect on cell wall synthesis of *S. aureus*	1 g/L (*in situ*)	Farnesol has icreased the bacteria susceptibility to the action of all antimicrobials tested (ampicillin, oxacillin, cefoxitin, bacitracin, teicoplanin, amikacin, ciprofloxacin) in a varied range, except the claritromicin agains strains of MSSA and MRSA. It has been observed a more significantly bactirial susceptibility when farnesol was associated with oxacillin and cefoxitin. These antibiotics increasing susceptibility by the association with farnesol, is due to the inhibition of the cell wall biosynthesis through the reduction of lipidic support, as well as by the suppression of stafiloxanthin production and the reduction of the β-lactamases enzyme activity. In addition, farnesol has supresed the protein A.
Henriques et al. (2007)	*In vitro* preclinical study (cell strains of *Candida dubliniensis*)	*trans,trans*-Farnesol (Sigma-Aldrich)	To investigate the effect of *trans,trans*-Farnesol on the morphology of *C. dubliniensis*	1.5, 15 and 150 $\mu M\, l^{-1}$ (*in situ*)	The tested concentration of farnesol has not inhibited the *C. dubliniensis* growth rate, nevertheless, this substance has inhibited hyphae and pseudohyphas development. At the concentration of 150 $\mu M\, l^{-1}$ farnesol has completely inhibited hyphae and pseudohyphas development.
Navarathna et al. (2007)	*In vivo* preclinical study (female CF-1 mice infected with *C. albicans*)	Mixed isomers or *trans,trans*-Farnesol (Sigma-Aldrich)	To evaluate whether farnesol affects the progression of disseminated candidiasis in mice	1 ml of 20 mM farnesol (po. and i.p.)	The mice infected by *C. albicans* which has received mixed isomers (1 mL a 20 mM, po.) *trans,trans*-Farnesol (1 mL a 20 mM, i.p.) had higher mortality, so that, the beginning of the group's mortality treated with intraperitoneal farnesol was 30 h earlier than the control group. It has been observed that mixed isomers and *trans,trans*-Farnesol has played, directly or

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					indirectly, an important role in the pathogenesis of the disease, which may represents a virulence factor of *C. albicans*.
Navarathna et al. (2007b)	*In vivo* and *in vitro* preclinical study (female CF-1 mice infected with *C. albicans* and macrophages collected from the peritoneal cavity)	*trans,trans*-Farnesol (Sigma-Aldrich)	To examine the possible role of *trans,trans*-Farnesol in modulating resistance against systemic candidiasis, as well as in T cell modulation and macrophage cytokine expression	1.2 mM in 0.5 of Tween 80 (i.p.) in the *in vivo* assays and 100 μM (*in situ*) in the *in vitro* assays	It was detected an elevation in the levels of TNF-α (tumor necrosis factor alpha) and IFN-γ (interferon gamma) in mice infected with *C. albicans*. The mince pre-treatment with *trans,trans*-Farnesol has significantly reduced the levels' elevation of IFN-γ and IL-12 (interleukin 12), but not of TNF-α. In addition, the mince treated with *trans,trans*-Farnesol has an anexpeted elevation in the levels of IL-5 (interleukin 5). These results have shown that *trans,trans*-Farnesol increases the mince susceptibility of developing systemic candidiasis.
Rossignol et al. (2007)	*In vitro* preclinical study (cell strains of *C. parapsilosis*)	*trans,trans*-Farnesol (Sigma-Aldrich)	To evaluate the transcriptional response of *C. parapsilosis* exposed to *trans,trans*-Farnesol	10–100 μM (*in situ*)	At the concentrations of 50 e 100 μM, farnesol has strongly inhibited *C. parapsilosis* growth, however this effect has not been detected at minor concentrations tested (10 e 20 μM). Evaluating the gene transcription caracteristics, *trans,trans*-Farnesol was tested at the concentration of 50 μM it was observed that *trans,trans*-Farnesol's addition produced a rising in the GRP2 expression by 15-fold of GRP2 (related with GRE2 dependent of NADPH methylglyoxal reductase) and an increase of 6-fold in the expression of ADH7 (a family member of the cinnamyl alcohol dependent of NADPH). Besides this, *trans,trans*-Farnesol has effected the distribution of sterols; affecting the expression of various gens related with phospholipid and amino acids metabolism.
Semighini et al. (2006)	*In vitro* preclinical study (cell strains of *Aspergillus nidulans* and *C. albicans*)	*trans,trans*-Farnesol (Sigma-Aldrich)	To examine the effect of *trans,trans*-Farnesol on filamentous fungi *A. nidulans*	10–250 μM (*in situ*)	The lowest tested concentration of *trans,trans*-Farnesol (10 μM) has completely inhibited the growth of *A. nidulans* hyphae. *trans,trans*-Farnesol has also induced rapid DNA (deoxyribonucleic acid) condensation, being observed an increased number of nucleotide condensation. The results have shown that *trans,trans*-Farnesol induces the apoptosis of *A. nidulans* filamentous cells, by a mechanism that requires functional mitochondria, ROS production and the heterotrimeric G protein complex.
Jabra-Rizk et al. (2006)	*In vitro* preclinical study (cell strains of *C. dubliniensis* and *C. albicans*)	IU (Sigma Chemical Co.)	To evaluate the antifungal effect of farnesol on *C. dubliniensis* and *C. albicans* as well as to determine its MIC and its effect on the integrity of the fungal cell membrane	10, 30 and 300 μM (*in situ*)	It was observed that *C. dubliensis* strains have had 40% of hyphae and pseudohyphae when cultivated in the absence of farnesol. On the other hand, when cultivated with farnesol (300 μM), it has reduced the *C. dubliensis* strains to less than 10%. Furthermore, regarding *C. albicans* strains, they have shown 90% of hyphae when cultivated in the absense of farnesol, however, when they have been cultivaited with farnesol, it has shown

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					a reduction up to only 10% of *C. albicans* hyphae. When evaluated the farnesol's effect on biofilm formation, it has shown that the incubation with farnesol (300 μM) has prevented the well succeed germination of yeast adherent cells, resulting in low levels of biofilm formation to both *C. dubliensis* and *C. albicans* strains tested. Evaluating the MIC of farnesol, it has shown MIC concentrations of 200 μM against *C. dubliniensis* and ≥300 μM against *C. albicans*; indicating that *C. albicans* has developed a higher tolerance to farnesol. The farnesol at concentrations of 30–50 μM has presented a synergetic effect against both *C. dubliensis* and *C. albicans* strains, when combined with fluconazole.
Shintre et al. (2006)	*In vitro* preclinical study (cell strains of *S. epidermidis*, *S. aureus*, *Enterobacter aerogenes*, *Serratia marcescens*, *E. coli*, *Klebsiella pneumoniae* and *P. aeruginosa* and clinical isolates cells of MRSA, *E. faecium* resistant to vancomycin, *Acinetobacter baumannii* and *C. albicans*) and clinical (group of people with 7 healthy volunteers).	IU (Symrise, Totowa, NJ)	To evaluate the synergistic effect of farnesol and different essential oils combined with antimicrobials and to select the most effective synergism for the use of hand hygiene in a group of healthy volunteers	NR	Farnesol has presented synergetic activity against *S. aureus* when it was associated with the following antibiotics: chlorhexidine gluconate, benzalkonium chloride, benzethonium chloride. When associated with benzalkonium chloride, farnesol has shown synergentic activity against *S. aureus* e *E coli* strains. It was elaborated a formulation of farnesol and benzalkonium chloride (ZBF) to be tested in volunteers; thus, it was observed that when ZBF was used by the professionals, it has rapidly killed the bacteria present on their hands surface. Besides this, the hands smear with ZBF can remain active against transient bacteria several minuts after application.
Saidi et al. (2006)	*In vitro* preclinical study (clinical isolates of *C. albicans*, epithelial cells and human gingival fibroblasts)	IU (Sigma-Aldrich)	To examine the effect of farnesol on *C. albicans* and epithelial cells and gingival fibroblasts	10–300 μM (*in situ*)	Farnesol has redued *C. albicans* growth only at higher concentrations (100, 150 e 300 μM), when this strains were cultivated alone during a patiod of 24 h. It was also evaluated the farnesol effect with repeated treatments (2, 4 and 8 h), showing that repeated treatments have reduced the fungal cells growth from approximately 240×10^6 to 120×10^6. The most significant cell growth reduction from these treatments, were obteined in 8 and 24 h, at both high and low concentrations of farnesol. Results suggests that farnesol was effective reducing *C. albicans* germ tube formation and, has inhibited more effectively the fungal filamentation when it has been added into culture medium with serum. Regarding the farnesol's effect in epithelial and fibroblasts gingival cells, this substance has not modified the epithelial cells morphology even at high concentrations (150 e 300 μM). On the other hand, regarding fibroblastos morphology,

