IJSRM
INTERNATIONAL JOURNAL OF SCIENCE AND RESEARCH METHODOLOGY
An Official Publication of Human Journals

Human Journals
Research Article
September 2022 Vol.:22, Issue:3

Evaluation of the Antibacterial and Antifungal Activities of the Monoterpene Eucalyptol (1, 8-Cineole): An *In Silico* Study

IJSRM
INTERNATIONAL JOURNAL OF SCIENCE AND RESEARCH METHODOLOGY
An Official Publication of Human Journals

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Submitted: 24 August 2022
Accepted: 30 August 2022
Published: 30 September 2022

Keywords: 1,8-cineol; eucalyptol; terpene; *in silico*; antibacterial; antifungal.

ABSTRACT

Microorganisms are the main cause of infectious diseases, data from the World Health Organization (WHO) inform that these are responsible for about 25% of deaths worldwide. Currently, the treatment of infections occurs mostly through the use of antimicrobials, however, some disadvantages such as resistance and toxicity of some control drugs have justified the increased demand for new methods of treatment against these pathogens. Phytotherapy, a practice based on the use of medicinal plants, is a therapeutic option that presents several advantages, such as fewer adverse effects, low cost, and greater popular access. The essential oil of eucalyptus presents as its major component the bicyclic monoterpene 1,8-cineole, also known as eucalyptol, which has shown effective antiviral and anti-inflammatory activity, among others. In this context, the present study aims to evaluate through an *in silico* assay the antibacterial and antifungal activities of this biological compound. As methodology was used the free software Pass Online for analysis of the probability of molecular activity. The 1,8-cineole presented a positive result for the probability of activation (Pa), in relation to the values of the probability of inactivation (Pi) for the antibacterial, antibiotic and antifungal activities, ratifying some studies previously published in the literature, using other methodologies. It is concluded that 1,8-cineole has strong antibacterial and antifungal activities against pathogens of clinical importance, even so, further *in vitro* and *in vivo* researches are essential to demonstrate the nuances of the therapeutic activities associated to this substance.

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INTRODUCTION

Infectious diseases are caused by microorganisms and are a current public health problem in Brazil [1,2]. According to the World Health Organization (WHO), infections are responsible for about 25% of deaths worldwide, including mycoses, diseases caused by fungi that have become increasingly common, especially in immunosuppressed individuals, favouring the action of opportunistic fungi such as *Candida albicans* [3,4,5]. Moreover, there are also bacterial infections, which involve bacteria such as *Pseudomonas aeruginosa*, one of the main agents that cause pneumonia [6,7].

Indeed, the effectiveness in treating infections presents several challenges, especially the growing microbial resistance, defined as the ability of a microorganism to resist the action of drugs. This attribute can be acquired through inappropriate use of antimicrobials, resulting in difficulties in disease control and consequent increase in morbidity and mortality rates in the population. The development of resistance mechanisms, as well as the adverse effects and toxicity of some control drugs have justified the increased search for new methods of treatment against these pathogens [8,9,10,11].

Among the therapeutic alternatives of great interest today is the phytotherapy, an ancient practice, passed down through generations and widely spread in traditional medicine. Considering its relevant advantages, such as efficacy, low cost, easy access, and cultural compatibility, several studies with medicinal plants have been developed and resulted in the discovery of active therapeutic compounds, which were then implemented in modern medicine [12,13,14]. In this context, studies developed by Da Silva, De Cantuario Mendes, and De Carvalho Abreu [15] (2020) show that the botanical species *Chenopodium ambrosioides* L., popularly known as mastiff, presents therapeutic and pharmacological effects such as anti-helminthic, anti-inflammatory, and healing action, thus illustrating great importance for the population.

The pharmacological activity of a medicinal plant is subject to its chemical compounds, which can be obtained from natural matrices such as stems, roots, leaves, and fruits. Among the diverse phytochemical constituents, the terpenes stand out; they are derived from the secondary metabolism of a botanical species, and are the majority elements of essential oils, which have proven efficacy against several pathologies [16,17]. An example is the monoterpene thymol, present in thyme essential oil, which shows effective anti-inflammatory, antioxidant, antimicrobial, and antiviral actions [18].

