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Citronellol, a monoterpene alcohol with promising pharmacological activities - A systematic review

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ABSTRACT

Many diseases, such as inflammatory and central nervous system disorders, currently have a limited number of effective side-effect free treatments. Citronellol (CT) is a monoterpene alcohol present in the essential oil of several plants used in cooking and traditional medicine, such as those of the genus *Cymbopogon* and *Citrus*, with pharmacological activities already described in the literature. The aim of this review was to summarize the pharmacological activities already attributed to CT that could be used in treatments for humans. The databases PubMed, MedLine, Scopus, Lilacs and Scielo were searched using the terms "Citronellol" and "Drug effect". 32 articles were identified and used in the study. Twenty-one articles demonstrated CT activities, including antibiotic and antifungal effects *in vitro*, and 11 properties including analgesic and anticonvulsant effects *in vivo*, besides presenting low toxicity. In view of the need to discover new drugs and the activities reported for CT, it can be stated that CT is a promising molecule to target in future pharmacological studies.

1. Introduction

It has become evident that existing therapies for the treatment of various diseases, including central nervous system disorders and diseases of inflammatory etiology such as rheumatic diseases, are not always effective (D'Angelo et al., 2018; Dubash et al., 2018; Gribkoff and Kaczmarek, 2017; Wegener and Rujescu, 2013) There is, therefore, a growing need for treatments that are not only more effective but also have fewer side effects. In addition, there are a growing number of antibiotic resistant microorganisms that can cause infection and even lead to death (González et al., 2018). One option is to search for new therapeutic alternatives among the various classes of drugs already in existence.

For thousands of years, natural products have been used in the treatment of many diseases. They are the source of various medications available today, such as morphine (derived from the plant *Papaver somniferum*) (Goerig and Schulte am Esch, 1991), aspirin (derived from the acetylsalicylic acid, extracted from the plant *Salix alba*) (Vane, 1971), ziconotide (cone snail toxin isolated from *Conus ssp*) (McGivern, 2007) and botulinum toxin (produced by the bacterium *Clostridium botulinum*) (Scott and Collins, 1973). These natural products need to be more fully investigated as many have not had their mechanisms of action defined, while many others have not been studied at all (Gu et al., 2013).

Medicinal plants have been used since the beginning of the humanity and popular knowledge, including in food, in the form of tea, soups and curries, such as *Cymbopogon citratus* in tropical countries (Petrovska, 2012; Shah et al., 2011). Medicinal plants has been used as a clue to the investigation of new active principles (Petrovska, 2012). The effects of several medicinal plants has been described in the literature, including the anti-inflammatory and antifungal effects of *Cymbopogon citratus* (Boukhatem et al., 2014), the cardiovascular effects of *Cymbopogon winterianus* (Menezes et al., 2010a,b), the antioxidant activity of *Lippia alba* (Chies et al., 2013) and the analgesic effect of *Ocimum basilicum* (Nascimento et al., 2015).

The essential oils of medicinal plants are rich in secondary metabolites whose main function is plant defense. Terpenes are composed of isoprene units and constitute a considerable part of the secondary metabolites found in plants, and have several pharmacological effects already described in the literature, such as the antihyperalgesic activity

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List of acronyms and abbreviations

(−)	S or sinister or left
(+)	R or rectus or right
(±)	R,S or racemic mixture
ACh	Acetylcholine
AGE	Advanced glycation end products
BV	Bilateral vagotomy
CFU	Colony-forming units
CG	Carrageenan
CT	Citronellol
DA	Dopamine
EFS	Electrical field stimulation
EVA	Poly(ethylene-co-vinyl acetate) copolymer
FICI	Fractional inhibitory concentration indices
GC	Gas chromatography
Hb	Hemoglobin
HbA1C	Glycated hemoglobin
HR	Heart rate
i.c:	Intracardiac
i.p.	intraperitoneal
i.v.	intravenous
IC_{50}	The half maximal inhibitory concentration
IgE	Immunoglobulin E
IR	Inhibition rate
IκBα	Inhibitor of nuclear factor kappa B, alpha
LPS	Lipopolysaccharide
MAP	Mean arterial pressure
MBC	Minimal bactericidal concentration
MFC	Minimal fungicidal concentration
MIC	Minimal inhibitory concentration
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
Nd	Not described
NF-κB	Nuclear factor kappa B
NO	Nitric oxide
p.o.	oral administration
PGE_2	Prostaglandin E_2
SOD	Superoxide dismutase
STZ	Streptozotocin
TNF-α:	Tumor necrosis factor-α
TRPA1	Transient receptor potential ankyrin-1
TRPV1	Transient receptor potential cation channel subfamily V member 1

of citronellal (Santos et al., 2016), the anti-inflammatory effects of carvacrol (Lima et al., 2013) and the antioxidant properties of linalool (Seol et al., 2016). Menthol, an alcoholic monoterpene, has been studied for many years and a number of formulations in which it is present are available on the market. (Eccles, 1994). In addition to the promising activities already described for terpenes, the possibility of synthesis of these compounds may result in reduced costs and time to discover new drugs (Jansen and Shenvi, 2014).

Citronellol (Fig. 1) is a monoterpene alcohol monoterpene found in the essential oil of plants of the genus *Cymbopogon* and has several pharmacological activities already described in the literature, such as anticonvulsant, antihyperalgesic and orofacial antinociceptive properties (Brito et al., 2015a,b, 2013a; Sousa et al., 2006). Therefore, in view of the need to identify new sources of drugs that are more effective and have less side effects, and given the fact that citronellol is a terpene whose class has already been found to have a number of beneficial pharmacological effects, this study aimed to review the pharmacological effects already described for citronellol that present possibilities for treatments in humans.

2. Methods

This systematic review used a literature search to find all relevant articles published up to June 2017. The search was performed through specialized databases (PubMed, MedLine, Scopus, Lilacs and Scielo - Scientific Electronic Library Online) using a combination of the keywords 'citronellol' and 'drug effects', either as Medical Subject Headings terms (MeSH terms) or as free-text words. Clinical and/or preclinical studies demonstrating some pharmacological activity of citronellol and written in English, Portuguese or Spanish were included in the manuscript. The exclusion criteria were review articles and studies that evaluated pharmacological activities not aimed at the subsequent use of citronellol in humans.

After searching the database using the keywords, 444 texts were identified. Two independent investigators (P.L.S. and J.P.S.C.F.M.) then examined the titles to identify relevant studies and went on to read the abstracts of the selected studies to compare the content with the inclusion and exclusion criteria. Any discrepancies between the selections were resolved by consensus between the investigators.

3. Results

The studies in this review examine various activities of citronellol. In the initial keyword search 444 articles were identified, distributed as follows in the databases: 129 from PubMed, 198 from Scopus, 117 from MedLine, 0 from Lilacs and 0 from Scielo. After reading the titles and abstracts and assessing the inclusion and exclusion criteria, 77 articles were selected: 31 from PubMed, 19 from Scopus and 27 from MedLine. Of these, 45 articles were indexed in two or more databases, resulting in 32 articles that were used in the study. Fig. 2 is a flowchart showing the study selection process. Twenty-one articles addressed *in vitro* activities of CT, and eleven, *in vivo* activities. The methodologies used in the articles included in the study are summarized in Tables 1 and 2.