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					farnesol concentrations up to 50 μM has not promoted morphology alterations. However, at hight concentrations the cells have began to separet from each other and degrade. In order to simulate *in vivo* conditions, farnesol effect was tested in fibroblasts in the presence of *C. albicans*. In the medium free of serum, farnesol has reduced adhesion and proliferantion of fibroblasts and has induced differentiation and reduction of epithelial cells proliferation up to 48 h after treatment. These effects have not been observed with serum presence. When gingival cells were present with farnesol and *C. albicans*, there was a greater inhibition from yeasts to hyphae, suggesting a synergistic effect between gingival cells and farnesol in inhibitin *C. albicans* transition. These results suggests that farnesol is effective against *C. albicans* and may have an effect on host cells at certain concentrations.
Jabra-Rizk et al. (2006b)	*In vitro* preclinical study (clinical isolates strains of MSSA and MRSA)	IU (Sigma Chemical Co.)	To evaluate the effect of farnesol on antimicrobial susceptibility and formation of *S. aureus* biofilms	0–300 μM - 0–66 μg/mL (*in situ*)	Farnesol et concentration of 200 μM (44 μg/mL) has inhibited oxidation-reduction reactions in cell viability tests. When tested at contrations from 0 to 50 μM, farnesol both strains of *S. aureus* (MSSA and MRSA) were able to form homogeneous biofilms. However, in the concentration of 100 μM this formation of biofilms was decreased and in the higher concentrations (200 and 300 μM) there was no formation of biofilms. The addition of farnesol, even at low concentrations, has induced a increase in staphylococci permeability to gentamicin, with consequently MIC reduction to MSSA, but this effect has not been observed against MRSA.
Katsuyama et al. (2005)	Clinical study (17 patients - 10 men and 7 women – with atopic dermatitis in the arms of mild to moderate severity)	IU (Dragoco Co.)	To examined the effects of FX cream (containing 0.2% farnesol + xylitol 5%) on the microflora balance of the skin of a patient with atopic dermatitis	farnesol 0.2% + xylitol 5% (topical use)	The tratmento with FX cream along one week has significantly reduced the proportion of *S. aureus* at the local of FX administration when compared with previous aplications of placebo. Besides this, the average condutance of the skin (parameter used as an indicator of the hydration state of the skin surface) where the FX cream was administrated has significantly increased, when compared with placebo. This results suggests that FX cream is a skin care agent useful for the treatment of atopic dermatitis, colonized by *S. aureus*.
Rodrigues Goulart et al. (2004)	*In vitro* preclinical study (clones of the parasite *P. falciparum*)	IU (Sigma-Aldrich)	To investigated the effects of various terpenes (farnesol, nerolidol, limonene, and linalool) and the *S*-farnesylthiosalicylic acid (FTS) on the biosynthesis of dolichol and the isoprenic side chain of ubiquinones as well as on	1–200 μM (*in situ*)	Farnesol has presented a IC_{50} of 60 μM. Both farnesol and the other terpenes evaluated have inhibited the dolichol biosynthesis in the stages of trophozoite and schizonts. Regarding the isopren chain biosythesis attached to the

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Table 1 (*continued*)

Reference	Type of study (species, cell strain and/or cell line)	Farnesol geometric isomers/origin (as described in the literature)	Aims	Dose/Concentration (route of administration)	Main results and conclusion (as described in the literature)
			protein isoprenylation in the intraerythrocytic stages of *P. falciparum*		benzoquinone ring of ubiquinones, farnesol has shown a stronger activity in the schizont stage. In addition, the parasites treatment with farnesol decreases the incorporation of isoprenyl precursors into proteins.
Akiyama et al. (2002)	*In vitro* preclinical study (*S. aureus* strains isolated of lesions per atopic dermatitis)	IU (Dragoco Co.)	To investigate the actions of farnesol and xylitol in the control of skin lesions due to atopic dermatitis colonized by *S. aureus*	100 and 2000 μM/mL (*in situ*)	Farnesol has shown MIC fo 1.200 μM/mL agains strains of *S. aureus.* It was observed that the coagulation coused by *S. aureus* cells was inhibited in plasma with farnesol at concentrations of 1/12 of the MIC (100 μM/mL). In addition, the production of superantigen exotoxins by *S. aureus* cells, in the presence of farnesol (100 μM/mL), were about 10-fold lesser than when produced by *S. aureus* cells alone. The farnesol concentrations above MIC produced an suppressor effect against *S. aureus* cells, in both exponential and stationary phase; showing to be a promising coadjutant in the treatment of cutaneous lesion colonized by *S. aureus*.
Ramage et al. (2002)	*In vitro* preclinical study (cell strains of *C. albicans*)	IU (Sigma Chemical Co.)	To evaluate the effect of farnesol on the formation of biofilms	3, 30 and 300 μM (*in situ*)	At concentrations of 300 μM, farnesol has prevented the well succeed germination and adhesion of yeast cells, resulting in scarce or nonexistent biofilms. However, when this concentraton was decreased 10 and 100-fold, it was observed the presence of pseudohyphae (farnesol 30 μM) end hyphae (farnesol 3 μM). Analyzing the *C. albicans* cells treated with farnesol, using the Northern blot technique, it has shown that this cells has expressed levels of HWP1 and mRNA lower than the cells not treated with farnesol.
Machida et al. (1998)	*In vitro* preclinical study (wild *S. cerevisiae* strains and isogenic petite mutants, which had been generated by ethidium bromide treatment)	IU	To evaluate the mechanism of action responsible for the inhibitory effect of farnesol against *S. cerevisiae*	6.25–200 μM (*in situ*)	Farnesol has inhibited the *S. cerevisiae* growth, inducing an increase in the levels of ROS in a dose dependet way, these increases were up to 5–8-fold in farnesol treated cells after an initial incubation of 30 min. The oxidative stress dependence induced by farnesol in the growth inhibition, was confirmed by the protection against this cells growth inhibition, in the presence of an antioxidant agent as α-tocopherol, probucol or N-acetylcysteine. Though, farnesol has increased ROS production only in wild strais of *S. cerevisiae* and not on isogenic mutants, which illustrates the role of mitochondrial function in the ROS generation induced by farnesol. Besides that, the addition of farnesol has inhibited the oxygene cellular use, however, It has not been able to inhibit any of the oxidase enzyme activity.

IU - Isomers unspecified; NR - Non reported.

Table 2
Descriptive summary of the studies investigating the antitumor effect of farnesol.

Reference	Type of study (species, cell strain and/or cell line)	Farnesol geometric isomers/origin (as described in the literature)	Aims	Dose/Concentration (route of administration)	Main results and conclusion (as described in the literature)
Lee et al. (2015)	*In vivo* and *in vitro* preclinical study [athymic *nu/nu* female mice and different tumor cell lines (human multiple myeloma U266 and MM1.S cells, human lung cancer A549 cells, human breast carcinoma MDA-MB231 cells, human pancreatic cancer BxPC-3 cells and human prostate carcinoma DU145 cells)]	IU (Sigma-Aldrich)	To evaluate the antitumor activity of farnesol alone and associated with bortezomib on the growth of human tumor xenografts	60 mg/kg (i.p.) in the *in vivo* assays and 25, 50, 75, 100, 125 and 150 μM (*in situ*) in the *in vitro* assays	Farnesol showed antitumor effect *in vitro* and *in vivo,* and the *in vivo* effect may be due to the block of the signal of transducer and activator of transcription 3 (STAT3) induced and constiutive. Farnesou 100 μM supressed the consitutive activation of STAT3 in 0.6-fold. Farnesol inhibited fosforilation and transcription of the constitutive STAT3 in U266 cells, but not in A549, MDAMB231, BxPC-3 and DU145, showing less effect on the total STAT3 expression in every cells' lines analyzed. This inhibitory effect of STAT3 was mediated by inhibition of Janus-like kinase (JAK1 e JAK2) and c-Src activation. In addition, farnesol induced apoptosis of U266 cells dependent of caspasis-3 activation.
Joo et al. (2015)	*In vitro* preclinical study (cell lines of human T lymphoblastic leukemia Molt4-Bcl2 and Molt4-hyg)	*trans,trans*-Farnesol (Sigma-Aldrich)	To examined the signaling pathways by which *trans,trans*-Farnesol induces apoptosis in human T lymphoblastic leukemia Molt4 cells	50–175 μM (*in situ*)	*trans,trans*-Farnesol induced effectively apoptosos in Molt4 cells of human lymphoblatic leukemia, this effect was mediated though a patheway involving apoptosome activation by the intrinsic pathway and by the induction of PERK-eIF2 α-ATF3/4 cascade in a manner independent of the activation induced by MAPKs.
Park et al. (2014)	*In vivo* and *in vitro* preclinical study (human prostate cancer DU145 cell lines and male nude mice)	IU (Sigma-Aldrich)	To identify the mechanism of farnesol-induced apoptosis in DU145 prostate cancer cells	0–100 μM (*in situ*) in the *in vitro* assays and 50 mg/kg (po.) in the *in vivo* assays	Results indicated that farnesol has chemotherapeutic potential against prostate DU145 cancer. Farnesol increase cellular apoptosis in a dose-dependent manner, this effect is mediated by protein kinase activated by por PI3K/Akt. When evaluated in *in vivo* models, farnesol inhibited tumor growth in mince, significantly decreasing the tumor size.
Qamar et al. (2012)	*In vivo* preclinical study (male *Wistar* rats)	IU (Fluka chemika)	To evaluate the chemopreventive effects of farnesol against lung injury induced by benzo(a)pyrene	100 and 200 mg/kg (po.)	Farnesol (100 e 200 mg/kg) induced a significant reduction in pulmonary lesion and inflammatory responses induced by intratracheal administration of benzo(a)pyrene. Besides this, farnesol exhibited a protective effect of the phospholipides levels when compared with control group. Activities of benzo(a)pyrene metabolization in pulmonary tissue of rats were modified by farnesol, which reduced NADPH-cytochrom P450 reductase and microsomal epoxide hydrolase and also induced an increase in the activities of the glutathione S-transferase enzyme. Results of this study suggest a protective effect of farnesol against pulmonary an toxic damage coused by benzo(a)pyrene in wistar rats.

