A recent review on nerolidol and their medicinal properties

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Abstract

Nerolidol (3,7,11-trimethyl-1,6,10-dodecatrien-3-ol) is a naturally occurring sesquiterpene alcohol, 15-carbon compounds formed from three isoprenoid units. Nerolidol is a sesquiterpene present as an essential oil in numerous plants that is used in scented products and has been approved by the FDA as a food-flavorings agent. It is also used as fragrance ingredient cosmetics, shampoos, soaps, non-cosmetic products such as household cleaners and detergents. In worldwide usage of nerolidol per annum ranges from 10 to 100 metric tons per year. It is appearing in clear pale yellow colour liquid, having a faint floral odor reminiscent of rose and apple. Sesquiterpenes occur in human food, but they are principally taken as components of many folk medicines and dietary supplements. Moreover, nerolidol is a common ingredient in many products has attracted researchers to explore more effective medicinal properties of nerolidol that may exert beneficial effect on human health. Therefore, the aim of the review highlights prospects of various pharmacological and biological studies of nerolidol as a promising in the field of agriculture and medicine.

Key words: *Nerolidol; Sesquiterpenes.*

Introduction

At present most of medicinal plant used to treat many diseases such as cancer, cardiovascular, diabetes etc. *[1]*. The advanced technology using medicinal plants to identify bioactive compounds in physiological, pharmacological and biological properties. Essential oil is volatile, present in various plants such as *Baccharis* dracunculifolia *[2] Piper claussenianum, Conyza bonariensis [*3*], Momordica charantia [4] Bougainvillea glabra, Burchardi umbellate*. Nerolidol is naturally occurring sesquiterpene alcohol, is a major component present in the several essential oil *[5]*, widely used in cosmetics and non-cosmetic cleaning products, health-supporting preparations folk medicines and has a worldwide consumption varying between 10

and 100 tons/year *[6]*. Nerolidol used as flavor enhancer in many food products since its approval by the U.S. Food and Drug administration. In the present reviews aims to focus on pharmacological and biological properties of nerolidol such as its antioxidant, anti tumor and antibacterial activities.

Chemical properties of nerolidol

Essential oils are made up of three elements almost exclusively carbon, hydrogen, and oxygen. By far the most widespread component class is the terpenes. Sesquiterpene, defined as 15-carbon compounds formed from three isoprenoid units, a heterogeneous and large group of natural compounds *[7]*. Essential oils as well as highly lipophilic in nature, can affect membrane structure and thus facilitate drug accumulation within cells *[8]*. Nerolidol is an allylic isomer and exists in two geometric isomers (*cis*-3,7,11-Trimethyl-1,6,10-dodecatrien-3-ol) and (*trans*-3,7,11-Trimethyl-1,6,10-dodecatrien-3-ol) form with *trans* being the most abundant *[9]*.

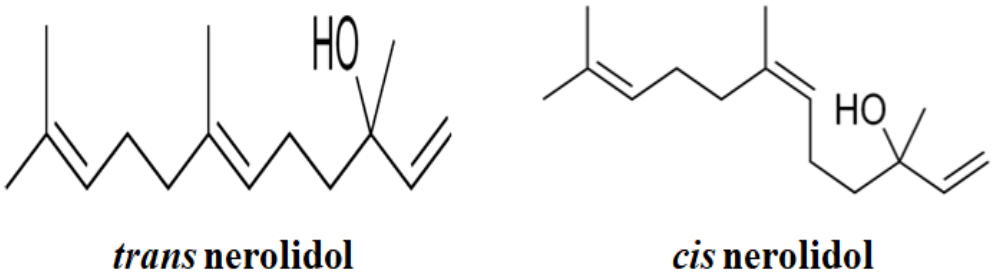

Figure 1. shows the structure of nerolidol

Extraction and analytical methods of nerolidol

The extraction methods of essential oil from various plants. The extracting nerolidol was carried out hydrodistillation method using the most common method of Clevenger-type apparatus *[10]*. Nerolidol extracted from various parts of plants such as leaves, roots and flowers. Essential oil of nerolidol among different plant species, *Hedychium coccineum* (*E*)-nerolidol (44.4%),*[11]*, Camellia sinensis, *Conyza bonariensis L* of flower (*Z*)-nerolidol, root (*Z*)-nerolidol (19.9%) *[12]*. The table 1 shows the types of nerolidol plant extract and their biological activities.

