Bioinformatics Study of *Cymbopogon citratus* as Active Compounds

Afran Marcelino Pratama[1], Syinta Gussri Fatmawati[2], Amalta Ferdinand[3]

[1]Universitas Negeri Padang, [2]Universitas Andalas, [3]Universitas Bung Hatta

*afranmarcelinopratama@gmail.com

Abstract. Lemongrass is a tropical plant that contains many active compounds in it. Active compounds consisting of volatile organic compounds with various structural forms and properties. This indicator really determines the character and role. Among them can cure diseases for humans and some also function as a distinctive aroma producer. These are all influenced by these structures, giving rise to these characteristics which have been studied by many scientists from all over the world by observing their structures to see the activity they cause. This study intends to prove the active compounds computationally by tracing the names of the compounds contained and scanning them to some well-known software such as Chemoffice. The information obtained is presented in an easy to understand tabular form.

1. Introduction

Cymbopogon citratus (DC) (*Gramineae*) is an herb worldwide known as lemongrass. The tea made from its leaves is popularly used as antispasmodic, analgesic, anti-inflammatory, antipyretic, diuretic and sedative [1]. The volatile oil obtained from fresh leaves of this plant is widely used by the perfumes, cosmetics industries and in traditional medicine for various purposes [2].

Fig. 1. Lemongrass plant

Citral is the major component of lemongrass oil which was extracted from its leaves, present at levels of, approximately, 65–85%. Citral (3,7-dimethyl-2,6-octadienal) is the name given to a natural mixture of two isomeric acyclic monoterpene aldehydes: geranial (*trans*-citral, citral A) and neural (*cis*-citral, citral B) (Fig. 2). In addition to citral, the lemongrass oil consists of small quantities of geranial, geranylacetate and monoterpene olefins, such as myrcene [2].

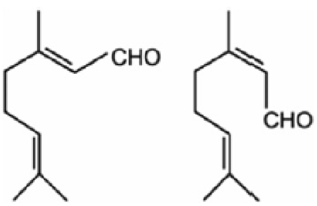
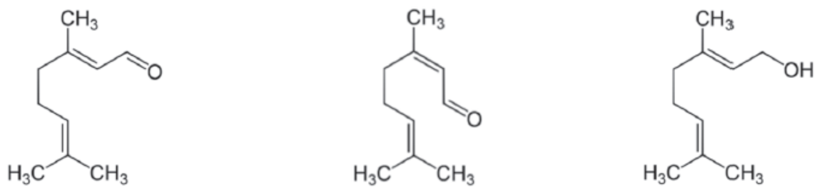


Fig. 2. Chemical structure of the citral

As a natural acyclic monoterpenes, citral was found in a wide variety of plants [3]. A number of dietary monoterpenes was shown to act effectively in chemoprevention and chemotherapy of different cancers in animal models, at cellular level, and in human clinical trials [4–6]. On the other hand, plant monoterpene citral is subjected to oxidation on exposure to air. Oxidation is enhanced by heat [7] and irradiation [8]. Furthermore, unsaturated trepenes are capable of trapping activated oxygen species in vivo to give intermediate epoxides which can alkylate DNAs, proteins, and other bimolecular [7–12]. In addition, some monoterpenes undergo oxidation by the action of peracid [13].

Research focusing on innovative therapeutic agents obtained from natural sources is increasingly growing [14-15]. Among them, essential oils, which mainly contain monoterpenes, are being widely used to prevent and treat human disease [16-17]. These volatile components show a wide range of biological activities, e.g. as antibacterials, antivirals or antioxidants [14],[18]. These plant-derived substances are potent anti-cancer agents as they have the potential to efficiently reduce the tumor volume and tumor cell proliferation without side effects [19]. Monoterpenes are also employed as flavors and fragrances in cosmetics, increasing their interest by a set of industries.



(a) (E)-3,7-dimetyloocta-2,6-dienal (b) (Z)-3,7-dimethylocta-2,6-dienal (c) (Z)-3,7-dimethyl-2,6-octadien-1-ol.