Several activities have been described for CT, such as antibacterial, antifungal and repellent properties in *in vitro* studies, and cardiovascular, antidiabetic and antinociceptive effects in *in vivo* studies. A summary of the results obtained by the studies included in the review is given in Table 3.

This review article presents papers that described pharmacological activities of CT relevant to use in humans. *In vitro* studies investigated possible antibacterial (Echeverrigaray et al., 2008; Kotan et al., 2007; Mulyaningsih et al., 2011; Ngan et al., 2012; Nostro et al., 2013), antifungal (Kim and Park, 2012; Mahmoud, 1994; Pereira et al., 2015; Shin, 2003; Shin and Lim, 2004; Viollon and Chaumont, 1994; Zore

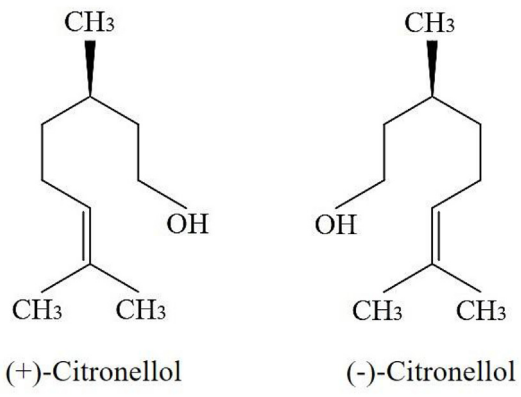

Fig. 1. Structural formulas of citronellol.

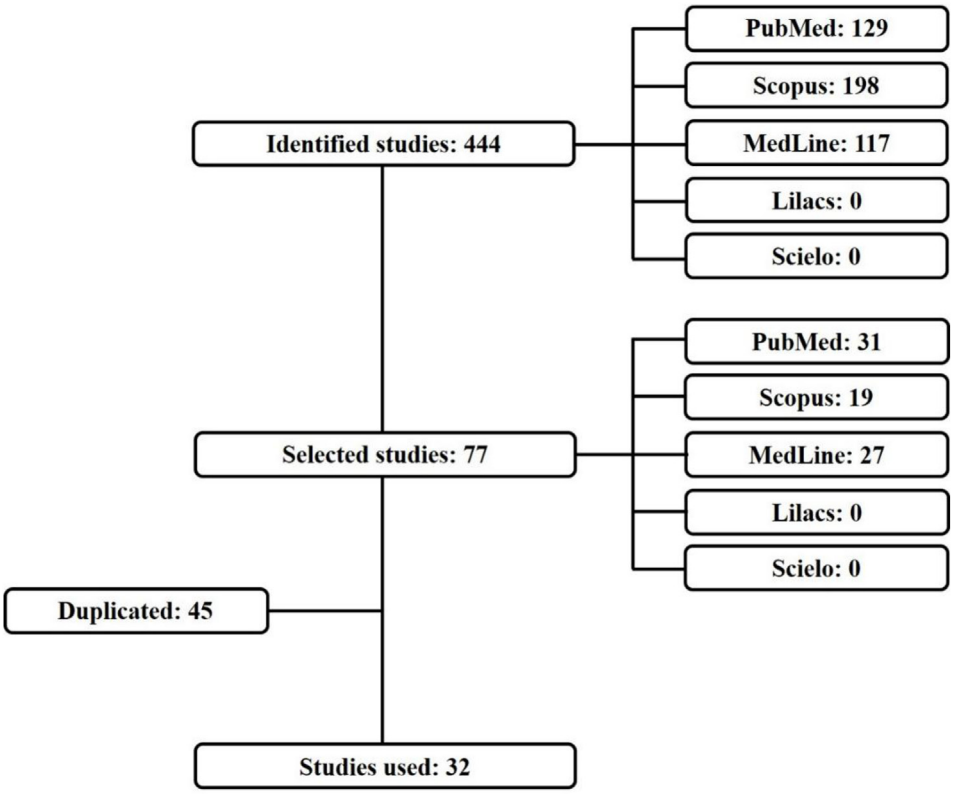

Fig. 2. Flow chart of the search and selection of the articles.

et al., 2011), anti-lice (Gonzalez-Audino et al., 2011), repellent (Michaelakis et al., 2014; Semmler et al., 2014), lipolytic (Choi, 2006), anti-allergic (Kobayashi et al., 2016), anti-inflammatory (Abe et al., 2003; Su et al., 2010) and antispasmodic (Sadraei et al., 2013; Vasconcelos et al., 2016) properties. *In vivo* studies investigated possible cardiovascular (Bastos et al., 2009; Menezes et al., 2010a,b; Ribeiro-Filho et al., 2016), antidiabetic (Jagdale et al., 2016; Srinivasan and Muruganathan, 2016), anti-cholesterol (Batubara et al., 2015), antinociceptive (Brito et al., 2012; Brito et al., 2013), antihyperalgesic (Brito et al., 2015a,b), anti-anxiety (Umezu et al., 2002) and anticonvulsant (Sousa et al., 2006) activities. Most of the *in vitro* studies did not describe the isomeric form of CT used in the study. Among those which did describe the isomeric form, 3 reported using only the isomeric form (±) (Mulyaningsih et al., 2011; Su et al., 2010; Vasconcelos et al., 2016), 1 used (+) and (−) (Ngan et al., 2012), and 1 used the (+), (−) and (±) forms (Kobayashi et al., 2016). *In vivo* studies mainly used the form (−) in studies that aimed to investigate antinociceptive and antihyperalgesic activities (Brito et al., 2012; Brito et al., 2015a,b), (±) in studies investigating cardiovascular activities (Bastos et al., 2009; Menezes et al., 2010a,b) and (+) for anticonvulsant activity (Sousa et al., 2006). In the following section, we examine the various properties of CT which were investigated in the studies.

3.1. Antibacterial

In 2007, Kotan et al. (2007) investigated for the first time the antibacterial activity of CT. The authors used a concentration of 30 mg/ml in the disk infusion method and described the effect of CT on various Gram positive and negative species of clinical relevance, such as *Staphylococcus aureus ATCC 29213, Streptococcus pyogenes ATCC 176, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Salmonella typhimurium*. One year later, Echeverrigarav et al. (Echeverrigaray et al., 2008) demonstrated the antibacterial effect of CT at a lower concentration (Minimal inhibitory concentration - MIC = 3 mg/l), using the broth microdilution method on *Proteus mirabilis*, which causes urinary tract infections.

The bacteriostatic and bactericidal effects of the racemic mixture (±) of CT were described by Mulyaningsih et al. (2011), which showed a better effect on Gram-positive (MIC and Minimal bactericidal concentration [MBC] = 0.125 mg/ml) than on Gram-negative bacteria (MIC = 0.125–0.25 mg/ml and MBC = 0.25–0.5 mg/ml), by the microdilution method. Ngan et al. (2012) studied the effect of CT in the enantiomer forms (+) and (−), by broth microdilution and noted that (−)-CT (MIC = 0.08–0.62 mg/ml) presented a better effect than (+)-CT (MIC = 0.16–0.62 mg/ml), acting on a greater number of different species.

Nostro et al. (2013) evaluated planktonic growth and biofilm formation of bacteria after the addition of CT on single (*L. monocytogenes*, *S. aureus*, *E. coli*, and *P. aeruginosa*) and mixed populations (*E. coli* + *S. aureus*), and found that in both populations high efficacy was maintained over a long (48–240 h) time period.