Cytotoxicity studies

Several studies documented that anti-tumor properties of nerolidol on *in-vitro* and *in-vivo* studies. A study conducted by matheus *et al [13]* has nanocapsulated against mammalian cells. Nerolidol does not cause any toxic effect in PBMC (Peripheral blood mononuclear cells). Moreover, Juliana Vinholes *et al [14]* reported to cis-nerolidol, at non cytotoxic conditions, were able to protect Caco-2 cells against toxicity caused by tert-BuOOH. Another study done by

Stefano Dall'Acqua *et al [15]* has shown (E)-nerolidol, the main volatile component of Thymus alternans EO, appeared to afford the major contribution to the cytotoxic activity of the essential oil. The significant cytotoxic activity of isolated nerolidol underlines the possible role of the plant as a potential source of bioactive compounds for therapeutical applications. Besides Ligia fernanda ceole *et al [16]* reported by nerolidol has low toxic potential *in-vivo* and presents anti-tumorigenic activity in female rats. Sperotto *et al [17]* showed that Piper gaudichaudianum essential oil and nerolidol (a racemic mixture of cis and trans-isomers) are not mutagenic but do induce significant cytotoxic effects in Saccharomyces cerevisiae that are related to ROS generation and the formation of single-strand breaks. At the highest concentration (100g/mL) used, nerolidol induced cytotoxicity that was at least five times higher than that induced by the essential oil of piper gaudichaudianum, regardless of the strain tested.

Antioxidant properties of nerolidol

The ROT-induced PD model was used to investigate the neuroprotective potential of the nerolidol phytochemical, which recently showed potential antioxidant activity conducted by Hayate Javed *et al [18]*. The essential Oil and hydrosol contained high levels of monoterpene and sesquiterpene constituents which have antioxidant activity close to that of phenolic constituents, break free-radical chain reactions and caused their irreversible oxidation into inert compounds reported by Djenane *[19]* . Dhifi *et al [20]* suggested that obtained in Neroli oil from methanol extract have a moderate antioxidant activity. Besides, nerolidol isolated from curcuma leaf may serve as an antioxidant and can be used as a potent candidate for the prevention of oxidative stress mediated damages by Priya *et al [21]*. Furthermore, Mohammed Falalu Hamza *et al [22]* was nerolidol has free radical scavenging activity with highest inhibition at 240 µg mL-1. This assay confirms the radical scavenging abilities of the compounds isolated from the leaves of C. latifolia supports its use in reducing oxidative stress in the body. Sureda *et al [23]* demonstrated that Sesquiterpene (caulerpenyne), significantly increased the liver antioxidant defense was observed. Sabir *et al [24]* reported that the hepatoprotective effects of sesquiterpene compounds, such as nerolidol, might be associated with its antioxidant capacity to scavenge ROS.

Antibacterial activity

Nerolidol, the antimicrobial action via cell membrane-disrupting mechanism, the results showed, leakage of K, C ions from bacterial cells. Terpene alcohols with carbon chains of C_{10} to C_{12}, as nerolidol, exhibit a strong antibacterial activity against *S. aureus*. Nerolidol is a therapeutic option to the development of drug combinations for antibacterial treatment, particularly against *S. aureus* and for multi-drug resistant bacteria reported by Cazella *et al [25]*. Besides, the chemical composition of propolis essential oil from the Cerrado biome in Midwest Brazil, along with the investigation of its mutagenic and antimicrobial potentials, revealed that the (E)-nerolidol exhibited antimicrobial properties. Fernandes *et al [26]*. Furthermore, Xiaxia Meng *et al [27]* reported to the antibacterial activity and mechanism of

action the essential oil from Juniperus rigida against *K. pneumoniae*. The trans-nerolidol 6.57% exhibited significant antibacterial activity against *K. pneumoniae*. Laura Scalvenzi et al *[28]* reported to trans-nerolidol is mainly responsible for the antibacterial activity of M. splendens essential oil. Trans-nerolidol in combination with synthetic antibiotics ciprofloxacin, erythromycin, and gentamicin enhances their antibacterial activity against *S. aureus* and *E. coli*. Essential oils containing trans-nerolidol have been reported to inhibit the growth of quite a number of bacteria including *S. aureus, S. epidermidis, E. coli and P. aeruginosa*.