Fig. 3. Chemical structure of Geranial (a), Neral (b), and Geraniol (c)

Citral ($C_{10}H_{16}O$), also known as 3,7-dimethylocta-2,6-dienal, is a monoterpene and corresponds to 70–85 wt% of the essential oil of Cymbopogon citratus, commonly known as lemon grass [20-21]. Because of its strong lemon-like aroma, this fragrance monoterpene is widely used in cosmetics and as a flavor additive in food industry [22]. Additionally, citral is used in the production of vitamin A. Scientific literature attributes to citral a broad spectrum of therapeutic activities, such as antimicrobial, anti-inflammatory and anticancer properties. The monoterpene is chemically unstable, suffering biodegradation into geranic acid and 6-methyl-5- heptene-2-on over time in aqueous solutions.

From the chemical viewpoint, citral is a mixture of two geometric isomers: geranial (Fig. 3a) – also called *trans* confirmation, *trans*-citral or citral A (approx. 55–70 wt%), and neral (Fig. 3b) – also called *cis* confirmation, *cis*-citral or citral B (35–45 wt%) [23]. Scientific literature reports that both of isomers of citral are formed during the autoxidation pathway of geraniol-1-hydroperoxide [23-25]. The natural form of citral consists of citral A and citral B in the ratio 3:2. Citral, occurring in many essential oils, constitutes 70–85 wt% of lemon grass oil [20-21].

Geraniol ($C_{10}H_{18}O$), chemically recognized as a terpenic alcohol (Z)-3,7-dimethyl-2,6-octadien-1-ol (Fig. 3c), is a commonly used monoterpene, occurring mainly in rose oil, palmarosa oil or citronella oil [23]. Additionally, small quantities of geraniol are also present in geranium, lemon and many other essential oils. Due to its strong flower (rose-like) scent, geraniol can be an important ingredient in wide range of cosmetic products [24], with particular emphasis on perfumes, and also as a pharmaceutical intermediates [26]. Geraniol appears as a clear to pale-yellow oil and it is insoluble in water, but soluble in most of organic solvents. Moreover, it has the potential to autoxidize under air exposure and form highly allergenic compounds, similar to other fragrance monoterpenes [23-24].

According to a study conducted by Hagvall and Christensson [24], *cis*/*trans*-isomeric aldehydes – geranial and neral –, formed from an unstable hydroperoxide, geraniol- 1-hydroperoxide, are the major oxidation products in the autoxidation of geraniol. Geraniol has especially significant properties in a form of geranial (citral A), useful as a starting material for other chemicals such as ionones, vitamin A, vitamin E and carotenoids [26].

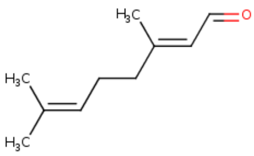
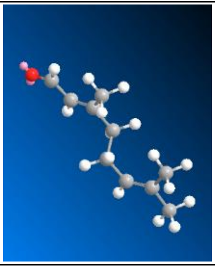
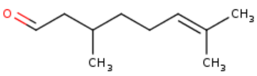
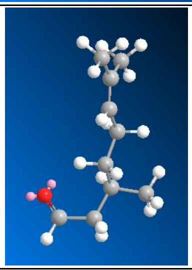
2. Methodology

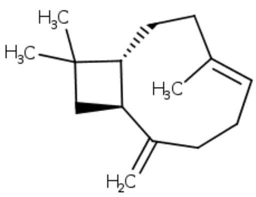
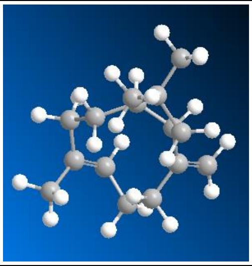
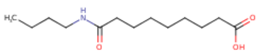
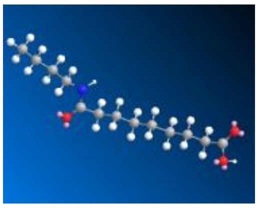
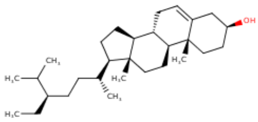
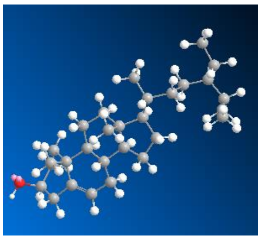
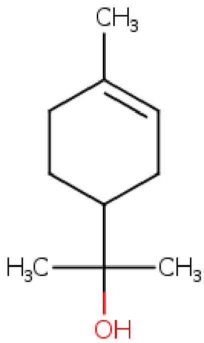
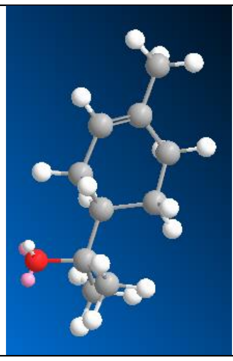
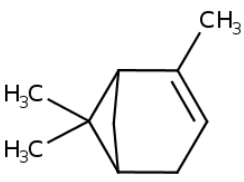
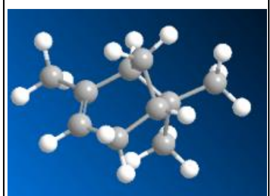
Hardware: personal laptop TOSHIBA Satellite L740 Intel(R) Core(TM) i3 CPU (2,53 GHz); RAM: 2,00 GB; Microsoft Version: Microsoft Windows 7 Ultimate with internet connection; Software: ChemDraw Pro 12.0 and Chem3D Ultra 12.0; Webserver: https://phytochem.nal.usda.gov/, https://pubchem.ncbi.nlm.nih.gov/, http://swisstargetprediction.ch/ .