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Table 2 (*continued*)

Reference	Type of study (species, cell strain and/or cell line)	Farnesol geometric isomers/origin (as described in the literature)	Aims	Dose/Concentration (route of administration)	Main results and conclusion (as described in the literature)
Chaudhary et al. (2009)	*In vivo* preclinical study [(*Swiss* mice (*Mus musculus*)]	IU (Sigma Chemical Co.)	To demonstrate the chemopreventive potential of farnesol on 9,10-dimethylbenz(a)anthracene (DMBA)-initiated and 12-O-tetradecanoylphorbol-13-acetate (TPA)-promoted skin tumorigenesis	25, 50 and 100 mg/kg (topical use)	At doses of 25 and 50 mg/kg farnesol reduced skin edema, hyperplasia, COX-2 expression and oxidative stresse response induced by TPA, however this effects were not observed at 100 mg/kg dose. It was observed that in smaller doses (25 e 50 mg/kg), farnesol inhibited the Ras/Raf/ERK1/2 signaling pathway in the skin tumours of mice, while the 100 mg/kg dose induced this same pathway. Moreover, all doses of farnesol changed the Bax/Bcl-2 ratio which leads to apoptosis induction. These Results showed that topical use of farnesol was effective as a chemoprotective, promoting an anti-inflammatory, antioxidant and apipitotic effect.
Journe et al. (2008)	*In vitro* preclinical study (ER-positive MCF-7 breast cancer cell line)	IU (MP Biomedicals)	To examine the effect of farnesol, an intermediate of the mevalonate pathway, on ER-positive MCF-7 breast cancer cells line	10–200 μM (*in situ*)	Farnesol activates FXR (farnesoid X receptor) with consequently induction of mitogenicity in MCF-7 cells thought a positive interference with ER, and this cell growth stimulation is completely suppressed by antiestrogens. Results suggest that farnesol induce a decrease in ER levels in MCF-7 cells, as a phenomenon of downregulation type in the receptor. Farnesol also increased the progesterone receptor (PgR) expression in these cells.
Au-Yeung et al. (2008)	*In vitro* preclinical study (human colon adenocarcinoma HT-29 cells with mutated p53 gene and HCT 116 cells with wild-type p53 gene)	IU (Sigma-Aldrich)	To elucidate the underlying anti-carcinogenic mechanism(s) of the herbal isoprenols (farnesol and geranylgeraniol) in human colon cancer cells	0–400 μM (*in situ*)	Farnesol supressed the growth of cancer cells HT-29 and HCT 116, and showed that the number of viable cells had been significantly decreased in a dose-dependent way at different treatment times. This growth inhibitory actions observed with the farnesol treatment, may be due to the apoptosis induction in colon cancer cells. It was estimated the effective concentrations of 25%, 50% and 75% (CE_{25}, CE_{50} and CE_{75}) of farnesol. Morphological changes in cells trated with farnesol and geranylgeraniol were invertigated using fluorescent coloring H33342. It was observed that cells treated with both substances, the condensation of nuclear chromatin was easily identified, and being also identified the presence of granular bodies. In this study results showed that both farnesol and geranylgeraniol reduced the expression of BclxL and survivin in HT-29 and HCT 116 and these substances may induce apoptosis by caspase 3 activation which leads the PARP. Furthermore, anti-apoptotic proteins inhibition may play a role during those processes. Another stage that is related with farnesosl's apopitotic effect is the activation of PPARγ (peroxisome proliferator-activated receptor gamma).

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Table 2 (*continued*)

Reference	Type of study (species, cell strain and/or cell line)	Farnesol geometric isomers/origin (as described in the literature)	Aims	Dose/Concentration (route of administration)	Main results and conclusion (as described in the literature)
Jahangir and Sultana (2008)	*In vivo* preclinical study (male *Swiss* mice)	IU	To evaluate the antigenotoxic effects of farnesol on benzo(a)pyrene-induced genotoxicity in mice	1 and 2%Kg^{-1} (po.)	Benzo(a)pyrene use has significantly promoted induction of metabolizing enzymes [Cytochrom P450 (CYP) and Aryl hydrocarbon hydroxylase (AHH)], loss of DNA integrity and modulation of the oxidant defence system. It was observed that treatment with farnesol (1 e 2%Kg^{-1}) supressed the CYP and AHH activity in modulator groups and restored the reduction of glutathione, quinone reductase and glutathione-*S*-transferase levels. Moreover, farnesol restored DNA integrity, promoting simultaneously a reduction in DNA chain breaks and in DNA adults' formation *in vivo*.
Wiseman et al. (2007)	*In vitro* preclinical study [human pancreatic ductal adenocarcinoma cell lines MIA PaCa-2 (CRL-1420) and BxPC-3 (CRL-1687)]	*trans*-Farnesol (Sigma-Aldrich)	Investigate the effects of three isoprenoids (perillyl alcohol, geraniol, and *trans*-Farnesol) on the cell cycle and to observed the mechanisms of antiproliferative action	0–120 μM (*in situ*)	*trans*-Farnesol induced inhibition of cell proliferation in a dose-dependent way in both MIA PaCa-2 and BxPC-3 cells. When administrated combined, *trans*-farnesol and isoprenoids, they showed an additional antiproliferative effect against the carcinogenic cells MIA PaCa-2. All of the three isoprenoids compounds induced the G0/G1 cellular cycles to stop, which coincided with a increase in the expression of cyclin kinase, p21Cip1 e p27Kip1 inhibitory protains, a reduction in cyclin A and B1 and also in Cyclin-dependent kinases 2 (CDK2). The results from this study strongly suggest that isoprenoids, as well as pharmacological agents which induce p21Cip1 and p27Kip1 expression, may have chemotherapeutic effects on pancreatic cancer treatment.
Jahangir et al. (2006)	In vivo preclinical study (male Wistar rats)	IU	To evaluated the antioxidant efficacy and inhibitory effects of farnesol on the appearance of early tumor promotion markers in Fe-NTA (ferric nitrilotriacetate) induced toxicity in rats	1 and 2%/Kg (po.)	Farnesol (1 and 2%/Kg) treatment in rats intoxicated with ferric nitrilotriacetate reverted the effects induced by this toxic agent: increasing of H_2O_2 (hydrogen peroxide), malondialdehyde, xanthine oxidase ornithine decarboxylase activity, and incorporation of 3H-thymidine of induced renal DNA, with simultaneous depletion on serum levels of toxicity markers (urea nitrogen in blood and creatinine). It was observed that profilatic treatment with farnesol induced restoration in the renal contents of glutation in a dose-dependent way, and in the Phase II metabolizing enzymes (catalase, glutathione-*S*-transferase and quinone reductase). Results from this study showed that farnesol reduces markedly the oxidative damage and that this compound can provide substantial protection against renal toxicity induced by Fe-NTA.

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Table 2 (*continued*)

Reference	Type of study (species, cell strain and/or cell line)	Farnesol geometric isomers/origin (as described in the literature)	Aims	Dose/Concentration (route of administration)	Main results and conclusion (as described in the literature)
Jahangir et al. (2005)	*In vivo* preclinical study (male *Swiss* mice)	IU	To evaluated the antigenotoxic and antioxidante efficacy of farnesol against cadmium chloride ($CdCl_2$) induced renal oxidative stress and genotoxicity in Swiss albino mice	1% and 2% per Kg of body weight (po.)	Farnesol promoted celullar protection against the damage induced by cadmium. Farnesol treatment decreased formation of cadmium-induced chromosomal aberration in the micronuclei. This antigenotoxic effect is coused by the phase II enzymes restoration, depletion in the levels of lipidic peroxidase, xanthine oxidase and by the concomitant increase of antioxidant status.
Rao et al. (2002)	*In vivo* preclinical study (male F344 rats)	IU (Robeco Inc.)	To assessed the chemopreventive efficacy of farnesol and lanosterol on azoxymethane (AOM)-induced colonic aberrant crypt foci in rats	1.5% (po. – in the diet)	Farnesol administration in anilams' diet has notpromoted liver, kidneys, intestine and lung changes. Regarding chemopreventive effects, it was observed that farnesol inhibited colonic aberrant crypt in about 34% a reduced the crypt formation in about 44%. Besides this, farnesol did not showed any effect on serum HDL levels (high-density lipoprotein) and cholesterol. Obtained data in this study demonstrated that farnesols' 1.5% administration inhibited the formation of colon pre-neoplastic lesion.
Voziyan et al. (1995)	*In vitro* preclinical study (acute leukemia cell line CEM-C1)	*trans,trans*-Farnesol (Aldrich Chemical Co.)	To verified the mechanisms of cytotoxicity of *trans,trans*-Farnesol	20 μM (*in situ*)	*trans,trans*-Farnesol (20 μM) reduced the rate of radioactive labels incorporation in DAG and cellular phosphocholine, phosphatidylcholine (PC) degradation products, indicating the inhibition of PLC specifically for PC after 1 h of incubation. It was observed that at the posterior incubation time (about 2 h) farnesol promoted the inhibition of phospholipase D, this effect were demonstrated by the decreasing in the PC synthesis and DAG formation, which were followed by the DNA apoptotic fragmentation and inhibition of cellular growth. Results demonstrate that the cytotoxic effect of farnesol involves cellular mechanism of signal transduction dependent of phospholipase C, once it was demonstrated that the synthesis of DAG (a physiologic activator of PKC), derived from PC, is inhibited in CEM-C1 cells at the early incubation time.