3.2. Antifungal

In 1994, Viollon and Chaumont (1994) showed the antifungal effect of CT (MIC = 100 µl/l and Minimal fungicidal concentration [MFC] = 150 µl/l; CT: liquid in physical state, boiling point = 112–113 °C, density = 0,857 g/cm^3) on *Cryptococcus neoformans*, an opportunistic fungus found in patients in the last phases of AIDS, by the dilution method. Mahmoud (1994) described the effect of CT on *Aspergillus flavus*, a fungus normally found in contaminated food and reported that CT (MIC = 500 ppm) inhibited growth of *A. flavus* and the formation of aflatoxins B1 and B2, in a concentration of 1000 ppm, when evaluated on the eighth and fifteenth day after incubation. Shin (2003) also studied the effect of CT (MIC = 0.78 and 0.79 µg/ml respectively) on *A. flavus* and *A. niger*, but by disk diffusion. A study by Shin and Lim (2004) showed that CT strongly inhibited

Table 1
Description of articles included in the systematic review that evaluated *in vitro* activities of citronellol.

Author	Isomeric form	Concentration or dose	Protocols used	Target organism
Kotan et al. (2007)	Nd	30 mg/ml	Disk infusion	*Aerococcus viridans, Clavibacter michiganense, Kocuria varians, Agrobacterium tumefaciens, Burkholderia pyriocinia, Chryseobacterium indologenes, Citrobacter freundii, Enterobacter intermedius, Erwinia amylovora, Erwinia ananas, Erwinia chrysanthem, Neisseria subflava, Pseudomonas syringae* pv. *glycinea, Serratia grimesii, Xanthomonas campestris* pv. *rhapontici, Sphingomonas capsulata, Xanthomonas pelargonii, Ralstonia pickettii, Arthrobacter spp., Bacillus mycoides, Staphylococcus aureus, Streptococcus pyogenes, Acinetobacter baumannii, Acinetobacter calcoaceticus, Acinetobacter radioresistens, Enterobacter cloacae, Klebsiella pneumoniae, Klebsiella planticola, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella typhimurium, Stenotrophomonas maltopholia* and *Vibrio alginolyticus.*
Echeverrigaray et al., 2008	Nd	3–10 mg/l	Broth microdilution, swarming behavior, measurement of cell length and membrane-associated haemolysin	*Proteus mirabilis*
Mulyaningsih et al. (2011)	(±)	0.125- > 8 mg/ml	Microdilution method	*Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia* and *Acinetobacter baumannii*
Ngan et al. (2012)	(+) and (−)	0.16–2.5 mg/ml	Broth microdilution	*Bacteroides fragilis, Bacteroides thetaiotaomicron, Clostridium difficile, Clostridium paraputrificum, Clostridium perfringens, Escherichia coli, Klebsiella pneumoniae, Salmonella typhimurium, Staphylococcus aureus, Bifidobacterium adolescentes, Bifidobacterium bifidum, Bifidobacterium breve, Bifidobacterium infantis, Bifidobacterium longum, Clostridium butyricum, Lactobacillus acidophilus* and *Lactobacillus casei*
Nostro et al. (2013)	Nd	3.5 and 7 wt%	Planktonic growth and biofilm formation	*Listeria monocytogenes, Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Pseudomonas aeruginosa*
Viollon and Chaumont, 1994	Nd	100 and 150 µl/l	Dilution method	*Cryptococcus neoformans*
Mahmoud (1994)	Nd	500 and 1000 ppm	Broth microdilution	*Aspergillus flavus*
Shin (2003)	Nd	25 mg and 12.5 mg	Disk diffusion	*Aspergillus niger* and *Aspergillus flavus*
Shin and Lim, 2004	Nd	0.25–2 mg/ml	Disk diffusion	*Trichophyton erinacei, Trichophyton schoenleinii* and *Trichophyton soudanense*
Zore et al., 2011	Nd	0.128, 0.256 and 0.5%	Disk diffusion and broth microdilution	*Candida albicans, C. parapsilosis, C. blankii, C. kefyr, C. glabrata, C. tropicalis* and *Saccharomyces cerevisiae*
Kim and Park, 2012	Nd	28×10^{-3} and 56×10^{-3} mg/ml	Fumigant effect in Petri dishes	*Aspergillus ochraceus*, *A. flavus*, and *A. niger*.
Pereira et al. (2015)	Nd	8–1024 µg/ml	Microdilution and human nail model *in vitro*	*Trichophyton rubrum*
Gonzalez-Audino et al., 2011	Nd	5%	Immersion method	*Pediculus humanus capitis*
Michaelakis et al. (2014)	Nd	1 mg cm^{-2}	Sugar-feeding behavioral bioassay	*Culex pipiens*
Semmler et al. (2014)	Nd	0.25 and 1%	Biting activity in human volunteers	*Aedes aegypti*
Choi (2006)	Nd	25, 50, 100, 150, and 200 µL	GC in solution of olive oil	–
Kobayashi et al. (2016)	(+), (−) and (±)	0.5–1 mM	Degranulation and cytokine production by mast cells induced by IgE	–
Abe et al. (2003)	Nd	0.1%	TNF-a-induced neutrophil adhesion	–
Su et al. (2010)	(±)	5, 50, 250, 500 and 750 µM	Determination of NO and PGE2 production in murine macrophage	–
Sadraei et al. (2013)	Nd	0.8–6.4 µg/ml	Ileum contraction induced by KCl, ACh and EFS	–
Vasconcelos et al. (2016)	(±)	100–1000 µM	Tracheal contraction induced by K, Ach, EFS and sodium orthovanadate	–

ACh: Acetylcholine; EFS: Electrical field stimulation; GC: Gas chromatography; Nd: Not described; NO: Nitric oxide; PGE_2: Prostaglandin E_2;TNF-α: Tumor necrosis factor-α; (+): R or *rectus* or right; (−): S or sinister or left; (±): R,S or racemic mixture.

Table 2
Description of articles included in the systematic review that demonstrated *in vivo* effects.

Author	Isomeric form	Dose/Route	Animals	n/Group	Protocols used
Bastos et al. (2009)	(±)	1, 5, 10 and 20 mg/kg/i.v and 1.9×10^{-1}, 6.4×10^{-1} and 1.9 M	Male Wistar rats	6	Haemodynamic parameters and percentage of relaxation in rat mesenteric artery rings
Menezes et al. (2010)	(±)	1, 5, 10, and 20 mg/kg i.v	Male Wistar rats	6	Citronellol-induced cardiovascular effects
Ribeiro-Filho et al. (2016)	Nd	1, 5, 10 and 20 mg/kg/i.v or i.c; 1–1000 μM	Male Wistar rats	4–10	Mean arterial pressure, heart rate and/or respiration
Srinivasan and Muruganathan, 2016	Nd	25, 50, and 100 mg/kg p.o	Male Wistar rats	6	Diabetes mellitus induced by STZ
Jagdale et al. (2016)	Nd	2 and 4 mg/day/p.o; 25 and 50 μg/ml	Male Wistar rats	6	Diabetes induced by STZ
Batubara et al. (2015)	Nd	1%/inhalation	Male Sprague-Dawley rats	6	High fat diet
Brito et al. (2012)	(−)	25, 50 and 100 mg/kg i.p	Male Swiss mice	6–8	Acetic acid, formalin and hot plate tests
Brito et al. (2013)	(−)	25, 50 and 100 mg/kg i.p	Male Swiss mice	6	Orofacial pain induced by formalin, capsaicin and glutamate
Brito et al. (2015)	(−)	25, 50 and 100 mg/kg i.p	Male Swiss mice	6	Mechanical hyperalgesia induced by CG, TNF-α, PGE_2 and DA
Umezu et al. (2002)	Nd	50, 100, 200 and 400 mg/kg/i.p	Male ICR mice	10–33	Geller and Vogel conflict tests
Sousa et al. (2006)	(+)	100, 200 and 400 mg/kg/i.p; 0.03, 0.32, 3.2, 4.5 and 6.4 mM	Male Wistar rats	8	Convulsion induced by pentylenetetrazol, picrotoxin or shock

CG: Carrageenan; DA: Dopamine; i.c: Intracardiac; i.p.: intraperitoneal; i.v.: intravenous; MAP: Mean arterial pressure; Nd: Not described; PGE_2: Prostaglandin; p.o.: oral administration; STZ: Streptozotocin; TNF-α: Tumor necrosis factor-α; (+): R or *rectus* or right; (−): S or sinister or left; (±): R,S or racemic mixture.