3. Result and Discussion

From the studies that have been carried out with a series of software used and the webserver that has been explored, some information has been obtained regarding the number and types of compounds contained in a lemongrass plant and its structure.

There are more than 60 active compounds with several chemical elements in the form of minerals, but what is described here are only a few active compounds which are of course more general and very functional in existence and have been widely applied both from small, medium, to industrial scales. The data is presented in the following table:

Compound Name	IUPAC Name	Physical and Chemical Properties	2D Structure	3D Structure	Minimize Energy
Citral	(2E)-3,7-dimethylocta-2,6-dienal	Boiling Point: 485,14 [K] Melting Point: 205,88 [K] Critical Temp: 683,88 [K] Critical Pres: 25,25 [Bar] Critical Vol: 574,5 [cm3/mol] Gibbs Energy: 77,14 [kJ/mol] Log P: 2,18 MR: 51,01 [cm3/mol] Henry's Law: 1,81 Heat of Form: -120,45 [kJ/mol] tPSA: 17.07 CLogP: 2.95 CMR: 4.8763			8.0551 kcal/mol
Citronellal	3,7-dimethyloct-6-enal	Boiling Point: 480,66 [K] Melting Point: 209,92 [K] Critical Temp: 660,53 [K] Critical Pres: 24,05 [Bar] Critical Vol: 587,5 [cm3/mol] Gibbs Energy: 3,03 [kJ/mol] Log P: 2,35 MR: 49,7 [cm3/mol] Henry's Law: 1,56 Heat of Form: -233,16 [kJ/mol] tPSA: 17.07 CLogP: 3.264 CMR: 4.8257			7.4352 kcal/mol