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Reference	Type of study (species, cell strain and/or cell line)	Farnesol geometric isomers/origin (as described in the literature)	Aims	Dose/Concentration (route of administration)	Main results and conclusion (as described in the literature)
Haug et al. (1994)	*In vitro* preclinical study (dexamethasone resistant cell line CEM-C1)	IU (American Radiolabeled Chemicals)	To verified the participation of phosphatidylcholine in the apoptotic effect of farnesol in human lymphoblastoid cells	10–30 μM (*in situ*)	Incubation of CEM-C1 cells with farnesol resulted in cell growth inhibition. However, when the cell proliferation was mantained at 0.05 mM of thymidine, the two concentrations of farnesol (18 e 27 μM) that were tested had no effect on the number of live cells for up to 48 h of incubation. In this study, among several teste phospholipids present in membrane, only PC could reverse the cellular growth inhibition coused by farnesol. The inhibition was also reversed by DAG. Results showed that, after cellular incubation with farnesol, the cells diminished its viability; and that it's nuclear DNA become fragmented in internucleosomic bindingregions, showing characteristic patterns of bands between 180 and 200 bases pair intervals. This farnesol-induced effect was also demonstrated by flow cytometry by staining the cellular DNA with propidium iodide and it was partially reversible with phosphatidylcholine.
Adany et al. (1994)	*In vitro* preclinical study [human acute leukemia cell cultures CEM-Cl and CEM-C7, human cervical carcinoma cell line C-4-1, human newborn foreskin fibroblasts CF-3, bovine aortic endothelial cells, porcine aortic endothelial cells, prostate cells, human promyelocytic leukemia cells HL-60, cells of human epithelioid carcinoma of cervix HeLa S3K, cells of human carcinoma of prostate DU- 145 and mouse lymphoma cells L5 178Y-R (tumorigenic) and L5 178Y−S (nontumorigenic)]	*trans,trans*-Farnesol (Aldrich Chemical Co.)	To compare the effect of *trans,trans*-Farnesol in several cell lines of neoplastic and non-neoplastic origin	0–45 μM (*in situ*)	*trans,trans*-Farnesol effect on growth inhibition and cellular death was more pronounced in neoplastic cells than in cells from normal tissue. It was observed that malignant cells inhibition were more significant at *trans,trans*-Farnesol concentratins of 10–33 μM. These inhibitory effects on malignant cells growth became evident after 24 h of incubation with 45 μM of trans,trans-farnesol and after 48 h of incubation almosnt all cells were dead. Regarding the growth of normal cells, it was observed that its gowth was inhibited by only 20–70% even after 72 h of incubation with 45 μM of trans, trans-farnesol. Among non-malignant cells tested, the foreskin fibroblasts FC-3 were not sensitive to the treatment with *trans,trans*-Farnesol. Results from this study demostrait for the first time that there is a selective toxicity of *trans,trans*-farnesol to malignant cells, Which increasis the possibility that this compound may be applied in cancer chemotherapy.

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Table 2 (*continued*)

Reference	Type of study (species, cell strain and/or cell line)	Farnesol geometric isomers/origin (as described in the literature)	Aims	Dose/Concentration (route of administration)	Main results and conclusion (as described in the literature)
Voziyan et al. (1993)	*In vitro* preclinical study (acute leukemia cell line CEM-C1)	*trans,trans*-Farnesol (Aldrich Chemical Co.)	To investigate the mechanism of inhibition of PC biosynthesis by *trans,trans*-Farnesol in a human acute leukemia cell line	20 μM (*in situ*)	*trans,trans*-Farnesol inhibited the incorporation of [3H]cholin in cellular lipids and decreased incorporation of radioactive label in PC. In the presence of *trans,trans*-Farnesol the biosynthesis of PC was not inhibited during the first 30 min of incubation, but it was inhibited at 30% between 30 and 60 min and at 45% between 60 and 90 min. It was observed that *trans,trans*-Farnesol did not promote any changes in enzymatic activity of CTP and DAG. However, *trans,trans*-Farnesol promoted a significant reduction in enzymatic activity of CPT (cholesterol phosphotransferase), consequently, inhibiting PC biosynthesis.
Melnykovych et al. (1992)	*In vitro* preclinical study (acute leukemia cell lines CEM-C1 and CEM-C7 and human promyelocytic leukemia cells HL-60)	*trans,trans*-Farnesol (Aldrich Chemical Co.)	To examine the effects of exogenous *trans,trans*-Farnesol on growth in Human T-cell leukemia	9–31.5 μM (*in situ*)	It was observed that after 72 h of incubation, *trans,trans*-Farnesol showed inhibitory effect in leukemic cells proliferation type CEM-C1, in a dose-dependent way. Taking in account the analysis of cellular size distribution, the data showed that the *trans,trans*-Farnesol concentrations used in this study did not promote cell destruction, which demonstrate that the *trans,trans*-Farnesol's effect on this cells was related with the inhibition of cell proliferation instead of cell lysis. The cellular growth inhibition coused by *trans,trans*-Farnesol, was also tested in CEM-C7 cell lines sensitive to glucocorticoids and in human promyelocytic cells HL-60. The CEM-C7 cells were more resistant and the HL-60 cells were more sensitive to *trans,trans*-Farnesol compared with the CEM-C1 line. This inhibitory effect coused by farnesol was prevented when the cells were incubated with phosphatidylcholine or diacylglycerol.

IU - Isomers unspecified.

Table 3
Descriptive summary of the studies investigating the nervous and cardiovascular system effects of farnesol.

Reference	Type of study (species, cell strain and/or cell line)	Farnesol geometric isomers/origin (as described in the literature)	Aims	Dose/Concentration (route of administration)	Main results and conclusion (as described in the literature)
Silva et al. (2017)	*In vivo* preclinical study (male *Swiss* mice)	IU (Sigma-Aldrich)	To evaluate the antinociceptive effect of farnesol (FAR) and the inclusion complex obtained with its incorporation into β-cyclodextrin (βCD/FAR) in animal models of orofacial pain	50 and 100 mg/kg (po.)	Both farnesol and the complex βCD/FAR (50 e 100 mg/kg) showed antinociceptive effect, promoting a reduction on behaviours associated with orofacial pain, possibly mediated by the K^+ channels dependent of ATP and by 5-hydroxytryptamine receptors (5-HT3). In order to investigate whether the possible impairment in motor coordination of mince, trated with farnesol, could influence the analgesic effect, it was used the rotarod test. It was observed that both substances tested did not promoted any significant alteration on the animal's motor performance. Besides that, the βCD/FAR complex showed to improve the pharmacological properties when compared with the active compound alone.
Vasconcelos et al. (2017)	*Ex vivo* preclinical study (male guinea pigs – *Cavia porcellus*)	IU (Sigma-Aldrich)	To evaluate the pharmacological effects of seven terpenes (farnesol, nerol, citronellol, geraniol, isoprenol, phytol and nerolidol) on contractility of the left atrial cardiac muscle	0.01–10 mM (*in situ*)	Farnesou promoted a negative inotropic effect, it was one of compounds that showed a higher negative potencial. Analysing the results, it was observed a direct relation between the relative power of the evaluated terpenes and their respective chemical classes, being the amount of isoprenic units a factor that directly influences the pharmacological power. For exemple, the farnesol (sesquiterpenoid) was 11-fold more powerful than its equivalent monoterpenoid (geraniol). Similarly, monoterpenes such as nerol, citronellol and geraniol presented a negative ionotropic effect higher than the hemiterpene isoprenol. From all terpenes tested only phytol was not capable of reducing the contractile response of the left atrium of guinea pigs.
Shahnouri et al. (2016)	*In vivo* preclinical study (*Swiss* albino male mice)	IU (Sigma-Aldrich)	To investigate the effects of farnesol on a classic murine animal model for depression and anxiety-like behavior	50 and 100 mg/kg (i.p.)	In order to evaluate farnesol central effects (ansiolitic, sedative, analgesic and depressor) were realized the open field, elevated plus-maze test, forced swim and hot plate tests. It was observed thatin the open field test farnesol, at doses of 100 mg/kg promoted a significant decrease in the locomotor activity. On the other hand, in the elevated plus-maze test, at the same dose, farnesol leaded to an increase in the number of entries and also in the permanence time of the animal in the opened arms. In the forced swim test, both farnesol doses of 50 mg/kg and 100 mg/kg promoted an increase in the immobility time. In the rot plate test evaluating the analgesic test, farnesol at doses of 100 mg/kg promoted a significant extention in the latency of response to nociceptive stimulus. It was observed that farnesol promoted a reduction in the plasma cortisol levels, which may explain the anxiolitic effect.