(MIC = 0.5–2 mg/ml and MFC = 1–4 mg/ml) the *Trichophyton* species, a cause of superficial mycosis in humans, using disk diffusion. CT also presented a synergic effect (Fractional inhibitory concentration indices [FICI] = 0.18) with ketoconazole.

CT was fungistatic on *Candida albicans*, probably by causing alterations in morphogenesis (66.6 μg ml^{-1}) with a 76% inhibition of germ tube induction and accumulation of the cells in the S phase of cell cycle. In a study by Zore et al. synergism of CT (MIC: 0.256%) with fluconazole (FICI: 0.046) was observed (Zore et al., 2011). Kim and Park (2012) evaluated the fumigant effect of CT in Petri dishes on *A. ochraceus* (Inhibition rate - IR: 83.7%), *A. flavus* (IR: 90%) and *A. niger* (IR: 81.1%) in air with a 56×10^{-3} mg/ml concentration. These results corroborated the study of Mahmoud (1994) and Shin (2003), described previously.

Finally, Pereira et al. (2015) described the antifungal activity of CT (MIC = 8–1024 μg/ml) on *Trichophyton rubrum* collected from nails of patients with dermatophytosis. CT reduced the percentage of dry mycelial weight and the percentage of germinated conidia of *T. rubrum* ATCC 1683 and LM 422 (MIC: 128 μg/ml), caused morphological changes in microculture of *T. rubrum* (conidiogenesis reduction, abnormal formation of hyphae and conidia) and increased the percentage of released intracellular material, probably by action of CT on the inhibition of ergosterol biosynthesis. The MIC of CT (MIC = 4096 μg/ml) was increased in the presence of sorbitol (0.8 M).

3.3. Anti-lice

This activity of CT was described by Gonzales-Audino et al. (Gonzalez-Audino et al., 2011) who showed that CT (5%) caused knockdown and mortality in permethrin-resistant adult head lice, *Pediculus humanus capitis* species, by the immersion method.

3.4. Repellent

Michaelakis et al. (2014) used the sugar-feeding behavioral bioassay to investigate the repellent effect of CT (1 mg cm^{-2}) on *Culex pipiens*, a vector of West Nile virus, and observed 100% repellence. However, CT (0.25–1%) did not present repellent activity on *Aedes aegypti*, evaluated by biting activity in human volunteers (Semmler et al., 2014).

3.5. Lipolytic

Choi (2006) studied the lipolytic activity of citrus peel oils and their components, by *in vitro* technique, using gas chromatography (GC), and reported that CT presented a low lipolytic effect (about 2%) in a solution of olive oil. The lipolytic effect was verified by the percentage of oleic acid produced from olive oil.

3.6. Anti-allergic

The anti-allergic activity of CT was evaluated recently by Kobayashi et al. (2016). The authors tested different enantiomers forms of CT (0.5–1 mM) in relation to degranulation and cytokine production by mast cells induced by immunoglobulin E (IgE). (−)-CT (0.5 mM) was more effective and inhibited degranulation by 69.4%, while (+)-CT (0.5 mM) inhibited degranulation by 21.3% and (±)-CT (1 mM) by 54.6%. CT significantly inhibited IgE-induced tumor necrosis factor -α (TNF-α) production in murine-cultured mast cells.

3.7. Anti-inflammatory

In 2003, Abe et al. (2003) showed that CT (IC_{50} < 0.00625%) presented strong anti-inflammatory effect on TNF-a-induced neutrophil adhesion. In 2010, Su et al. (2010) studied the anti-inflammatory effect of (±)-CT on the determination of nitric oxide (NO) and prostaglandin-E_2 (PGE_2) production in murine macrophage. (±)-CT

Table 3
Summary of the results of the articles included in the systematic review.