Caryophyllene	(1R,4E,9S)-4,11,11-trimethyl-8-methylidenebicyclo[7.2.0]undec-4-ene	Boiling Point: 576,5 [K] Melting Point: 323,21 [K] Critical Temp: 737,59 [K] Critical Pres: 20,27 [Bar] Critical Vol: 716,5 [cm3/mol] Gibbs Energy: 196,63 [kJ/mol] Log P: 4,48 MR: 67,73 [cm3/mol] Henry's Law: -1,45 Heat of Form: -112,68 [kJ/mol] tPSA: 0 CLogP: 3.81132 CMR: 6.6238			63.4406 kcal/mol
Caprylic Acid	9-(butylamino)-9-oxononanoic acid	Boiling Point: 767,46 [K] Melting Point: 562,58 [K] Critical Temp: 888,77 [K] Critical Pres: 19,46 [Bar] Critical Vol: 815,5 [cm3/mol] Gibbs Energy: -344,41 [kJ/mol] Log P: 2,27 MR: 66,32 [cm3/mol] Henry's Law: 10,02 Heat of Form: -774,13 [kJ/mol] tPSA: 66.4 CLogP: 2.266 CMR: 6.8			0.5044 kcal/mol
Beta-Sitosterol	(3S,8S,9S,10R,13R,14S,17R)-17-[(2R,5R)-5-ethyl-6-methylheptan-2-yl]-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol	Boiling Point: 992,9 [K] Melting Point: 534,43 [K] Critical Temp: 886,4 [K] Critical Pres: 9,59 [Bar] Critical Vol: 1427,5 [cm3/mol] Gibbs Energy: 217,88 [kJ/mol] Log P: 8,14 MR: 130,21 [cm3/mol] Henry's Law: 1,92 Heat of Form: -533,79 [kJ/mol] tPSA: 20.23 CLogP: 6.52764 CMR: 13.0457			60.4658 kcal/mol
Alpha-Terpinol	2-(4-methylcyclohex-3-en-1-yl)propan-2-ol	Boiling Point: 541,04 [K] Melting Point: 285,86 [K] Critical Temp: 667,92 [K] Critical Pres: 29,5 [Bar] Critical Vol: 522,5 [cm3/mol] Gibbs Energy: -55,88 [kJ/mol] Log P: 2,1 MR: 48,57 [cm3/mol] Henry's Law: 3,19 Heat of Form: -310,08 [kJ/mol] tPSA: 20.23 CLogP: 2.629 CMR: 4.7657			10.4925 kcal/mol
Alpha-Pinene	2,6,6-trimethylbicyclo[3.1.1]hept-2-ene	Boiling Point: 445,86 [K] Melting Point: 267,26 [K] Critical Temp: 632,45 [K] Critical Pres: 28,91 [Bar] Critical Vol: 484,5 [cm3/mol] Gibbs Energy: 149,85 [kJ/mol] Log P: 2,9 MR: 45,05 [cm3/mol] Henry's Law: -0,64 Heat of Form: -69,08 [kJ/mol] tPSA: 0 CLogP: 4.702 CMR: 4.4352			38.7381 kcal/mol