Anti leishmanial activity

This study showed that, antileishmanial activity of nerolidol was evaluated in cultures of L. amazonensis promastigotes. The calculated IC_{50} of nerolidol for L. amazonensis promastigotes was 85.22±5.45µM. Furthermore, the activity of nerolidol was also tested against two other leishmania species. The IC_{50} determined for L. braziliensis and L. chagasi promastigotes were 74.15±10.51 and 75.10± 22.90µM, respectively. In another study, The essential oil extracted from the leaves of P. claussenianum is a natural product rich in (E)-nerolidol that has a surprising biological activity, showing efficient growth inhibition of promastigote forms of L. amazonensis, and a significant inhibition on its arginase activity as well as an important enhancement in the nerolidol levels in infected macrophages induced by this essential oil. The results presented in this study points to the P. Claussenianum leaves essential oil as an important source in the searching for new alternatives for the treatment and management of cutaneous leishmaniasis André Mesquita Marques *et al* [5]. According to a study conducted by Ligia fernanda ceole *et al [16]* reported that anti-leishmanial potential of Promastigotes. Essential oil and nerolidol was confirmed *in-vitro*, obtaining nerolidol derivatives with better spin labeling can be the source for promising candidates in the search for new compounds to kill leishmania parasites.

Anticancer activity of nerolidol

The administration of nerolidol effectively inhibits DMBA induced mammary cancer. Nerolidol relies on its anti-lipid peroxidative and antioxidant function as well as modulatory effects on phase I and II detoxification enzymes to excrete the carcinogenic metabolites reported by suganthi *et al [29]*. Further a remarkable reducing effect of natural and synthetic nerolidol on the viability of tumor cells were screened. General effects of nerolidol on the viability of tumor cells and mouse polyomavirus infection provide the basis for further investigations about the mechanisms responsible for the activity of nerolidol by Boris Ryabchenkoa *et al [30]*. Veronika Hanusova *et al [31]* conducted by trans-nerolidol significantly suppressed adhesion of TNFα-induced cells probably due to down-regulation of ICAM-1. The presence of TNFα, trans-nerolidol B andκdecreased activation (phosphorylation) of NF- increased activity of caspases, thus inducing apoptosis of cancer cells. *Chan et al [32]* reported by isolation of the bioactive phytochemicals may lead to the development of potential anticancer agent for human colorectal cancer.

Anti ulcer activity of nerolidol

Nerolidol possesses gastro protective activity as evidenced by its significant inhibition in the formation of ulcers induced by physical and chemical agents. However, further pharmacological and toxicological investigations, to delineate the mechanisms of action and the toxic effects, are required to allow the use of nerolidol for the treatment of gastric ulcer reported by Klopell *et al [33]*. Massignani *et al [34]* reported by phytochemical analysis carried out on B. dracunculifolia essential oil indicated that nerolidol (23.58%) could be the constituent primarily responsible for its anti-ulcer activity. The constituents of essential oils as promising agents in the management of gastric ulcers, a global disease in which there is high unmet needs related to current treatments in terms of efficacy, safety and low cost.

Genotoxicity of nerolidol

Píc ulo *et al [35]* analyzing high doses of one monosubstance, indicates a clastogenic and weak genotoxic potency of nerolidol in mouse cells. Hence, great care should be taken while using it as a therapeutic agent or food flavor enhancer at high concentrations. Baldissera *et al [36]* reported by the inhibition of cerebral NOx production can be a pathway associated with protect brain tissue and neuroprotective properties of nerolidol-loaded in nanospheres against genotoxic and cytotoxic damage induced by T. evansi.