Author	Results	Action
Kotan et al., 2007	CT presented broader antibacterial effect (Gram-positive and negative species of clinic and food origins: *Arthrobacter spp., Bacillus mycoides, Staphylococcus aureus ATCC 29213, Streptococcus pyogenes ATCC 176, Acinetobacter baumannii, Acinetobacter calcoaceticus, Acinetobacter radioresistens, Enterobacter cloacae, Klebsiella pneumoniae, Klebsiella planticola, Proteus vulgaris, Pseudomonas aeruginosa ATCC 27859, Salmonella typhimurium, Stenotrophomonas maltopholia, Vibrio alginolyticus*).	Antibacterial
Echeverrigaray et al. (2008)	CT exhibited MIC of 3 mg/l about *Proteus mirabilis* and inhibited swarming, reducing swimming/swarming cell differentiation and haemolysin activity at 1/10 MIC concentration.	Antibacterial
Mulyaningsih et al. (2011)	CT presented bacteriostatic and bactericidal effect about Gram-positive (1678/98: MIC and MBC: 0.125 mg/ml; MR131/98: MIC: 0.125 mg/ml and MBC: 0.5 mg/ml) and negative bacteria (*Acinetobacter baumannii*: MIC: 0.125–0.25 mg/ml and MBC: 0.25–0.5 mg/ml).	Antibacterial
Ngan et al., 2012	(+)-CT presented high levels of growth inhibition against *B. fragilis*, *B. thetaiotaomicron*, *S. typhimurium, B. breve* and *B. longum* (MIC: 0.16–0.62 mg/ml) and (−)-CT presented this activity against *B. fragilis*, *B. thetaiotaomicron*, *S. typhimurium*, *C. paraputrificum*, *B. adolescentis*, *B. bifidum*, *B. breve*, *B. longum* and *L. acidophilus* (MIC: 0.08–0.62 mg/ml).	Antibacterial
Nostro et al. (2013)	After incubation for 24–48 h, the EVA + CT film at 7 wt% reduced the optical density of *E. coli* (46–50%) and *P. aeruginosa* (35–55%). From 48 to 240 h, EVA + CT maintained their high inhibitory efficacy (40–70%) about *L. monocytogenes*, *S. aureus*, *S. epidermidis*, and *E. coli*.	Antibacterial
Viollon and Chaumont, 1994	CT exhibited antifungal activity about *Cryptococcus neoformans* with MIC of 100 µl/l and MFC of 150 µl/l.	Antifungal
Mahmoud (1994)	CT completely inhibited growth of *Aspergillus flavus* and consequently formation of aflatoxins B1 and B2, in concentration of 1000 ppm, 8 and 15 days after incubation. CT presented MIC of 500 ppm.	
Shin (2003)	CT reduced growth of *Aspergillus flavus* and *Aspergillus niger* in two concentrations tested, with MIC of 0.78 and 0.39 µg/ml respectively.	Antifungal
Shin and Lim, 2004	CT presented strong inhibition of > 39 mm (1–25 mg per disk), with MIC of 0.5–2 mg/ml and MFC of 1–4 mg/ml about *Trichophyton* species. Synergic effect (FICI of 0.18) was observed with ketoconazole.	Antifungal
Zore et al., 2011	CT was fungistatic without fungicidal activity in the concentration tested on *Candida albicans*. CT (MIC: 0.256%) presented synergism with fluconazole (FICI: 0.046) and showed only 4% killing of HeLa cells.	Antifungal
Kim and Park, 2012	CT showed antifungal activity on *Aspergillus ochraceus* (IR: 83.7%), *Aspergillus flavus* (IR: 90%) and *Aspergillus niger* (IR: 81.1%) in an air with 56×10^{-3} mg/ml concentration.	Antifungal
Pereira et al. (2015)	CT presented antifungal activity on *Trichophyton rubrum* (MIC: 8–1024 µg/ml) and inhibited 50% of the strains tested to 64 µg/ml. In the presence of sorbitol, citronellol had an increased MIC for 4096 µg/ml.	Antifungal
Gonzalez-Audino et al. (2011)	CT caused knockdown and mortality in permethrin-resistant adult head lice.	Anti-lice
Michaelakis et al. (2014)	CT presented 100% of repellent activity about *Culex pipiens* and LC_{50} = 28.8–33.6 mg/l.	Repellent
Semmler et al. (2014)	CT did not present repellent activity about *Aedes aegypti* in low concentrations.	–
Choi (2006)	CT presented slight lipolytic effect (about 2%) in solution of olive oil.	Lipolytic
Kobayashi et al. (2016)	(±)-CT reduced cell degranulation of mast cells in all concentrations tested (1 mM: 54.6%) without change cell viability after 24 h of incubation. (−)-CT (0.5 mM) inhibited degranulation by 69.4% while (+)-CT (0.5 mM) by 21.3%. CT (0.5–1 mM) significantly inhibited IgE-induced TNF-α production.	Anti-allergic
Abe et al. (2003)	CT presented strong anti-inflammatory effect with IC 50 < 0.00625%.	Anti-inflammatory
Su et al. (2010)	(±)-CT inhibited the production of NO in all concentrations. Treatment with (±)-CT had no effect on cell viability by MTT up to 500 µM. (±)-CT (5 µM) presented reduction in the production of PGE_2. (±)-CT inhibited LPS-induced COX-2 protein expression in aldose-dependent manner and suppressed the PGE2 production. (±)-CT (500 µM) reduced NF-κB p65 levels, and increased (50, 250 and 500 µM) the amount of cytosolic IκBα.	Anti-inflammatory
Sadraei et al. (2013)	CT (IC_{50} = 2.9 ± 0.3 µg/ml) inhibited ileum contraction induced by KCl in concentration dependent manner. The first and second contractions induced by EFS and Ach also were inhibited by CT (IC_{50} = 5.4 ± 0.9 and 3.4 ± 0.9 µg/ml, IC_{50} = 7.5 ± 1.2 µg/ml, respectively).	Antispasmodic
Vasconcelos et al. (2016)	(±)-CT presented antispasmodic effect in tracheal contraction of rats induced by K^+ (IC_{50} = 120.8 µM), ACh (IC_{50} = 210.7 µM), EFS (IC_{50} = 240.9 µM) and sodium orthovanadate (IC_{50} = 243.0 µM). CT also inhibited contractions that involved voltage-operated, when contractions were evocated by selective recruitment of extracellular Ca^{2+}.	Antispasmodic
Bastos et al. (2009)	(±)-CT induced hypotension with tachycardia in normotensive rats. CT (6.4×10^{-1} and 1.9 M) induced relaxation in mesenteric artery rings pre-contracted with phenylephrine or KCl with and without the endothelium or after administration of tetraethylammonium. CT also inhibited contractions induced by $CaCl_2$ in rat mesenteric artery rings without endothelium and without $CaCl_2$ solution. Besides that, CT also inhibited contractions induced by phenylephrine and caffeine in mesenteric rings under a Ca^{2+} free solution.	Cardiovascular
Menezes et al. (2010)	(±)-CT caused transitory hypotension associated with tachycardia in normotensive rats at all doses tested.	Cardiovascular
Ribeiro-Filho et al. (2016)	In anesthetized animals, CT (1 mg/kg) decreased MAP and HR. At doses of 5 and 10 mg/kg, CT presented hypotensive and bradycardic activities in anesthetized rats. Rats treated with CT (10 mg/kg) did not have the hypotensive effect reverted by BV or perineural treatment with capsaicin in prolonged phase, but bradycardic effect was reduced. In non- anesthetized rats, CT presented similar effects at lower doses (5 mg/kg) and hypotensive and bradycardic effects at higher doses (10 and 20 mg/kg) in the immediate and prolonged phases. CT (IC_{50}: 131.4) reduced amplitude of contraction of superior mesenteric artery, previously contracted with phenylephrine.	Cardiovascular
Srinivasan and Muruganathan, 2016	CT (all doses) decreased intake of food and water and plasma glucose, and increased body weight with less increase in insulin when compared to the control. Blood glucose levels on oral glucose tolerance test decreased significantly in rats treated with CT. Treatment with CT (50 mg/kg) inverted the activities of glucose metabolic enzymes and the levels of Hb, HbA_{1C}, glycogen, liver and kidney damage biomarkers induced by diabetes in rats. CT reduced histological damage in liver induced by STZ. CT (50 mg/kg) reversed histological damage in islets of Langerhans in the pancreas and increased insulin-positive cells in diabetic rats.	Antidiabetic
Jagdale et al. (2016)	After 45 days of study, CT (2 mg/kg) reduced tissue damage induced by diabetes. CT (2 mg/kg) was able of control kidney damage decreasing the excretion of albumin and creatinine. In *in vitro* studies, CT presented an anti-cataract effect (25 µg/ml) with increased SOD activity and reduction in the level of sorbitol. Viability of hepatocyte cells was higher than/or about 90%, but damage to hepatocytes treated with 50 µg/ml of CT was higher than in cells treated with 25 µg/ml.	Antidiabetic
Batubara et al. (2015)	CT reduced cholesterol plasma levels in animals subjected to high fat diet without changing the level of the liver enzymes alanine transaminase (ALT) and aspartate aminotransferase (AST).	Anti-cholesterol

(*continued on next page*)

Table 3 (*continued*)