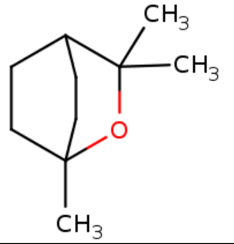
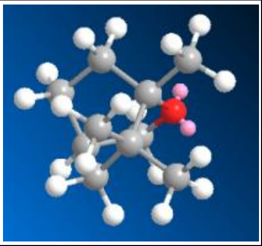
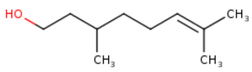
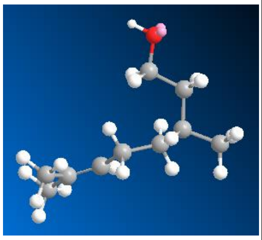
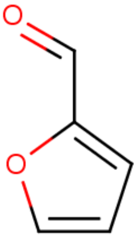
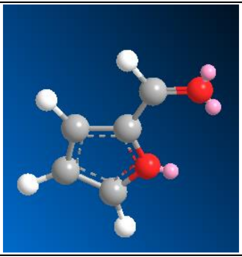
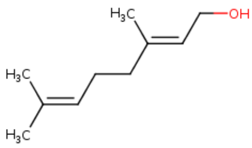
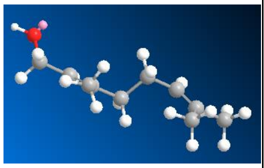
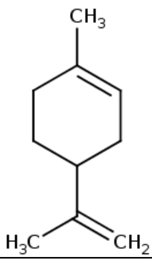
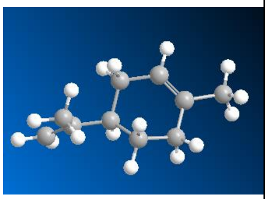
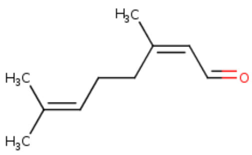
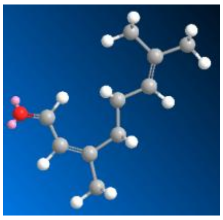
1,8-Cineol (Eucalyptol)	1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane	Boiling Point: 473,18 [K] Melting Point: 300,93 [K] Critical Temp: 657,75 [K] Critical Pres: 30,19 [Bar] Critical Vol: 509,5 [cm3/mol] Gibbs Energy: 25,81 [kJ/mol] Log P: 1,86 MR: 45,68 [cm3/mol] Henry's Law: 2,08 Heat of Form: -238,31 [kJ/mol] tPSA: 9.23 CLogP: 2.826 CMR: 4.6137			27.6531 kcal/mol
Citronellol	3,7-dimethyloct-6-en-1-ol	Boiling Point: 524,18 [K] Melting Point: 228,74 [K] Critical Temp: 664,48 [K] Critical Pres: 24,48 [Bar] Critical Vol: 589,5 [cm3/mol] Gibbs Energy: -34,27 [kJ/mol] Log P: 2,82 MR: 50,82 [cm3/mol] Henry's Law: 7,01 Heat of Form: -299,81 [kJ/mol] tPSA: 20.23 CLogP: 3.253 CMR: 4.9431			9.8142 kcal/mol
Furfural	furan-2-carbaldehyde	Boiling Point: 412,86 [K] Melting Point: 243,36 [K] Critical Temp: 656,48 [K] Critical Pres: 53,83 [Bar] Critical Vol: 267,5 [cm3/mol] Gibbs Energy: -99,87 [kJ/mol] Log P: 0,33 MR: 24,95 [cm3/mol] Henry's Law: 3,26 Heat of Form: -179,2 [kJ/mol] tPSA: 26.3 CLogP: 0.671 CMR: 2.402			16.7451 kcal/mol
Geraniol	(2E)-3,7-dimethylocta-2,6-dien-1-ol	Boiling Point: 528,66 [K] Melting Point: 224,7 [K] Critical Temp: 684,9 [K] Critical Pres: 25,71 [Bar] Critical Vol: 576,5 [cm3/mol] Gibbs Energy: 39,84 [kJ/mol] Log P: 2,49 MR: 51,64 [cm3/mol] Henry's Law: 11,16 Heat of Form: -187,1 [kJ/mol] tPSA: 20.23 CLogP: 2.969 CMR: 4.9177			6.0171 kcal/mol
Limonene	1-methyl-4-prop-1-en-2-ylcyclohexene	Boiling Point: 448,65 [K] Melting Point: 206,9 [K] Critical Temp: 645,99 [K] Critical Pres: 27,56 [Bar] Critical Vol: 496,5 [cm3/mol] Gibbs Energy: 157,39 [kJ/mol] Log P: 3,01 MR: 46,86 [cm3/mol] Henry's Law: -1,19 Heat of Form: -33,46 [kJ/mol] tPSA: 0 CLogP: 4.352 CMR: 4.5872			6.1335 kcal/mol
Neral	(2Z)-3,7-dimethylocta-2,6-dienal	Boiling Point: 485,14 [K] Melting Point: 205,88 [K] Critical Temp: 683,88 [K] Critical Pres: 25,25 [Bar] Critical Vol: 574,5 [cm3/mol] Gibbs Energy: 77,14 [kJ/mol] Log P: 2,18 MR: 51,01 [cm3/mol] Henry's Law: 10,16 Heat of Form: -120,45 [kJ/mol] tPSA: 17.07 CLogP: 2.95 CMR: 4.8763			12.7427 kcal/mol

Table. 1. Information on active compounds in lemongrass

Citral is an active compound that is abundant in a lemongrass plant which is found in the stems and leaves. With molecular activity or movement of 1000 steps of movement, the resulting minimized energy is 8.0551 kcal/mol and is volatile with a boiling point of 485.14 K, it turns out that it has the ability to produce flavors and fragrances in cosmetics. Besides, it also acts as anti-inflammatory and antimicrobial. It can be observed in the diagram below, that the biomolecule targets the target site for citral to bind to in parts of the human body.