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Table 3 (*continued*)

Reference	Type of study (species, cell strain and/or cell line)	Farnesol geometric isomers/origin (as described in the literature)	Aims	Dose/Concentration (route of administration)	Main results and conclusion (as described in the literature)
					Results foud in this study suggest that farnesol has promising ansiolytic-like effects and induce depression and alteration of locomotor activity, giving pharmacological evidence supporting the use of farnesol as a sedative to the relief of anxiety disorders.
Santhanasabapathy and Sudhandiran (2015)	*In vivo* preclinical study (*Swiss* albino male mice)	*trans*-Farnesol (Sigma-Aldrich)	To investigate the protective effect of *trans*-Farnesol on lipopolysaccharide (LPS) induced neurodegeneration through modulation of intrinsic apoptotic cascade in the cortex and hippocampus	25, 50, 100, 150 and 200 mg/kg (po.)	*trans*-Farnesol promoted a neuroprotective effect attenuating degenerative changes in the cortex and hippocampus of rats. This effect is due to the intrinsic apoptotic cascade regulation, as a result of the oxidative damage protection in neurons.
Szücs et al. (2013)	*In vivo* preclinical study (male *Wistar* rats)	IU (SAFC Supply Solution)	To examine the cardioprotective effect of farnesol and its cellular mechanism against ischemic lesions	0.2, 1, 5 and 50 mg/kg/day (po.)	Farnesol diminished the infarct extention in a dose-dependent way, this cardioprotective effect may probably be mediated by an increase number of proteins, coused by geranylgeranylation (mevalonate pathway) and it appears to be independent from the antioxidant effect of farnesol.
Luft et al. (1999)	*In vivo* and *in vitro* preclinical study (rat aortic A7r5 cells, chinese hamster ovary C9 cells expressing smooth muscle Ca^{2+} channel α_{1C} subunits and males rats salt-resistant SBN/yr and salt-sensitive SBH/yr)	IU (Aldrich)	To characterize the effects of farnesol on vascular Ca^{2+} channels L	100 mmol/L (*in situ*) in the *in vitro* assays and 500 mg/kg (po.) in the *in vivo* assays	Farnesol blocked the Ca^{+2} channels conductance in the resting state, with the initial blockade being 63 ± 6% in A7r5 cells and 50 ± 9% in CHOC9 cells, with a retention potencial of 280 mV. In both cellular lines, the farnesol inhibition was prominent along all tension range, without changing the pics of current-tension. Neither the intracellular infusion of stable GDP (guanosine diphosphate) analogue (100 mmol/L) nor the strong conditioning membrane depolarization prevented the inhibitory effect of farnesol, which can indicate that the inhibition is independent from Ca^{+2} channels dependent of G protein action. Evaluating the farnesol effects in normotensive and hypertensive rats, it was administered dose of 500 mg/kg and it was observed that farnesol significantly decreased the blood pressure in hypertensive rats in less than 48 h. With the obtained results, it can be concluded that the farnesol could represent a Ca^{+2} channels agonist of vascular smooth muscle. Once farnesol is active in cells that express only the α_1 subunity, the data suggest that this subunity represents the molecular target to farnesol binding. Furthermore, the farnesol has a hypotensive action that may be relevant to *in vivo* models.
Ferdinandy et al. (1998)	*In vivo* preclinical study (male *Wistar* rats)	IU (Sigma-Aldrich)	To evaluate the cardioprotective effect of farnesol in the recovery of preconditioning and synthesis of cardiac nitric oxide in rats with high cholesterol diet	5 μM/kg (i.p.)	Treatment with farnesol restores the preconditioning, but not the basal synthesis of nitric oxide in hypercholesterolemic rats. Besides this, it was observed, that the treatment with farnesol do not significantly affect the severity of ischemia in non preconditioning protocols in hearts of rats feeded with cloesterol.
Roullet et al. (1997)	*In vitro* preclinical study (rat aortic muscle A7r5 cell line)	*trans,trans*-Farnesol (Aldrich)	To examine the effect of *trans,trans*-Farnesol on vascular smooth muscle cell membrane fluidity	10 and 30 μM (*in situ*)	*trans,trans*-Farnesol reduced signicantly the Ca^{+2} transient induced by KCl, but did not modify the

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Table 3 (*continued*)

Reference	Type of study (species, cell strain and/or cell line)	Farnesol geometric isomers/origin (as described in the literature)	Aims	Dose/Concentration (route of administration)	Main results and conclusion (as described in the literature)
					dynamic properities of the cell membrane. Moreover, the *trans,trans*-Farnesol administration reduced the Ca^{+2} voltage-dependent signaling in isolated cells of smooth muscle, and this effect is neither consequence of Ca^{+2}-ATPase enzyme activation nor of the nonspecific increase in cell membrane fluidity.
Roullet et al. (1997)	*Ex vivo* and *in vitro* preclinical study (arteries isolated from the mesenteric arterial bed of male *Wistar* rats and vascular smooth muscle A10 and A7r5 cells)	*trans,trans*-Farnesol (Aldrich)	To explore the vasoactive properties of *trans,trans*-Farnesol	5–30 μM (*in situ*)	*trans,trans*-Farnesol reduced the Ca^{+2} signaling in arteries and in smooth muscle cells and inhibited the voltage-dependent L-type Ca^{+2} channels. The L-type $Ca+^{2}$ channels blockage also occurred under tight seal (giga-ohm) configuration using single-channel analysis attached to the cell, thus, suggesting a possible *trans,trans*-Farnesol action into the cell. Moreover, it was observed that farnesol did not effect the Ca^{+2} sensitive pathways in the smooth muscle contraction. Results indicate that *trans,trans*-Farnesol is an ihibiter of Ca^{+2} signaling in vascular smooth muscle, acting as a blocker of L-type Ca^{+2} channels present on the plasma membrane.
Roullet et al. (1996)	*Ex vivo* preclinical study (thoracic aorta isolated from male *Wistar* rats and arterial segments of patients with peripheral vascular diseases)	*trans,trans*-Farnesol (Aldrich Chemical Co.)	To characterize the vasoactive properties of farnesyl analogs in the inhibition of norepinephrine-induced vasoconstriction in rats and humans	15 and 30 μM (*in situ*)	All *trans,trans*-Farnesol concentration evaluated has presented an inhibitory effect on norepinephrine-induced contraction, in a dose dependent way. Besides this, it was observed that farnesol was also effective inhibiting contractions coused by KCl and NaF, suggesting a complex action on Ca^{+2} channels coupled with G protein. When tested in human arteries, *trans,trans*-Farnesol showe to be a powerful inhibitor of vasoconstriction, so that, it was observed that after 30 min of farnesol administrated at concentration of 30 μM, it was obtained a maximum contriction of 34.6 ± 5.8%, in contractions induced by norepinephrine.

IU - Isomers unspecified.

Table 4
Descriptive summary of the studies investigating the metabolic and hepatic effects of farnesol.