Author	Results	Action
Brito et al. (2012)	(−)-CT reduced significantly nociceptive behavior in acetic acid and formalin tests at all doses tested. The two higher doses of citronellol increased the time of latency on the hot plate at all evaluation times. Naloxone reversed the antinociceptive effect of citronellol in the hot plate test. CT reduced the number of total leukocytes, neutrophils and TNF-α, without reduced the number of mononuclear cells in pleurisy induced by carrageenan, in mice.	Antinociceptive
Brito et al. (2013)	(−)-CT reduced nociceptive orofacial behavior in the second phase of the formalin test, and in capsaicin and glutamate tests in all doses tested. Besides that, CT activated expression of Fos protein in the olfactory bulb, piriform cortex, retrosplenial cortex and periaqueductal grey.	Antinociceptive
Brito et al. (2015)	(S)-(−)-β-Citronellol reduced hyperalgesia induced by CG and TNF-α, in all doses tested, between 30 and 180 min after induction. However, in the mechanical hyperalgesia induced by PGE_2 and DA, citronellol reduced the hyperalgesia only at the time points of 120 and 180 min after induction. CT (100 mg/kg, i.p) reduced Fos expression in spinal cord of mice after injection of CG.	Anti-hiperalgesic
Umezu et al. (2002)	CT significantly increased the response rate during the alarm period in the Geller conflict test (600 mg/kg), and the number of electric shocks the mice received in the Vogel conflict test (400 mg/kg).	Anti-anxiety
Sousa et al. (2006)	(+)-CT reduced the time of latency of the first post-injection convulsion induced by pentylenetetrazol (in all doses studied) or picrotoxin (200 and 400 mg/kg). The higher dose of CT reduced the percentage of tonic convulsion induced by electroconvulsive shock or pentylenetetrazol. CT (3.2–6.4 mM) depressed the compound action potential in sciatic nerves of rats.	Anticonvulsant

ACh: Acetylcholine; AGE: Advanced glycation end products; BV: Bilateral vagotomy; CFU: Colony-forming units; CG: Carrageenan; CT: Citronellol; DA: Dopamine; EFS: Electrical field stimulation; EVA: Poly(ethylene-co-vinyl acetate) copolymer; FICI: Fractional inhibitory concentration indices; GC: Gas chromatography; Hb: Haemoglobin; HbA_{1C}: Glycated haemoglobin; HR: Heart rate; i.c: Intracardiac; IC_{50}: The half maximal inhibitory concentration; IgE: Immunoglobulin E; i.p: intraperitoneal; IR: Inhibition rate; IκBα: Inhibitor of nuclear factor kappa B, alpha; LPS: Lipopolysaccharide; MAP: Mean arterial pressure; MBC: Minimal bactericidal concentration; MFC: Minimal fungicidal concentration; MIC: Minimal inhibitory concentration; MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NF-κB: Nuclear factor kappa B; NO: Nitric oxide; PGE_2: Prostaglandin E_2; p.o: Oral; SOD: Superoxide dismutase; STZ: Streptozotocin; TNF-α: Tumor necrosis factor-α; TRPA1: Transient receptor potential ankyrin-1; TRPV1: Transient receptor potential cation channel subfamily V member 1; (+): R or *rectus* or right; (−): S or sinister or left; (±): R,S or racemic mixture.

inhibited the production of NO in all tested concentrations (50–750 μM). Similar results were observed about the reduction of the production of PGE_2 (5–250 μM). CT did not inhibit the expressions of the inducible nitric oxide synthase (iNOS) protein or mRNA induced by lipopolysaccharide (LPS) but reduced the iNOS activity by reduction of the conversion from [3H]-arginine to [3H]-citrulline. Pretreatment with CT reduced the phosphorylation of ERK induced by IgE (0.5 mM), but not p38 phosphorylation. (±)-CT inhibited LPS-induced cyclooxygenase-2 (COX-2) protein expression in a dose-dependent manner and suppressed PGE_2 production. (±)-CT reduced nuclear factor-κB (NF-κB) p65 levels and increased inhibitor of nuclear factor kappa B, alpha (IκBα) in the cells' cytosol.

3.8. Antispasmodic

Sadraei et al. (Sadraei et al. (2013)) described the antispasmodic effect of CT by the method of ileum contraction induced by KCl, acetylcholine (Ach) and electrical field stimulation (EFS). CT was more effective in reducing contraction induced by KCl (IC_{50} = 2.9 ± 0.3 μg/ml), the first and second contractions induced by ESF (IC_{50} = 5.4 ± 0.9 and 3.4 ± 0.9 μg/ml, respectively), and those induced by ACh (IC_{50} = 7.5 ± 1.2 μg/ml), respectively. Vasconcelos et al. (2016) showed an antispasmodic effect of (±)-CT in the tracheal contraction of rats induced by K^+ ((IC_{50} = 120.8 μM), ACh (IC_{50} = 210.7 μM), EFS (IC_{50} = 240.9 μM) and sodium orthovanadate (IC_{50} = 243.0 μM). When contractions were evoked by selective recruitment of extracellular Ca^{2+}, (±)-CT inhibited the contractions induced by activation of voltage-operated channels, but not receptor-operated channels. Contractions induced by restoration of external Ca^{2+} levels after depleting internal Ca^{2+} stores also were inhibited by (±)-CT. The antispasmodic effect of (±)-CT was not reversed by L-N^G-nitroarginine methyl ester (L-NAME), an inhibitor of nitric oxide synthase, indomethacin and tetraethylammonium, or inhibition of transient receptor potential cation channel subfamily V member 1 (TRPV1) or Transient receptor potential ankyrin-1 (TRPA1).

3.9. Cardiovascular effects

The first study to evaluate the effect of CT on the cardiovascular system was developed by Bastos et al. (2009). The authors reported that (±)-CT was able to reduce blood pressure in normotensive rats, associated with tachycardia. CT-induced tachycardia was reversed with the use of atropine and hexamethonium, however hypotension was maintained. In addition, (±)-CT was able to cause relaxation in the mesenteric artery rings of rats, with or without endothelium, pre-contracted by phenylephrine, KCl, $CaCl_2$, and caffeine. In the following year, Menezes et al. (Menezes et al., 2010a,b) tested the hypotensive activity of several monoterpenes and confirmed the results obtained by Bastos et al. (2009).

Bilateral vagotomy or perineural treatment with capsaicin was not able to reverse the hypotensive effect of the CT treatment, but reduced the bradycardic effect. Capsazepine (Transient receptor potential cation channel subfamily V member 1 [TRPV1] antagonist), ondansetron (serotonin 5-HT3 receptor antagonist) and HC-030031 (Transient receptor potential ankyrin-1 [TRPA1] selective antagonist) did not reverse the CT effect, but suramin (a competitive antagonist of purinergic (P2x)-receptors) reduced the appearance of apnea observed in anesthetized rats. Administration of CT by the intracardiac pathway presented similar effects to intravenous administration, but without apnea episodes. When studying non-anesthetized rats, CT presented similar effects but at lower doses, and hypotensive and bradycardic effects at higher doses (5, 10 and 20 mg/kg) both immediately after administration and for an extended period. Methylatropine (a muscarinic antagonist) reversed the effects in the immediate phase, but only reversed bradycardic effect in the prolonged phase. These results show that the short-term cardiovascular effect of CT does not involve the activation of TRPV1, TRPA1, P2x or $5\text{-}HT_3$ receptors. In the longer-term, the use of CT was characterized by hypotension and bradycardia. The effect of CT on apnea is due to action on the purinergic pathway (Ribeiro-Filho et al., 2016).

3.10. Antidiabetic

Recently, Srinivasan and Murugunathan (Srinivasan and Muruganathan, 2016) demonstrated the antidiabetic effect of CT (25, 50 and 100 mg/kg) on diabetes mellitus induced by streptozotocin, chemical agent that is toxic to the insulin-producing beta cells of the pancreas in mammals. CT reduced food/water intake but body weight

increased with less insulin increase than in a control group. Plasma glucose of rats also increased less in the CT group than control group. Treatment with CT (50 mg/kg) inverted the activities of glucose metabolic enzymes and the levels of hemoglobin, glycated hemoglobin, glycogen, and liver and kidney damage biomarkers induced by diabetes. Liver damage and damage in the islets of Langerhans in the pancreas induced by streptozotocin were reduced by the treatment with CT, and insulin-positive cells were increased in diabetic rats (Srinivasan and Muruganathan, 2016).