S. No	Plants and parts of plant	Type of nerolidol	Title of the Research	References
1	-	*trans*-nerolidol	The effects of β-caryophyllene oxide and *trans*-nerolidol on the efficacy of doxorubicin in breast cancer cells and breast tumor-bearing mice	Veronika Hanusova, *et al*
2	-	Nerolidol *cis*-nerolidol	Evaluation of the mutagenicity of sesquiterpenic2 compounds and their influence on the susceptibility towards antibiotics of two clinically relevant bacterial strains	Odete Gonc¸alves, *et al*
3	*Myrica rubra (leaves)*	*trans*-nerolidol	Sesquiterpenes α-humulene and β-caryophyllene oxide enhance the efficacy of 5-fluorouracil and oxaliplatin in colon cancer cells	Martin ambroz, *et al*
4	-	*cis*-nerolidol *trans*-nerolidol	Nerolidol and Farnesol Inhibit Some Cytochrome P450 Activities but Did Not Affect Other Xenobiotic-Metabolizing Enzymes in Rat and Human Hepatic Subcellular Fractions	Alena Spicakova, *et al*
5	*Myrica rubra*	*trans*-nerolidol	The Effects of Selected Sesquiterpenes from *Myrica rubra* Essential Oil on the Efficacy of Doxorubicin inSensitive and Resistant Cancer Cell Lines	Martin Ambroz, *et al*
6	*Myrica rubra (leaves)*	*trans*-nerolidol	The Influence of Sesquiterpenes from Myrica rubra on the Antiproliferative and Pro-Oxidative Effects of Doxorubicin and Its Accumulation in Cancer Cells	Martin Ambroz, *et al*
7	-	Nerolidol	Nerolidol nanospheres increases its trypanocidal efficacy against Trypanosoma evansi: New approach against diminazene aceturate resistance and toxicity	Matheus D, *et al*
8	-	Nerolidol	Solving the challenge of the blood–brain barrier to treat infections caused by Trypanosoma evansi:	Matheus D, *et al*

			evaluation of nerolidol-loaded nanospheres in mice	
9	-	Nerolidol	Protective effect of nerolidol-loaded in nanospheres against cerebral damage caused by Trypanosoma Evansi	Matheus D, *et al*
10	*Zornia brasiliensis* (leaves)	*trans*-nerolidol	Antitumor Properties of the Leaf Essential Oil of Zornia brasiliensis	Emmanoel V. Costa, *et al*
11	-	Nerolidol	Neuroprotective effect of nerolidol against neuroinflammation and oxidative stress induced by rotenone	Hayate Javed, *et al*
12	-	*cis*-nerolidol *trans*-nerolidol	Antimicrobial Activity of Nerolidol and its Derivatives against Airborne Microbes and Further Biological Activities	Sabine Krist, *et al*
13	-	Nerolidol	In vitro and in vivo activity of three sesquiterpenes against L3 larvae of Anisakis type I	Concepción Navarro-Moll, *et al*
14	-	Nerolidol	Antimalarial activity of the terpene nerolidol	Alexandre, *et al*
15	-	Nerolidol	In vitro sensitivity of poultry Brachyspira intermedia isolates to essential oil components and in vivo reduction of Brachyspira intermedia in rearing pullets with cinnamaldehyde feed supplementation	M. Verlinden, *et al*
16	-	*cis*-nerolidol	Assessment of the antioxidant and antiproliferative effects of sesquiterpenic compounds in in vitro Caco-2 cell models	Juliana Vinholes, *et al*
17	*Lippia sidoides*	Nerolidol	The effect of the essential oils from five different Lippia species on the viability of tumor cell lines	Mayna da S, *et al*
18	-	E, Z-(±)-Nerolidol	Pharmacological interactions of essential oil constituents on the in vitro growth of Plasmodium falciparum	R.L. Van Zyl, *et al*
19	*Citrus aurantium L.*	(*E*)-nerolidol	Relationship between volatile	Huseyin Degirmenci,*et*

	(Flower)		components,antimicrobial andantioxidant properties of the essential oil, hydrosol and extracts of Citrus aurantium L. Flowers	*al*
20	*Apis mellifera L.* (Fresh brown propolis)	(*E*)-nerolidol	Evaluation of mutagenic and antimicrobial properties of brownpropolis essential oil from the Brazilian Cerrado biome	Fábio H. Fernandes, *et al*
21	*Piper aduncum* (leaves)	Nerolidol	Nerolidol, the main constituent of Piper aduncum essential oil, has anti-Leishmania braziliensis activity	Ligia fernanda ceole, *et al*
22	-	Nerolidol	Antimicrobial activity of essential oils and five terpenoid compounds against Campylobacter jejuni in pure and mixed culture experiments	Cemil Kurekci, *et al*
23	*Myrica rubra (leaves)*	*trans*-nerolidol	Essential oil from Myrica rubra leaves inhibits cancer cell proliferationand induces apoptosis in several human intestinal lines	Lenka Langhasova, *et al*
24	*Juniperus rigida (Leaves)*	*trans*-nerolidol	Chemical composition, antibacterial activity and related mechanism of the essential oil from the leaves of Juniperus rigida Sieb. et Zucc against Klebsiella pneumonia	Xiaxia Meng, *et al*
25	*Curcuma longa L. (leaves*)	(*E*)-nerolidol	Chemical composition and in vitro antioxidative potential of essential oil isolated from Curcuma longa L. leaves	R. Priya, *et al*
26	-	Nerolidol	In vitro antileishmanial and cytotoxic activities of nerolidol are associated with changes in plasma membrane dynamics	Lais Alonso, *et al*
27	-	Nerolidol	Dose dependent chemopreventive efficacy of nerolidol on chemical induced mammary carcinogenesis in rats	Suganthi S, *et al*
28	-	*trans*-	The effect of Myrica rubra essential oil and its	Veronika Hanusova, *et*