Reference	Type of study (species, cell strain and/or cell line)	Farnesol geometric isomers/origin (as described in the literature)	Aims	Dose/Concentration (route of administration)	Main results and conclusion (as described in the literature)
Špičáková et al. (2017)	*In vitro* preclinical study (liver hepatocytes from of male *Wistar* rats and from human livers excluded from transplantation for medical reasons)	IU (Sigma-Aldrich)	To test and compare the potential inhibitory effect of acyclic sesquiterpenes (farnesol, *trans*-nerolidol and *cis*-nerolidol) on the activities of the main xenobiotic-metabolizing enzymes (CYPs, CBR1, NQO1, AKRs, GSTs, UGTs and SULTs) in rat and human liver	0–100 μM (*in situ*)	Farnesol and the other sesquiterpenes tested at concentration of 100 μM promoted a significant inhibition of the cytochromes P450 enzymatic activity (subfamilies: CYP1A, CYP2B e CYP3A) in rat liver and also in human liver microsomes. On the other hand, all sesquiterpenes tested did not significantly affect the activities of carbon-reducing enzymes (AKR1A, AKR1C, CBR1 e NQO1) and conjugation enzymes (GSTs, UGT e SULT). Obtained results in this study demonstrated that frnesol and the other sesquiterpenes evaluated may promote interaction when administered in association with other drugs, once the first enzyme CYP3A4 (belonging to the CYP3A subfamily) is responsible to the metabolization of about 50% of all drugs.
Vinholes et al. (2014)	*In vitro* preclinical study (liver hepatocytes of female *Wistar* rats)	*trans,trans*-Farnesol (Sigma-Aldrich)	To investigate the potential hepatoprotective activity of sesquiterpenoids [*trans,trans*-Farnesol, *cis*-nerolidol, (−)-*α*-bisabolol, *trans*-*β*-farnesene, germacrene D, *α*-humulene, *β*-caryophyllene, isocaryophyllene, (+)-valencene, guaiazulene, (−)-*α*-cedrene, (+)-aromadendrene, (−)-*α*-neoclovene, (−)-*α*-copaene, and (+)-cyclosativene) against lipid peroxidation	1 mM (*in situ*)	With the exception of α-humulene, all sesquiterpenes tested (1 mM) were effective reducing the malonaldehyde levels (MDA) in the induced endogenous lipidic peroxidation. *trans,trans*-Farnesol was one of the compound that promoted a greater hepatoprotective effect, with a percentage of MDA reduction of 69.72 ± 1.82%.
Goto et al. (2011)	*In vivo* preclinical study (obese male KK-Ay mice)	*trans,trans*-Farnesol (Sigma-Aldrich)	To investigated whether *trans,trans*-Farnesol functions as a dietary dual agonist to activate PPARα (peroxisome proliferator-activated receptor alpha) and PPARγ (peroxisome proliferator-activated receptor gamma) in *in vivo* models	0.5% (po. – in the diet)	*trans,trans*-Farnesol administered into the mice diet was effective preventing hyperglycemia and hepatic steatosis induced by the high fat diet, promoting a significant reduction in blood glucose levels, glycosuria and the incidence of hepatic triglyceride content. These effects may be due to the dual activation of FXR and PPARα (*α*-peroxisome proliferator activated receptors). The *trans,trans*-Farnesol promoted a upregulated increase in the expression of mRNA and PPARα in the target genes involved in the oxidation of fatty acids in the liver. On the other hand, *trans,trans*-Farnesol was not effective in regulating PPARγ mRNA expression (receptors activated by peroxisome proliferators γ). In addition, *trans,trans*-Farnesol increased the level of mRNA expression in FXR target genes and decreased those of the steroid response element binding protein 1c and of fatty acid synthase. These findings suggest that *trans,trans*-farnesol can improve metabolic abnormalities in mice through PPARα-dependent and independent pathways and that the FXR activation by the trans,trans-farnesol may partially contribute with PPARα effect in reducing the hepatic triglyceride content.
		trans,trans-Farnesol (Sigma-Aldrich)			*trans,trans*-Farnesol reduced the serum triglyceride concentration. The mechanism that possibly mediate

(*continued on next page*)

Table 4 (*continued*)

Reference	Type of study (species, cell strain and/or cell line)	Farnesol geometric isomers/origin (as described in the literature)	Aims	Dose/Concentration (route of administration)	Main results and conclusion (as described in the literature)
Duncan and Archer (2008)	*In vivo* and *in vitro* preclinical study (male *Sprague–Dawley* rats and Clone-9 rat hepatocytes cells)		To evaluate the effect of *trans,trans*-Farnesol on serum triglyceride levels as well as to verify the possible mechanisms of action responsible for these effects	500 mg/kg (po.) in the *in vivo* assays and 10, 20 and 30 μM (*in situ*) in the *in vitro* assays	this response included include the impaired on oxidation the fatty acids present in hepatocytes, which is a result of the PPARα activation and the upregulation of gens envoved in the *β*-mitochondrial oxidation, as well as the downregulation in the synthesis of fatty acids resulting from decreased levels of mRNA.

IU - Isomers unspecified.

isomer. In other studies the authors investigated the metabolic or hepatic effects of *trans,trans*-Farnesol.

In Špičáková et al. (2017) study, three sesquiterpenes (farnesol, *trans*-nerolidol and *cis*-nerolidol) were evaluated regarding their inhibition of the cytochrome P450 family enzymes (CYPs, CBR1, NQO1, AKRs, GSTs, UGTs and SULTs). The results showed that both farnesol and other sesquiterpenes inhibited enzyme activity of the CYPs subfamily (CYP1A, CYP2 and CYP3A) at the concentration of 100 μM CYP3A4 is one of the major enzymes involved in drug metabolism, suggesting that the sesquiterpenes evaluated in this study may interact and influence metabolism when given in combination with other drugs.

Another effect of farnesol and other sesquiterpene compounds on the hepatic system is hepatoprotection. Vinholes et al. (2014) observed the that *trans,trans*-Farnesol and other sesquiterpene compounds at the concentration of 1 mM effectively promoted hepatoprotection against lipid peroxidation, it was observed that from all the sesquiterpenes evaluated, *trans,trans*-Farnesol more efficiently promoted a reduction in malonaldehyde levels (MDA).

As for metabolic effects, studies have demonstrated a reduction in serum triglyceride concentration (Goto et al., 2011; Duncan and Archer, 2008), prevention of hyperglycemia and hepatic steatosis in obese animals with a high fat diet (Goto et al., 2011) mediated by *trans,trans*-Farnesol. Both studies suggest that the effect of *trans,trans*-Farnesol improving metabolic abnormalities is due to an upregulation of PPARα mRNA expression, an increase in target-genes involved with the oxidation of fatty acids (Goto et al., 2011; Duncan and Archer, 2008) and of genes involved with *β*-mitochondrial oxidation. Additionally, Goto et al. (2011) noted that *trans,trans*-Farnesol increases mRNA expression in farnesoid X receptor (FXR) target-genes and decreases the expression of protein 1c genes, which bind to steroids and fatty acid synthase response elements.

3.5. Other pharmacological and toxicological effects

A total of 6 articles were included in this category, which evaluated the following pharmacological and/or toxicological properties of farnesol: anti-inflammatory, antioxidant, cell growth and differentiation effect in the epidermis, excipient action to improve drug transdermal absorption and mechanisms of action related to apoptotic effects (Table 5). As far as the type of isomer of the farnesol investigated is concerned, only the study of Hanley et al. (2000) specifies the type of isomer, and in their research the authors verified the mechanisms of action responsible for the effect of *trans,trans*-Farnesol on cell growth and differentiation in the epidermis.

According to Qamar and Sultana (2008), which aimed to evaluate the protective effect of farnesol against damage induced by intratracheal administration of CSE, the farnesol (isomers unspecified) treatment in rats at 50 and 100 mg/kg doses effectively protected the animal's lungs against damage caused by CSE. The authors observed that farnesol (isomers unspecified) in bronchoalveolar lavage fluids resulted in a reduction of lactate dehydrogenase levels, total cell count and in malondialdehyde levels. Additionally, treatment with farnesol reduced pulmonary edema, increased glutathione levels, decreased membrane cytotoxicity and lipid peroxidation. These results were convalidated with histopathological findings, which demonstrated a reduction in cellular infiltration, edema and an intact alveolar architecture.

Lateef et al. (2013) also investigated the protective effect of farnesol (isomers unspecified) at 50 and 100 mg/kg doses (po.) in rats exposed to CSE. The results obtained showed that farnesol (isomers unspecified) possesses a protective effect against CSE-induced stratification in nuclei from testes and prostate cells, with this effect being possibly due to the antioxidant activity of farnesol (isomers unspecified) by decreasing the enzymatic activities of xanthine oxidase and lipid peroxidation.

Khan and Sultana (2011) evaluated the protective effect of farnesol (isomers unspecified) against tissue damage induced by 1,2-

Table 5
Descriptive summary of the studies investigating the other pharmacological and toxicological effects of farnesol.

Reference	Type of study (species, cell strain and/or cell line)	Farnesol geometric isomers/origin (as described in the literature)	Aims	Dose/Concentration (route of administration)	Main results and conclusion (as described in the literature)
Lateef et al. (2013)	*In vivo* preclinical study (male Wistar rats)	IU (Fluka chemika)	To investigate the protective effects of farnesol against CSE (cigarette smoke extract) induced oxidative stress in prostate and histological alterations in the testes and prostate of rats	50 and 100 mg/kg (po.)	Farnesol (50 and 100 mg/kg) diminished significantly the enzymatic activity of xanthine oxidase and lipid peroxidation, both enzymes are responsible for free radicals production. CSE promoted a reduction in glutathione levels and in the activities of glutathione-dependent enzymes and antioxidant enzymes, and the groups treated with farnesol had this effect reversed. Regarding the histologic findings, it was observed that farnesol exhibited a protective effect against the stratification of nuclei induced by the SSC. In addition, the animals treated with farnesol presented prostate with normal architecture. It has also been shown that treatment with CSE resulted in decreased leydig cells, and pre-treatment with farnesol showed significant protective effects against this CSE-induced reduction in the testes of Wistar rats.
Khan and Sultana (2011)	*In vivo* preclinical study (male Wistar rats)	IU (Fluka chemika)	To evaluate the protective efficacy of farnesol against 1,2-dimethylhydrazine (DMH) induced oxidative stress, inflammatory response and apoptotic tissue damage	50 and 100 mg/kg (po.)	Farnesol treatment promoted a significant improvement in the oxidative damage induced by DMH, reducing the lipid peroxidation of the tissue accompanied by the increase of enzymatic activities of the following enzymes: superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, glutathione-S-transferase and quinone reductase. In addition, treatment with farnesol significantly decreased the activity of caspase-3 in colonic tissue. Histological findings also revealed that treatment with farnesol significantly reduced the severity of submucosal edema, regional destruction of the mucosal layer and intense infiltration of inflammatory cells into the mucous and submucosal layers of the colon. Data from the present study suggest that farnesol effectively suppresses DMH-induced damage in the colonic mucosa of Wistar rats, improving oxidative, inflammatory and apoptotic responses.
Qamar and Sultana (2008)	*In vivo* preclinical study (male Wistar rats)	IU (Fluka chemika)	To evaluate the protective effect of farnesol against massive pulmonary inflammation, oxidative stress and consequent pulmonary lesions induced by intratracheal administration of the CSE	50 and 100 mg/kg (po.)	Farnesol (50 e 100 mg/kg) treatment was effective protecting the lungs against the damages coused by CSE, showing a reduction in the levels of lactate dehydrogenase, total cell count, total protein and malondialdehyde in the in the bronchoalveolar lavage fluids of rats exposed to CSE. Farnesol treatment increased glutathione content, reduced pulmonary edema and promoted a significant decrease in membrane lipid cytotoxicity and peroxidation, which indicates that farnesol has a protective effect against pulmonary toxicity of the CSE. These effects correlate with histopathological findings, which exhibit a significant reduction in cell infiltration and edema and shows intact alveolar