Moreover, the monoterpene 1,8-cineole, also known as eucalyptol, is the main constituent of the essential oil of *Eucalyptus globulus*, and is widely used in the pharmaceutical and cosmetic industries as a flavouring agent, where different studies have shown promising antiviral, anti-inflammatory, anti-asthmatic, and analgesic activity of this element, besides having a low toxicological potential [19,20,21,22].

In this excerpt, in view of the salutary pharmacological potential presented by the monoterpene 1,8-cineole, the present study aims to evaluate, through an *in silico* assay, the antibacterial and antifungal activities of this biological compound.

MATERIALS AND METHODS

This study is an applied, experimental, and quantitative research. According to Turato [23] (2004) quantitative research uses data collected through the use of value measurements, the measurement performed through numbers with their respective units. Therefore, there is a need to apply this method to verify the results obtained from the objectives proposed in the study.

Test Substance

To perform the *in silico* studies, all chemical information (chemical structure of the molecule, molecular mass, polarity, CAS-number) of the monoterpene used (1,8-cineol) was obtained from the free website (http://www.chemspider.com/).

***In silico* pharmacological test**

The study of theoretical bioactive properties of 1,8-cineole was analyzed by the free online Prediction of Activity Spectrum for Substances (PASS) software. This computational tool uses software designed to assess the overall biological potential of an organic molecule *in silico* on the human organism. In this way, it provides simultaneous predictions of various types of biological activities based on the structure of the organic compounds. Thus, it is possible to have simultaneous predictions of many types of biological activities based on the chemical structure of the molecule, allowing the estimation of the activity potential of a substance classifying it in indexes: Pa (probability "to be active") and Pi (probability "to be inactive"), and can be accessed at: (http://www.pharmaexpert.ru/passonline/) [24].

RESULTS AND DISCUSSION

In the evaluation of the biological potential by the software Pass Online®, through the *in silico* study, the 1,8-cineole showed a positive result for the probability of activation (Pa), in relation to the values of the probability of inactivation (Pi) for all tested activities, thus revealing that it has the antimicrobial potential, especially for the antibacterial effect, with a greater difference between the values of Pa and Pi. Alternatively, it showed less antifungal potential against the Pneumocystis genus, where the Pa value did not show significant results compared to the Pi value, as presented in Table 1.

Table No. 1: Antibacterial and antifungal activities of 1,8-cineole

Pa	**Pi**	**Activity**
0,298	0,061	Antibacterial
0,148	0,061	Ophthalmic antibacterial
0,172	0,037	Antibiotic
0,214	0,128	Antifungal
0,051	0,042	Antifungal (*Pneumocystis*)

Source: Authors (2022).

Secondary metabolites, such as essential oils, are a mixture of complex substances elaborated by plants that function as a plant defense against external deleterious agents, besides presenting a high therapeutic index [25]. An example is the eucalyptus essential oil, whose major ingredient (30% to 90% content) is the terpene 1,8 cineol, also called eucalyptol; it is obtained from the plant leaves and is chemically characterized as a bicyclic monoterpene, i.e., a molecule with two closed cycles [26,27].

The literature reports that eucalyptol (1,8 cineol) is currently used in the treatment of inflammatory pathologies of the respiratory system and, as a rule, has strong antibacterial activity, this through mechanisms such as stimulation of oxidative stress and rupture of the bacterial cell membrane, causing irreversible damage [28,29,30]. It is also worth noting that this sensitivity of bacteria to monoterpenes is established by their chemical composition, the charge of external structures, and the permeability of the microbe's membrane [31].

Moo and co-workers (2021) [31] postulated that the monoterpene 1,8 cineole presents antibacterial activity against strains of *Klebsiella pneumoniae* that produce carbapenemases; this process occurs through oxidative stress induced by 1,8 cineole, causing membrane rupture through lipid peroxidation and leakage of intracellular material, leading to bacterial lysis. *K. pneumoniae* is a multidrug-resistant bacterium that causes nosocomial infections in the blood, urinary tract, and respiratory tract, responsible for mortality rates as high as 49% of the cases [32,33].