		nerolidol	components α-humulene and trans-nerolidol on adhesion and apoptosis of colorectal cancer cells	*al*
29	-	*cis*-nerolidol	Cis-Nerolidol Induces Endoplasmic Reticulum Stress and Cell Death in Human Hepatocellular Carcinoma Cells through Extensive CYP2C19 and CYP1A2 Oxidation	Bruna Isabela Biazi, *et al*
30	*Myrcia splendens* (Leaves)	*trans*-nerolidol	Myrcia splendens (Sw.) DC. (syn. M. fallax (Rich.) DC.) (Myrtaceae) Essential Oil from Amazonian Ecuador: A Chemical Characterization and Bioactivity Profile	Laura Scalvenzi, *et al*
31	-	Nerolidol	Antiparasitic activity of nerolidol in a mouse model of schistosomiasis	Marcos P, *et al*
32	-	Nerolidol	Nerolidol Protects Against LPS-induced Acute Kidney Injury via Inhibiting TLR4/NF-κB Signaling	Lu Zhang, *et al*
33	-	Nerolidol	Preventive effect of nerolidol on isoproterenol induced myocardial damage in Wistar rats: Evidences from biochemical and histopathological studies	L. Asaikumar, *et al*
34	*Artemisia scoparia (Callus culture)*	Nerolidol	Biosynthesis of anti-leishmanial natural products in callus cultures of Artemisia scoparia	Reema Yousaf, *et al*
35	*Lippia origanoides (Aerial parts of plant)*	(*E*)-nerolidol	Tyrosinase inhibitory activity, molecular docking studies and antioxidant potential of chemotypes of Lippia origanoides (Verbenaceae) essential oils	AlessandraP.daSilva, *et al*
36	*Cryptocarya latifolia* (Leaves & fruits)	Nerolidol	Phytochemical, elemental and biotechnological study of cryptocarya latifolia	Mohammed Falalu Hamza, *et al*
37	*Diospyros discolor (*Flower*)*	(*E*)-nerolidol	Composition, in vitro Cytotoxic, and Antimicrobial Activities of the Flower Essential Oil of Diospyros discolor from Taiwan	Yu-Chang Su, *et al*

38	*Snapdragon* (flowers)	Nerolidol	Two nearly identical terpene synthases catalyze the formation of nerolidol and linalool in snapdragon flowers	Dinesh A, *et al*
39	*Camellia sinensis* (bud & leaves)	(*E*)-nerolidol	Formation of (E)-nerolidol in tea (Camellia sinensis) leaves exposed to multiple stresses during tea manufacturing	Ying Zhou, *et al*
40	-	(*E*)-nerolidol	Cytotoxic mechanism of Piper gaudichaudianum Kunth essential oil and its major compound nerolidol	A.R.M. Sperotto, *et al*
41	-	Nerolidol	In vivo genotoxicity assessment of nerolidol	FernandaPículo, *et al*
42	*Piper claussenianum* (Leaves)	(*E*)-nerolidol	Chemistry and Biological Activity of Essential Oils from Piper claussenianum (Piperaceae)	André M. Marques, *et al*
43	*Thymus alternans* (flower)	(*E*)-nerolidol	Antimicrobial and antioxidant activity of the essential oil from the Carpathian Thymus alternans Klokov	Luca A. Vitali, *et al*
44	-	Nerolidol	Investigation of Anticancer and Antiviral Properties of Selected Aroma Samples	Boris Ryabchenko, *et al*
45	-	Nerolidol	First evaluation of drug-in-cyclodextrin-in-liposomes as an encapsulating system for nerolidol	Joyce Azzi, *et al*
46	*BaccharisDracunculifolia* (Aerial parts of plant)	*trans*-nerolidol	Activity of compounds isolated from Baccharis dracunculifolia D.C. (Asteraceae) against Paracoccidioides braziliensis	Susana johann, *et al*
47	*Thymus alternans* (flower)	(*E*)-nerolidol	Phytochemical investigations and antiproliferative secondary metabolites from Thymus alternans growing in Slovakia	Stefano Dall'Acqua, *et al*
48	*Amomum subulatum* (fruits)	Nerolidol	GC-MS analysis, antibacterial and antioxidant study of Amomum subulatum Roxb	Ram Lal Shrestha
49	-	Nerolidol	Nerolidol-loaded nanospheres prevent hepatic oxidative stress of mice infected by Trypanosoma	Matheus D, *et al*