(*continued on next page*)

Table 5 (*continued*)

Reference	Type of study (species, cell strain and/or cell line)	Farnesol geometric isomers/origin (as described in the literature)	Aims	Dose/Concentration (route of administration)	Main results and conclusion (as described in the literature)
					architecture in the lungs of animals treated with farnesol.
Marcuzzi et al. (2008)	*In vivo* preclinical study (BALB/c male mice)	IU (Euphar group s.r.l.)	To evaluate the effect of exogenous isoprenoids (geraniol, farnesol and geranylgeraniol) in mice with inflammatory disorder similar to amidinobiphosphonate and muramyl dipeptide-induced mevalonate kinase deficiency (MKD)	250 and 500 mg/kg (i.p.)	Only the farnesol dose of 500 mg/kg was effective in preventing inflammation induced by alendronate/muramyl dipeptide, inhibiting the levels of SAA (serum amyloid A) and the PEC (number of cells in peritoneal exudate) values. Results suggest that this compound, as well as the other isoprenoids tested, may be effective in the treatment of human MKD.
Nokhodchi et al. (2007)	*In vitro* preclinical study (abdominal skin of male Wistar rats)	IU (Merck)	To investigate the effect of different concentrations of terpenes on the transdermal absorption of diclofenac sodium	0.25–2.5% (*in situ*)	From the evaluated terpenes, farnesol was the second most effective substance in increasing the permeability coefficient of diclofenac sodium, promoting a 78-fold increase in transdermal absorption of this drug; and this effect is probably due to the lipophilic characteristics of farnesol.
Lagace and Ridgway (2005)	*In vitro* preclinical study (chinese hamster ovary cell lines K1 − CHO−K1).	IU (sigma-Aldrich)	To determine how phosphatidylcholine synthesis and CCTα (phosphocholine cytidylyltransferase α) activity contribute to the induction of apoptosis by farnesol and oleyl alcohol	0–60 μM (*in situ*)	The intial effect from farnesol administration (60 μM - apoptotic concentration) was a rapid (10–30 min) transient activation of phosphatidylcholine synthesis. During this period, it was observed a decrease of 40% in the mass of DAG. Subsequently, after 1 h, farnesol promoted the cleavage of caspases and nuclear export of CCTα, which was prevented by treatment with oleyl or DiC8 (dioctanylglycerol). Protection against farnesol-induced apoptosis required the synthesis of phosphatidylcholine and CCTα activity.
Hanley et al. (2000)	*In vivo* and *in vitro* preclinical study (mice and human epidermis isolated from newborn foreskins and keratinocytes)	*trans,trans*-Farnesol (sigma-Aldrich)	To verify the mechanisms of action responsible for the effect of *trans,trans*-Farnesol on cell growth and differentiation in the epidermis	5 and 10 μM (*in situ*) in the *in vitro* assays and 40 mL/cm^2 1 mM *trans,trans*-Farnesol (in propylene glycol/ethanol, 7:3 - topical use on the flank) in the *in vivo* assays	The formation of cornified cellular envelopes, a marker of the terminal differentiation of keratinocytes, as well as the levels of protein and mRNA of two protains needed to the formation of cornified envelopes, involucrin and transglutaminase, increased 2–3 fold in normal human keratinocytes treated with *trans,trans*-Farnesol. Topic aplications in mice promoted an increase in the levels of mRNA and protein of differentiation of specific gens, prophylagrin and loricrin, determined by immunohistochemistry and *in situ* hybridization. These findings suggest a new role for intermediate isoprenoids of intermediate cholesterol isoprenoids in the regulation of transcription regulated by PPARα of differentiation-specific genes.

IU - Isomers unspecified.

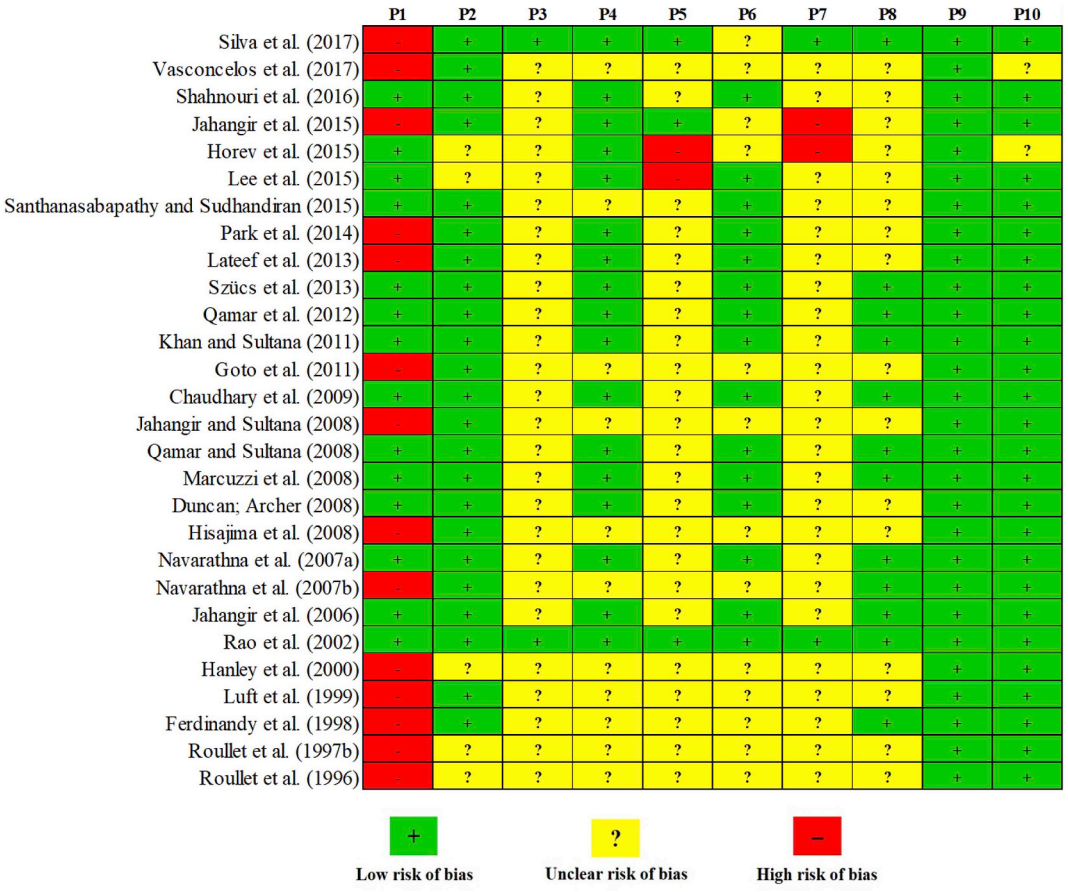

Fig. 3. Methodological quality summary for preclinical trials: review of authors judgments about each methodological quality item for each study included (**P1** - Was the allocation sequence adequately generated and applied?; **P2** - Were the groups similar at baseline or were they adjusted for confounders in the analysis?; **P3** - Was the allocation to the different groups adequately concealed during?; **P4** - Were the animals randomly housed during the experiment?; **P5** - Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?; **P6** - Were animals selected at random for outcome assessment?; **P7** - Was the outcome assessor blinded?; **P8** - Were incomplete outcome data adequately addressed?; **P9** - Are reports of the study free of selective outcome reporting?; **P10** - Was the study apparently free of other problems that could result in high risk of bias?).

dimethylhydrazine (DMH) and observed that the treatment of rats with farnesol (50 and 100 mg/kg doses, po. - isomers unspecified) suppressed DMH-induced damage due to its anti-inflammatory activity and its protection against oxidative damage through a reduction in lipid peroxidation and enzymatic activities (superoxide dismutase, catalase, gutatya peroxidase, glutathione reductase, glutathione-*S*-transferase and quinone reductase). In addition to protecting tissues from CSE and DMH-induced inflammatory damage, farnesol (500 mg/kg, i.p. - isomers unspecified) was shown to be capable of preventing inflammation induced by alendronate/muramyl dipeptide which promotes an inflammatory disorder similar to mevalonate kinase deficiency (Marcuzzi et al., 2008).