Other authors (Jagdale et al., 2016) used the same model and reported that after 45 days of treatment CT (2 mg/kg/day) was able of reduce tissue damage induced by diabetes mainly in the liver, kidney and eye lens of rats. An anti-cataract effect was investigated by *in vitro* studies and this action of the CT was found to occur simultaneously with an increase in antioxidant enzyme superoxide dismutase, and a reduction in sorbitol level, a sugar produced by the polyol pathway in diabetes. The cell viability of hepatocytes was greater than 90% after administration of CT, indicating that CT did not produce considerable cell death, which would negate the positive effects of CT.

3.11. Anti-cholesterol

The anti-cholesterol activity of CT was studied by Batubara et al. (2015), who treated animals subjected to a high fat diet with CT inhalation and plasma cholesterol was reduced. CT did not change the level of the liver enzymes alanine transaminase (ALT) or aspartate aminotransferase (AST).

3.12. Antinociceptive

Brito et al. (2012) showed the antinociceptive effect of (−)-CT on nociception induced by acetic acid, formalin and hot plate. This effect was reverted by naloxone, indicating a probable effect of (−)-CT on opioid receptors. In pleurisy induced by carrageenan (CG), (−)-CT reduced the number of total leucocytes, neutrophils and TNF-α, without reducing the number of mononuclear cells. In 2013, Brito et al. (Brito et al., 2013) tested (−)-CT in orofacial nociception induced by formalin, capsaicin and glutamate, and noted that (−)-CT reduced nociceptive behavior and activated expression of Fos protein in the olfactory bulb, piriform cortex, retrosplenial cortex and periaqueductal grey, suggesting action on the descending pain pathway.

3.13. Antihyperalgesic

To investigate the antihyperalgesic effect of (−)-CT, Brito et al. (Brito et al., 2015a,b) used CG, TNF-α, PGE_2 and dopamine (DA). (−)-CT (25, 50 and 100 mg/kg, i.p) reduced hyperalgesia induced by carrageenan and TNF-α at all times of evaluation (30–180 min), but in the mechanical hyperalgesia induced by PGE_2 and DE, (−)-CT reduced the hyperalgesia only at 120 and 180 min after induction. In addition, (−)-CT reduced Fos expression in the spinal cord of mice after injection of CG, which corroborates the antihyperalgesic effect of (−)-CT.

3.14. Anti-anxiety

The anti-anxiety effect of CT was investigated by Umezu et al. (2002) using the Geller and Vogel conflict tests in mice. CT was able of increase the response rate during the alarm period in the Geller conflict test and the number of electric shocks in the Vogel conflict test.

3.15. Anticonvulsant

Sousa et al. (de Sousa et al., 2006) described the anticonvulsant effect of (+)-CT and showed that it reduced the time of latency of the first post-injection convulsion induced by pentylenetetrazol or picrotoxin. Only the higher dose of (+)-CT (400 mg/kg, i.p) reduced the percentage of tonic convulsion induced by electroconvulsive shock or pentylenetetrazol, showing more difficulty in relation to action by this pathway. In addition, the authors observed that (+)-CT (3.2–6.4 mM) depressed the compound action potential in the sciatic nerves of rats, suggesting that the anticonvulsant effect of (+)-CT may be due to a reduction of the action potential amplitude.

4. Discussion

The lack of effective side-effect free treatments for numerous clinical conditions highlight the need for the discovery and use of new drugs. Examples of these conditions are those which require a treatment against multiresistant microorganisms (Lessem et al., 2015), in addition to inflammatory and chronic pain conditions, whose existing treatment is not always effective. Severe diseases, such as tuberculosis, present a multi-resistant etiological agent (Lessem et al., 2015). Chronic inflammatory diseases like arthritis have long-term treatments that can have a number of side effects (Ma et al., 2014). Chronic pain conditions such as fibromyalgia require effective medications with less side effects to enable a better quality of life for individuals who are affected by these syndromes (Yelland, 2017).

Previous studies have already demonstrated the benefits of monoterpenes in the treatment of various signs and symptoms, from those of acute manifestations, to those of chronic manifestation, pointing to this class of natural products as an alternative for the development of new drugs (Guimarães et al., 2014, 2013; Melo et al., 2011; Seol et al., 2016). In addition, medicinal products containing terpenes in their formulation are already available in the market, such as menthol used in the treatment of pain, again showing the importance of these products (Pergolizzi et al., 2018).

In this review, we highlighted the numerous benefits of the use of CT, with activities ranging from the antibacterial to the anticonvulsant. CT was able to act against important microorganisms causing diseases in humans, such as *Streptococcus pyogenes, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhimurium, Cryptococcus neoformans*, *Candida albicans,* and *Aspergillus* and *Trichophyton* (Echeverrigaray et al., 2008; Kim and Park, 2012; Kotan et al., 2007; Mahmoud, 1994; Mulyaningsih et al., 2011; Ngan et al., 2012; Nostro et al., 2013; Pereira et al., 2015; Shin, 2003; Shin and Lim, 2004; Viollon and Chaumont, 1994; Zore et al., 2011). In addition, CT also showed anti-lice activity (Gonzalez-Audino et al., 2011) as well as a repellent effect against *Culex pipiens*, limiting the possible impact caused by the West Nile virus (Michaelakis et al., 2014). CT showed it was effective against a range of microorganisms, and had characteristics such as anti-lice and repellent properties while not presenting high toxicological activity when tested in *in vitro* studies, making it a possible source for new medicines (Kotan et al., 2007; Zore et al., 2011).

In *in vitro* tests, CT showed low lipolytic activity (Choi, 2006). This result may explain the low toxicity of CT demonstrated by Gonzales-Audino and collaborators (Gonzalez-Audino et al., 2011). Substances with lipolytic action can trigger chronic elevation of circulating fatty acids that may present toxic action at tissue level (Engin, 2017).

However, with respect to the anti-allergic and anti-inflammatory effects, CT was effective, acting through the TNF-α, COX-2, PGE_2, NF-κB and IκBα pathways, important mechanisms already described in the literature in relation to anti-inflammatory drugs (Abe et al., 2003; Kobayashi et al., 2016). These results can explain the data reported by Brito et al. (2012), where CT presented an antinociceptive effect in the second phase of the formalin test (inflammatory phase). The reduction of the inflammation induced by the formalin probably resulted in the reduction of nociceptive behavior of mice. In addition, CT also reduced leukocyte migration and the level of TNF-α in the pleural fluid of animals submitted to the CG-induced pleurisy test. Another study also demonstrated that CT reduced the inflammatory mechanical hyperalgesia of mice induced by CG and TNF-α more quickly than that

induced by PGE_2 and DA (Brito et al., 2015a,b), which suggests that CT is acting directly on the TNF-α pathway.