			evansi	
50	*Citrus aurantium L.* (flower)	Nerolidol	Analgesic and anti-inflammatory activities of Citrus aurantium L. blossoms essential oil (neroli): involvement of the nitricoxide/cyclic-guanosine monophosphate pathway	Pariya Khodabakhsh, *et al*

Table 1. shows the types of nerolidol plant extract and their biological activities.

Conclusions

In conclusion, essential oils are natural products which consist of several volatile molecules. Nerolidol is one of the widespread components found in the essential oil of a variety of medicinal plants. They have been used as several applications in agricultural, pharmaceutical and cosmetic. The present review reveled that biological properties of the nerolidol, the several studies are documented that nerolidol have the cytotoxicity effect against cancer cell lines, not a normal cells and anti-bacterial activity, antioxidant, anti leishmanial activity and anti-cancer properties. Nerolidol has a great potential to be used as a new phytochemical or therapeutic drug in the field of agriculture and medicine. This literature provides the root for the evaluation of sesquiterpenic compounds as alternative or possible synergistic compounds for current antibiotics and chemotherapeutics drugs.

References

1. *W. K. Chan, L. T. Tan, K. G. Chan, L. H. Lee, B. H. Goh, Nerolidol: A Sesquiterpene Alcohol with Multi-Faceted Pharmacological and Biological Activities, Molecules. 21(5), (2016), 529.*
2. *N. A. Parreira, L. G. Magalhaes, D. R. Morais, S.C. Caixeta, J. P. de Sousa, J. K. Bastos, W. R. Cunha, M. L. Silva, N. P. Nanayakkara, V. Rodrigues, Antiprotozoal, schistosomicidal, and antimicrobial activities of the essential oil from the leaves of Baccharis dracunculifolia, Chemistry & Biodiversity. 7, (2010), 993–1001.*
3. *S. Mabrouk, A. Elaissi, H. BenJannet, F. Harzallah-Skhiri, Chemical composition of essential oils from leaves, stems, flower heads and roots of Conyza bonariensis L. from Tunisia, Natural Product Research. 25(1), (2011),77-84.*
4. *A. Braca, T. Siciliano, M. D'Arrigo, M. P. Germanò, Chemical composition and antimicrobial activity of Momordica charantia seed essential oil, Fitoterapia. 79, (2008), 123–125.*
5. *André Mesquita Marques, Anna Léa Silva Barreto, José Alexandreda R. Curvelo, Maria Teresa Villela Romanos, Rosangela M. de A. Soares, Maria Auxiliadora C. Kaplan. Antileishmanial activity of nerolidol-rich essential oil from Piper claussenianum. Revista Brasileira de Farmacognosia, Brazilian Journal of Pharmacognosy. 21(5), (2011), 908-914.*
6. *D. McGinty, C.S. Letizia, A.M. Api, Addendum to fragrance material review on nerolidol (isomer unspecified), Food and Chemical Toxicolog. 48(3), (2010), 43–45.*
7. *G.M. Konig, A.D. Wright, New and unusual sesquiterpenes: Kelsoene, prespatane, epi-gamma-gurjunene, and t-cadinthiol, from the tropical marine sponge cymbastela hooperi. The Journal of Organic Chemistry. 62, (1997), 3837–3840.*
8. *M.J. Park, K.S. Gwak, I. Yang, , K.W. Kim, E.B. Jeung, J.W. Chang, I.G. Choi, Effect of citral, eugenol, nerolidol and terpineol on the ultrastructural changes of Trichophyton mentagrophytes. Fitoterapia. 80, (2009), 290–296.*