When evaluating cellular growth and epidermis differentiation, Lagace and Ridgway (2005) noted that farnesol (isomers unspecified) promotes an apoptotic effect through a caspase cleavage dependent pathway and nuclear CCTα export, which corroborates with other studies that evaluated the farnesol apoptotic effect in different cell types (Lee et al., 2015; Liu et al., 2010; Au-Yeung et al., 2008).

As for the use of farnesol (isomers unspecified) as an excipient to improve transdermal drug absorption, Nokhodchi et al. (2007) investigated the effect of different types of terpenes (carvone, limonene oxide, menton, farnesol and nerolidol) on diclofenac sodium transdermal absorption and found that from all the terpenes evaluated farnesol was the second most effective substance at increasing the permeability coefficient of this drug. In pharmaceutical industries terpenic compounds are already used for this purpose and as active phytopharmaceutical principles (Oliveira et al., 2014), where this use is probably derived from the lipophilic characteristics of these compounds (Nokhodchi et al., 2007).

3.6. Methodological quality/bias risks

Methodological quality and bias risk evaluation is an essential SR step (Hooijmans et al., 2014; Higgins et al., 2011), since to get confident results it is important that a research projected is well planned, efficiently executed, correctly analyzed and one in which the data are interpreted and presented in a correct and comprehensible way (Festing and Altman, 2002).

As showed in Fig. 3, only the pre-clinical study with non-human animals, made by Rao et al. (2002), were classified with low bias risk. In Fig. 4, 50% of studies do not describes an allocative sequence properly generated and applied, and in 92.82% of articles was not clear if happened allocation hiding. Besides, 85.71% of the studies do not make clear if the results evaluation were blind made. However, 100% of the studies showed low bias risk concerning selective/biased results and 90% of the selected studies were free from other bias problems, as contamination by grouping drug and influence of funders and errors of analysis unit.

In this review, from the 28 preclinical studies with non-human animals, 26 do not clearly state if blinding during group allocation occurred. Bebarta et al. (2003) state that studies without adequate allocation and blinded evaluations are more likely to report errors in

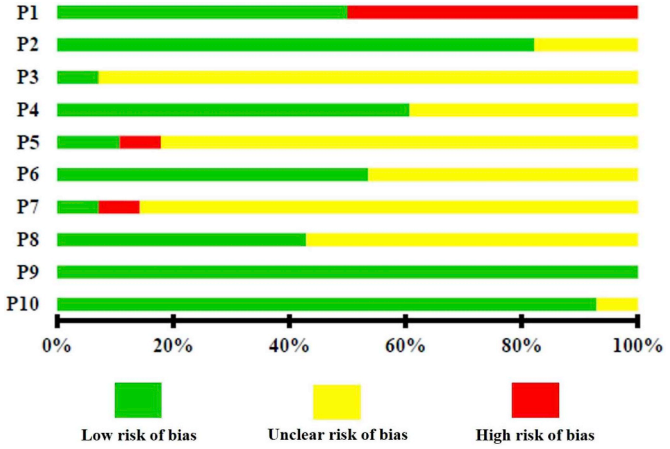

Fig. 4. Methodological quality graph for preclinical studies: review of authors judgments about each methodological quality item presented as percentages across all studies included. (**P1** - Was the allocation sequence adequately generated and applied?; **P2** - Were the groups similar at baseline or were they adjusted for confounders in the analysis?; **P3** - Was the allocation to the different groups adequately concealed during?; **P4** - Were the animals randomly housed during the experiment?; **P5** - Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?; **P6** - Were animals selected at random for outcome assessment?; **P7** - Was the outcome assessor blinded?; **P8** - Were incomplete outcome data adequately addressed?; **P9** - Are reports of the study free of selective outcome reporting?; **P10** - Was the study apparently free of other problems that could result in high risk of bias?).

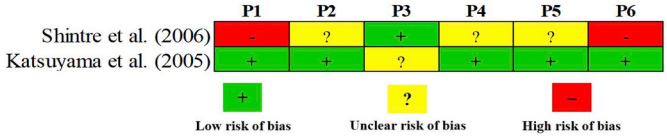

Fig. 5. Methodological quality summary for clinical trials: review of authors judgments about each methodological quality item for each study included. [**P1** - Random sequence generation; **P2** - Allocation concealment; **P3** - Incompleate outcome data; **P4** - Source of funding bias; **P5** - Blinding (participant); **P6** - Blinding (outcome assessor)].

treatment effects than studies which adopt these methodologies.

As for the clinical studies, only Katsuyama et al. (2005) clearly state that random sequence generation, concealment of allocation, participant and evaluator blindness and no financial bias occurred. Moreover, only in the study carried out by Shintre et al. (2006) had the uncompleted results properly judged (Figs. 5 and 6). Studies have argued that a lack of randomization, blinding, sample size calculations, inadequate sample size calculations and statistical analysis as the causes of bias and false positive results (Tsilidis et al., 2013; Sena et al., 2007).

3.7. Outcomes and limitations

This SR has shown that different isomers of farnesol possesses different pharmacological and toxicological properties, permitting its use as an active or coadjuvant drug. It was observed that from the articles included in this SR, a minority informed the type of farnesol isomer that was investigated; which becomes a major limitation for the development of future experimental trials. Besides, it is known that the type of geometric isomer, source of isolation and method of compound preparation directly influence the pharmacological and/or toxicological activity.

A predominance for studies reporting the antimicrobial effect and action mechanism of farnesol against different microorganisms (bacteria, fungi and protozoa) occurred; and that farnesol possesses a broad spectrum of activity, which is useful for inhibiting the growth of microorganisms or increasing their susceptibility to the action of antimicrobial drugs.

For its action as an antitumor agent, farnesol demonstrated great pharmacological potential in the prevention and treatment of different types of cancers, showing selective toxicity by inducing apoptosis of damaged cells.

In the nervous system, farnesol promotes neuroprotective and behavioral effects that may be useful in the treatment of central nervous system disorders such as anxiety, insomnia, neurodegenerative disease and pain.

In the cardiovascular system, farnesol acts as cardioprotective and hypotensive agent, with the latter owing to its negative ionotropic action on cardiac muscle and its vasodilatory effect due to L-type Ca^{+2} channel inhibition.

In the hepatic system, farnesol protects hepatocytes from steatosis and oxidative damage due to lipid peroxidation and inhibits the metabolic activity of enzymes belonging to the cytochrome P450 family. As for its metabolic effect, studies have demonstrated that farnesol reduces triglyceride concentration and prevents glycemic level increase.

For other pharmacological and toxicological properties, antioxidant and anti-inflammatory properties have been shown to be responsible for the cytoprotective action observed, further reinforcing the use of this substance as a useful agent in different disease treatments, especially for those caused by free radical action and inflammatory processes.

Despite the large number of preclinical studies that report the pharmacological and toxicological effects of farnesol, demonstrating

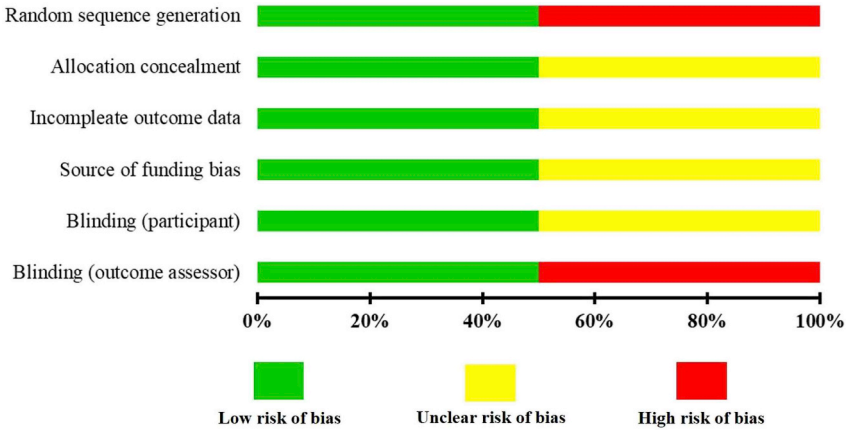

Fig. 6. Methodological quality graph for clinical studies: review of authors judgments about each methodological quality item presented as percentages across all studies included.

the broad action spectrum of this substance, there is a lack of clinical trials evaluating its efficacy and safety. One of the possible reasons for this lack of clinical trials with farnesol may be due to the fact that review articles have not been found in the literature that compile the studies that investigated the pharmacological and toxicological potential of this substance. This demonstrates and reinforces the importance of the development of this SR, which is the first study developed for this purpose.

Methodological biases have been observed both in pre-clinical studies with non-human animals and in clinical trials, mainly in group allocation and blinding. This result requires special attention, since studies presenting rich methodological bias do not give us reliable results. A major challenge faced during the conduction of this SR was the lack of a validity scale that allowed the classification of bias risks *in vitro* preclinical studies. In addition, due to the methodological heterogeneity of the studies included in this SR, it was not possible to perform the meta-analysis, being this factor a negative point, since the clustering statistic would allow outcomes with greater scientific support.

4. Conflict of interest

The authors declare that they have no conflict of interest.

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Transparency document

Transparency document related to this article can be found online at https://doi.org/10.1016/j.fct.2019.04.037.

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