The antispasmodic effect of CT on isolated ileum and tracheal contraction of rats was also described, through action on channels Ca^{2+} (Sadraei et al., 2013; Vasconcelos et al., 2016). According to the authors, CT reversed the contraction of ileum induced by KCl (80 mM), electrical field stimulations (EFS) and acetylcholine (ACh, 2 μM). The control used by the authors to reverse the contraction of the ileum induced by KCl was loperamide, an opioid that acts by inhibiting the release of neurotransmitters. Because opioid receptors are present in the ileum and may reduce the influx of Ca^{2+}, it is believed that CT has reduced the contractility of the ileum by reducing the influx of Ca^{2+} in the presynaptic neuron, like loperamide (Sadraei et al., 2013).

Vasconcelos et al. (2016) also demonstrated the antispasmodic effect of CT. The authors investigated the effect of CT on tracheal contraction induced by K^+, electrical field stimulation and sodium orthovanadate and observed that CT inhibited tracheal contractions by action on voltage-operated channels when Ca^{2+} was recruited in extracellular space. These findings may be related to the cardioinhibitory and vasodilatory effects of CT, which result in reduced blood pressure and heart rate. The authors also observed that these effects of CT are not related to the activation of TRPV1, TRPA1, P2x or 5-HT3 receptors (Bastos et al., 2009; Menezes et al., 2010a,b).

Srinivasan and Murugunathan (Srinivasan and Muruganathan, 2016) reported the antidiabetic effect of CT, stimulating the production of insulin by the islets of Langerhans in the pancreas. The presence of cataracts, a complication found in diabetic patients, was reversed by CT, probably via an antioxidant effect thorough an increase of superoxide dismutase enzyme, and the reduction of sorbitol level (Jagdale et al., 2016). Blood cholesterol was also reduced after the administration of CT, without altering the levels of the liver enzymes ALT and AST, demonstrating the absence of hepatic injury (Batubara et al., 2015).

CT actions on the central nervous system were also described. The antinociceptive effect in the first phase of the formalin test and in the hot plate test are indicative of this effect. In addition, the effect of CT was reversed by naloxone, suggesting its action on opioid receptors (Brito et al., 2012). Another indication of the central action of CT was the its antinociceptive effect on orofacial pain induced by formalin, capsaicin and glutamate, which reinforces the effect of CT on the modulation of Ca^{2+} channels, as well as suggesting other possibilities of action, such as the glutamatergic and substance P pathways. When investigating the encephalic areas activated after the administration of CT, activation of the retrosplenial area and the periaqueductal gray matter were observed, both areas of importance in the modulation of pain (Brito et al., 2013).

The anti-anxiety (Umezu et al., 2002) and anticonvulsant (de Sousa et al., 2006) actions described for CT again demonstrate the effect of this monoterpene on the central nervous system, which may be derived from a reduction of compound action potential amplitude (de Sousa et al., 2006).

The studies described several pharmacological activities for CT, and some mechanisms of action have already been defined, especially those involving anti-inflammatory (Abe et al., 2003; Brito et al., 2015a,b; Kobayashi et al., 2016), antioxidant (Jagdale et al., 2016) and analgesic (Brito et al., 2012; Brito et al., 2015a,b; Brito et al., 2013b) pathways (Fig. 3), indicating this compound as an alternative treatment for such disorders.

One possible explanation for the diversity of CT actions described in the literature could be the presence of pharmacological activity in different isomeric forms. Most of the *in vitro* studies that described the isomeric form used, opted to use the racemic mixture (Mulyaningsih

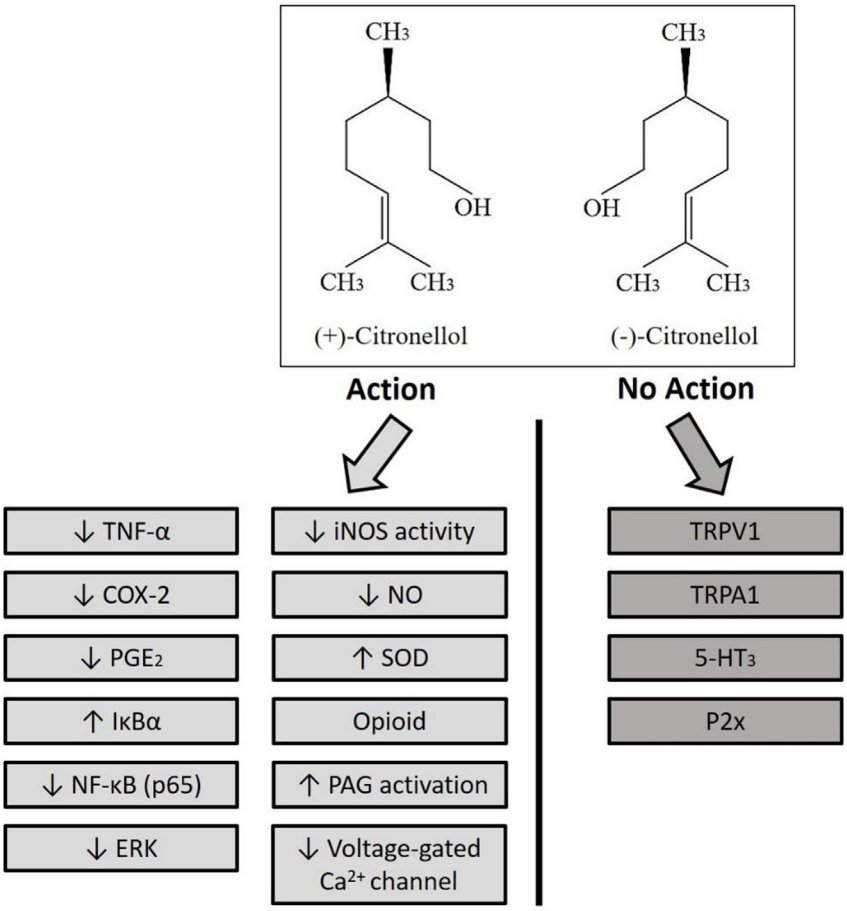

Fig. 3. Main targets of action of citronellol. TNF-α: Tumor necrosis factor-α. COX-2: Cyclooxygenase-2. PGE_2: Prostaglandin E_2. IκBα: Inhibitor of nuclear factor kappa B, alpha. NF-κB (p65): Nuclear factor kappa B. ERK: Extracellular Signal-regulated Kinase. iNOS: Inducible nitric oxide synthase. NO: Nitric oxide. SOD: Superoxide dismutase. PAG: Periaqueductal grey. TRPV1: Transient receptor potential cation channel subfamily V member 1. TRPA1: Transient receptor potential ankyrin-1.5-HT_3: Serotonin receptor type 3. P2x: Purinergic receptor P2x.

et al., 2011; Su et al., 2010; Vasconcelos et al., 2016). In some activities investigated in *in vivo* studies, such as the cardiovascular ones, the racemic mixture was also preferred (Bastos et al., 2010; Menezes et al., 2010a,b). To investigate the effect of CT on pain sensitivity, (−)-CT was more frequently used (Brito et al., 2012; Brito et al., 2015a,b, 2013a). (+)-CT rather than (−)-CT was only used in *in vivo* studies investigating its anticonvulsant effect (Sousa et al., 2006).

5. Conclusion

In view of the need for new medicines for various health conditions, we would highlight natural products, especially terpenes, as important alternatives for the development of new drugs. CT's antibacterial, antifungal, antispasmodic, anti-inflammatory, antinociceptive, anticonvulsive and anti-anxiety activities have already been described in the literature, besides presenting low toxicity. The range of pharmacological activities found in CT's different isomeric forms make it a promising molecule to study in many areas of research.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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