9. *V. Schubert, A. Dietrich, T. Ulrich, A. Mosandl, The stereoisomers of nerolidol: Separation, analysis and olfactoric properties. Zeitschrift für Naturforschung C. 47, (19920, 304–307.*
10. *H. A. Hesham, Rassem, H. Abdurahman, Nour, M. Rosli Yunus, Techniques For Extraction of Essential Oils From Plants: A Review. Australian Journal of Basic and Applied Sciences. 10(16), (2016), 117-127.*
11. *Ameenah Gurib-Fakim, Naheeda Maudarbaccus, David Leach, Luigino Doimo & Hans Wohlmuth, Essential Oil Composition of Zingiberaceae Species from Mauritius, Journal of Essential Oil Research. 14(4), (2002),271-273.*
12. *S. Mabrouk, A. Elaissi, H. BenJannet, F. Harzallah-Skhiri, Chemical composition of essential oils from leaves, stems, flower heads and roots of Conyza bonariensis L. from Tunisia, Natural Product Research. 25(1), (2011),77-84.*
13. *M. D. Baldissera, T. H. Grando, C. F. Souza, L. F. Cossetin, M. R. Sagrillo, K. Nascimento, S.G. Monteiro, Nerolidol nanospheres increases its trypanocidal efficacy against Trypanosoma evansi: New approach against diminazene aceturate resistance and toxicity. Experimental Parasitology. 166, (2016), 144–149.*
14. *J. Vinholes, P. Gonçalves, F. Martel, M. A. Coimbra and S. M. Rocha, Assessment of the antioxidant and antiproliferative effects of sesquiterpenic compounds in in-vitro Caco-2 cell models, Food Chemistry. 156, (2014), 204–211.*
15. *S. Dall'Acqua, G. Peron, S. Ferrari, V. Gandin, M. Bramucci, L. Quassinti, F. Maggi, Phytochemical investigations and antiproliferative secondary metabolites from Thymus alternans growing in Slovakia. Pharmaceutical Biology. 55(1), (2017), 1162–1170.*
16. *Ligia fernanda ceole, Maria das graças cardoso and Murilio josé soares. Nerolidol, the main constituent of Piper aduncumessential oil, has anti-Leishmania braziliensisactivity, Parasitology. 144, 9, (2017), 1179-1190.*
17. *A. R. M. Sperotto, D. J. Mourac, V.F. Péresc, F. C. Damascenod, E. B. Caramãod, J. A. P. Henriquesa, J. Saffia, Cytotoxic mechanism of Piper gaudichaudianum Kunth essential oil and its major compound nerolidol, Food and Chemical Toxicology. 57, (2013), 57–68.*
18. *Hayate Javed, Sheikh Azimullah, B. Salema, Abul Khair, Shreesh Ojha, and M. Emdadul Haque, Neuroprotective effect of nerolidol against neuroinflammation and oxidative stress induced by rotenone. BMC Neuroscience. 17:58, (2016).*
19. *D. Djenane, Chemical profile, antibacterial and antioxidant activity of Algerian citrus essential oils and their application in Sardina pilchardus, Foods. 4(4), (2015), 208–28.*
20. *Dhifi W, Mnif W, Jelali N, El Beyrouthy M, Ben Salem N. Citrus aurantium (bitter orange) blossoms essential oil and methanolic extract: composition and free radical scavenging activity. International Symposium on Medicinal and Aromatic Plants 2013:195–200.*