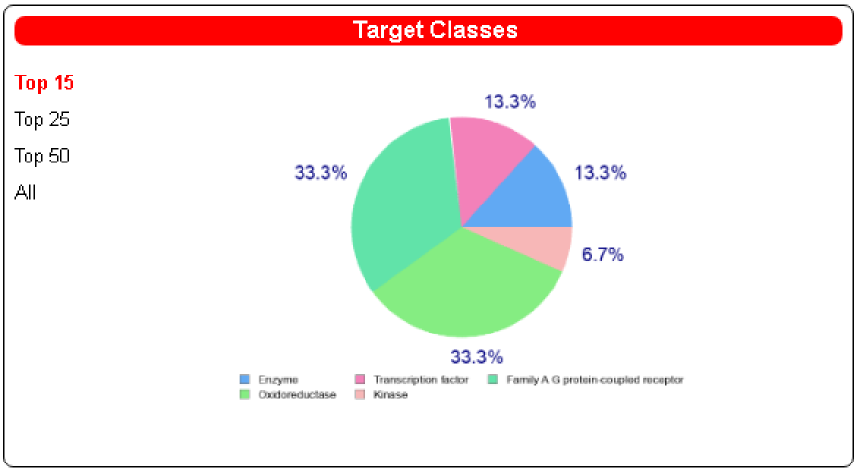


Fig. 4. The target class of citral activities

Apart from citral, there are also active compounds such as geraniol which have the same function. Geraniol is a monoterpenoid and alcohol with the main components of rose oil, palmarosa oil and lemongrass oil. Classified as colorless oil, although the sample generally looks yellowish with low solubility in water, but dissolves in common organic solvents. Therefore it can be an important ingredient in various cosmetic products [24], with particular emphasis on perfume, and also as a pharmaceutical intermediate.

So diverse are the atoms that make up each of the compounds contained in a lemongrass plant and it is proven that even so, it turns out that each of them has differences in both its properties and structure, but so far from the results of research by chemical analysts, In general, lemongrass consists of non-polar organic compounds which are volatile and have almost similar characteristics such as antipyretic, analgesic, anti-inflammatory and so on.

Data in Table. 2. Shows the amount of activity of each compound and their exact location.

Activity	Chemical	Part of Plant	Low PPM	High PPM	Std Dev
53	Citral	Plant	1080,0	25500,0	1,93
20	Citronellal	Plant	-	-	-
31	Caryophyllene	Plant	-	-	-
5	Caprylic acid	Plant	-	-	-
47	beta-Sitosterol	Plant	-	-	-
23	alpha-Terpinol	Plant	-	-	-
28	alpha-Pinene	Plant	-	-	-
67	1,8-Cineol (Eucalyptol)	Plant	-	-	-
15	Citronellol	Plant	-	-	-
6	Furfural	Plant	-	-	-

35	Geraniol	Plant	10.0	36.0	-0,44
60	Limonene	Plant	-	-	-
4	Neral	Leaf	-	-	-

Table. 2. The content of compounds in lemongrass

4. Conclusion

It can be concluded that the lemongrass plant contains more than 60 active compounds in it, some of which are medicinal for humans. The active compound that acts as a drug works by tracing the target to bind to the substrate, namely a pathogenic biomolecule or disease in the human body, so that the target is made inactive to stop its activity in spreading diseases that can damage the immune system or the human immune system. Of course, the number of active compounds must be included in the right amount so that the compound has an optimum work to cure.

Apart from that, there are also active compounds such as geraniol which function as a delicious and distinctive scent that is used by the industry in general as an ingredient for making perfumes or aromatherapy fragrances.

References

[1] E.A. Carlini, J.D.P. Contar, A.R. Silva-Filho, Pharmacology of lemongrass (*Cymbopogon citratus Stapf*) I. Effects of teas prepared from the leaves on laboratory animals, J. Ethnopharmacol. 17 (1986) 37–64.

[2] M.S.C. Ferreira, M.C. Fonteles, Aspectos etnobotânicos e farmacológicos do *Cymbopogon citratus Stapf* (capim limão), Revista Brasil. Farmácia 70 (1989) 94–97.

[3] D.H. Grayson, Monoterpenoids, Nat. Prod. Rep. 15 (1998) 435–439.

[4] P.L. Crowell, Prevention and therapy of cancer by dietary monoterpenes, J. Nutr. (1999) 129–775.

[5] J.J. Mills, R.S. Chari, I.J. Boyer, M.N. Gould, R.L. Jirtle, Induction of apoptosis in liver tumors by the monoterpene perillyl alcohol, Cancer Res. (1995) 955–979.

[6] S. Carnesecchi, Y. Schneider, J. Ceraline, B. Duranton, F. Gosse, N. Seller, F. Raul, Geraniol, a component of plant essential oils inhibit growth and polyamine synthesis in human colon cancer cells, J. Pharm. Exp. Ther. 197 (2001) 298.

[7] E.M. Elgendy, Epoxidation reactions of natural limonene piperine and piperic acid as intercalative alkylating agents for DNA, Boll. Chim. Farm. 27 (1997) 36– 532.

[8] E.M. Elgendy, Photooxygenation of natural limonene, Chim. Pharm J. (1998) 50–225.

[9] A. Méou, M.A. Garcia, P. Brun, Oxygen transfer mechanism in the Mn-salen catalysed epoxidation of olefins, J. Mol. Catal. A Chem. 23 (1999) 138–221.

[10] E.M. Elgendy, Photooxygenation of natural ã-terpinene, Boll. Chim. Farm. (2004) 143–337. [11] N.W.A. Geraghty, Photochemistry, in: I. Dunkin (Ed.), London: Royal Soc. Chem. 27 (2005) 35–116.

[12] S. Richter, B. Gatto, D. Fabris, K.I. Takao, S. Kobayashi, S.M. Palumbo, Clerocidin alkylates DNA through its epoxide function: evidence for a fine tuned mechanism of action, Nucleic Acids Res. 31 (2003) 5149.

[13] E.M. Elgendy, S.A. Khayyat, Oxidation studies on some natural monoterpenes: citral, pulegone, and camphene, Russ. J. Org. Chem. 44 (2008) 814.

[14] Carbone, C., Martins-Gomes, C., Caddeo, C., Silva, A.M., Musumeci, T., Pignatello, R., Puglisi, G., Souto, E.B., 2018. Mediterranean essential oils as precious matrix components and active ingredients of lipid nanoparticles. Int. J. Pharm. 548, 217–226.

[15] Sampaio, A.C., Aires, A., Souto, E.B., Silva, A.M., 2017. Essential oils, polyphenols and glycosides: secondary plant metabolites against microbes. Frontiers in clinical drug research-anti infectives. vol. 3, Chapter 4. Bentham Science Publishers, pp. 139–186.
[16] Pereira, I., Severino, P., Santos, A.C., Silva, A.M., Souto, E.B., 2018. Linalool bioactive properties and potential applicability in drug delivery systems. Colloids Surf., B Biointerfaces 171, 566–578.
[17] Severino, P., Andreani, T., Chaud, M.V., Benites, C.I., Pinho, S.C., Souto, E.B., 2015. Essential oils as active ingredients of lipid nanocarriers for chemotherapeutic use. Curr. Pharm. Biotechnol. 16, 365–370.
[18] Astani, A., Schnitzler, P., 2014. Antiviral activity of monoterpenes beta-pinene and limonene against Herpes simplex virus in vitro. Iran. J. Microbiol. 6, 149–155.
[19] Edris, A.E., 2007. Pharmaceutical and therapeutic potentials of essential oils and their individual volatile constituents: a review. Phytother. Res. 21, 308–323.
[20] Bhalla, Y., Gupta, V.K., Jaitak, V., 2013. Anticancer activity of essential oils: a review. J. Sci. Food Agric. 93, 3643–3653.
[21] Pereira, S.L., Marques, A.M., Sudo, R.T., Kaplan, M.A.C., Zapata-Sudo, G., 2013. Vasodilator activity of the essential oil from aerial parts of Pectis brevipedunculata and its main constituent citral in rat aorta. Molecules 18, 3072–3085.
[22] Marcus, J., Klossek, M.L., Touraud, D., Kunz, W., 2013. Nano-droplet formation in fragrance tinctures. Flavour Fragrance J. 28, 294–299.
[23] Hagvall, L., Bäcktorp, C., Svensson, S., Nyman, G., Börje, A., Karlberg, A.-T., 2007. Fragrance compound geraniol forms contact allergens on air exposure. identification and quantification of oxidation products and effect on skin sensitization. Chem. Res. Toxicol. 20, 807–814.
[24] Hagvall, L., Brared Christensson, J., 2014. Cross-reactivity between citral and geraniol - can it be attributed to oxidized geraniol? Contact Dermatitis 71, 280–288.
[25] Rudbäck, J., Islam, N., Nilsson, U., Karlberg, A.T., 2013. A sensitive method for determination of allergenic fragrance terpene hydroperoxides using liquid chromatography coupled with tandem mass spectrometry. J. Sep. Sci. 36, 1370–1378.
[25] Weng, D.C.J., Latip, J.B., Hasbullah, S.A.B., Sastrohamidjojo, H., 2015. Separation of geraniol from citronellol by selective oxidation of geraniol to geranial. Sains Malaysiana 44, 1183–1188.