21. *R. Priya, A. Prathapan, K. G. Raghu, A. Nirmala Menon, Chemical composition and in vitroantioxidative potential of essential oil isolated from Curcuma longa L. Leaves, Asian Pacific Journal of Tropical Biomedicine. (2012), 695-699.*
22. *Mohammed Falalu Hamza, Shakira Shaik, Roshila Moodley, Phytochemical, elemental and biotechnological study of cryptocarya latifolia. African Journal of Traditional, Complementary and Alternative Medicines. 13(4), (2016), 74-80.*
23. *A. Sureda, A. Box, M. Enseñat, E. Alou, P. Tauler, S. Deudero, and A. Pons, Enzymatic antioxidant response of a labrid fish (Coris julis) liver to environmental caulerpenyne, Comparative Biochemistry and Physiology. 144, (2006), 191–196.*
24. *S. M. Sabir, J. B. T. Rocha, Water-extractable phytochemicals from Phyllanthus niruni exhibit distinct in vitro antioxidant and in vivo hepatoprotective activity against paracetamol-induced liver damage in mice, Food Chemistry. 111, (2008), 845–851.*
25. *L. N. Cazella, J. Glamoclija, M. Sokovic, J. E. Goncalves, G. A. Linde, N. B. Colauto, Z. C Gazim, Antimicrobial Activity of Essential Oil of Baccharis dracunculifolia DC (Asteraceae) Aerial Parts at Flowering Period, Frontiers in Plant Science. 29, (2019), 10-27.*
26. *F. H. Fernandes, Z. Guterres, IMP I. M. P. Violante, T. F. S. Lopes, Evaluation of mutagenic and antimicrobial properties of brown propolis essential oil from the Brazilian Cerrado biome. 1(2), (2015), 1482-1488.*
27. *Xiaxia Meng, Dengwu Li, Dan Zhou, Dongmei Wang, Qiaoxiao Liu and Sufang Fan, Chemical composition , antibacterial activity an d related mechanism of the essential oil from the leaves of Juniperus rigida Sieb . et Zucc against Klebsiella pneumoniae, Journal of Ethnopharmacology. 194, (2016), 698–705.*
28. *L. Scalvenzi, A. Grandini, A. Spagnoletti, M. Tacchini, D. Neill, J. Ballesteros, A. Guerrini, Myrcia splendens (Sw.) DC. (syn. M. fallax (Rich.) DC.) (Myrtaceae) Essential Oil from Amazonian Ecuador: A Chemical Characterization and Bioactivity Profile. Molecules, 22(7), (2017). 1163.*
29. *S. Suganthi, P. Pugalendhi, S. Uma, R. Jayaganesh, Dose dependent chemopreventive efficacy of nerolidol on chemical induced mammary carcinogenesis in rats, Research journal of life sciences, Bioinformatics pharmaceutical and chemical sciences. 5(1), (2019), 437.*
30. *Boris Ryabchenkoa, Elena Tulupovab, Erich Schmidtc , Katrin Wlcekd , Gerhard Buchbauerd , and Leopold Jirovetzd, Investigation of Anticancer and Antiviral Properties of Selected Aroma Samples . Natural Product Communications. 3, (2008),1085 – 1088.*
31. *Veronika Hanusova , Lenka Sklova, Martin Ambroz, Vera Kralova, Lenka Langhansova, Petra Matouskova, The effect of Myrica rubra essential oil and its components α-humulene and trans-nerolidol on adhesion and apoptosis of colorectal cancer cells . Cancer Cell & Microenvironment. 2,(2015), 1058.*

32. *C. K. Chan, H. Supriady, B. H.Goh, & H. A. Kadir, Elephantopus scaber induces apoptosis through ROS-dependent mitochondrial signaling pathway in HCT116 human colorectal carcinoma cells, Journal of Ethnopharmacology, 168, (2015), 291–304.*
33. *F. C. Klopell, M. Lemos, J. P. Sousa, E. Comunello, E. L. Maistro , J. K. Bastos , S.F. de Andrade,*
Nerolidol,an antiulcer constituent fromthe essential oil of Baccharis dracunculifolia DC (Asteraceae), Zeitschrift fur Naturforschung. C, Journal of biosciences. 62(7-8), (2007), 537-42.
34. *J. J. Massignani, M. Lemos, E. L. Maistro, H. P. Schaphauser, R. F. Jorge, R. F. Sousa, J. K. Bastos, S. F. Andrade, Antiulcerogenic Activity of the Essential Oil of Baccharis dracunculifolia on Different Experimental Models in Rats, Phytotherapy Research. 23,(2009), 1355–1360.*
35. *F. Pículo, C. Guiraldeli Macedo, S.F. de Andrade, E. Luis Maistro, In vivo genotoxicity assessment of nerolidol, Journal of Applied Toxicology. 31(7), (2011),633-9.*
36. *M. D. Baldissera, C. F. Souza, R. C. Riéffel, , M. C. Velho, A. P. Ramos, K. Nascimento, S. G. Monteiro, Protective effect of nerolidol-loaded in nanospheres against cerebral damage caused by Trypanosoma evansi, Naunyn-Schmiedeberg's Archives of Pharmacology. 391(7),(2018),753–759.*