According to Yoro *et al.* (2020) [34], the eucalyptol isolated from the essential oil of *Eucalyptus alba* showed strong antibacterial activity against the species *Staphylococcus aureus* ATCC 29213; the value of the Minimum Inhibitory Concentration (MIC) for this strain was 1.25 mg/mL. Corroborating Yoro's results, Li *et al.* (2014) [35] evidenced structural changes in the shape and size of gram-positive and gram-negative bacteria in the presence of 1,8 cineol. Treatment with eucalyptol resulted in apoptosis of *Staphylococcus aureus* and necrosis of *Escherichia coli*, injuring the cell wall and plasma membrane of the latter. Therefore, the antimicrobial action of 1,8 cineole is attributed to its hydrophobicity, since there is a greater susceptibility of bacteria with an external lipopolysaccharide membrane to this component.

Besides the antibacterial activity associated with eucalyptol, its antifungal property is also worth mentioning. Fungi are responsible for systemic infections correlated to a high risk of life,

especially in immunocompromised patients; data suggest that mortality exceeds 1.6 million people around the globe [36]. Specifically *Candida albicans*, the main microorganism associated with fungal infections in humans, is shown to be resistant to commonly used antifungal drugs [37,38].

According to Karpiński (2020) [39], the monoterpene 1,8 cineole demonstrates antifungal activity, especially anti-Candida. Ratifying Karpiński's findings, Müller-Sepúlveda *et al.*, (2020) [40] point out that the plant species *Lavandula dentata*, belonging to the Laminaceae family, contains mostly in its essential oil 60.85% of the monoterpene 1,8 cineol that, when tested against *Candida albicans* strains, presented an MIC of 156 µg/mL, a promising result that suggests strong antifungal action. All this explains the vast commercial use of essential oils in hygiene products, as an example we can cite the toothpaste "Paradontax" that presents in its composition essential oils from the Laminaceae family, showing strong antifungal activity against *Candida albicans* [41].

CONCLUSION

Therefore, it can be concluded from this *in silico* study that the monoterpene 1,8-cineole (eucalyptol) has strong antibacterial and antifungal activities against pathogens of clinical importance. Still, further *in vitro* and *in vivo* research is essential to demonstrate the nuances of the therapeutic activities associated with this substance, as well as its mode of action, associated toxicity, safety and optimal routes of administration. Thus, enabling its use in the technical and scientific development of safe, easily accessible, and highly therapeutic treatments.

ACKNOWLEDGMENTS

I would like to thank all the authors who decisively contributed to the elaboration of this work, especially Prof. Dr. Abrahão Alves de Oliveira Filho for his orientations.

REFERENCES

1. Araujo JC, De Oliveira Lima E, De Ceballos BS, Freire KR, De Souza EL, Santos Filho L. Antimicrobial action of essential oils on microorganisms potentially causing opportunistic infections. Rev Patol Trop [Internet]. January 22, 2008 [cited May 21, 2022];33(1):55-64. Available from: https://www.revistas.ufg.br/iptsp/article/view/3189.

2. Oliveira EP, De Sousa Andrade F, De Lima-Neto RG. Occurrence of superficial mycoses in a health center. Rev bras anal clin. 2017;49(3):289-93. Available at: http://www.rbac.org.br/wp-content/uploads/2017/11/RBAC-vpl-49-3-2017-ref.-64-corr2.pdf.
3. Matos MP, De Souza AP, Silva AB, Seabra PR, Oliveira LN. Retrospective analysis of mycosis mortality: Review Article. RRS-FESGO [Internet]. April 9, 2020 [cited May 21, 2022];3(01):100-5. Available from: https://estacio.periodicoscientificos.com.br/index.php/rrsfesgo/article/view/205.
4. Fajardo AD, Da Silva RR, Costa AP, Rossetto AL, Cruz RC. Epidemiological study of superficial fungal infections in Itajaí, Santa Catarina. Rev bras anal clin. 2017;49(3):396-400. Available at: http://www.rbac.org.br/wp-content/uploads/2018/01/RBAC-vol-49-4-2017-ref-584.pdf.
5. Queiroz-Fernandes G, Dos Santos Magalhães JC. Resistance profile of opportunistic mycosis agents in Brazil. IAJMH [Internet]. 2020 Dec.6 [cited 2022May21];4. Available from: https://www.iajmh.com/iajmh/article/view/149.
6. Alonso B, Fernández-Barat L, Di Domenico EG, Marín M, Cercenado E, Merino I, *et al.* Characterization of the virulence of *Pseudomonas aeruginosa* strains causing ventilator-associated pneumonia. BMC Infect Dis. 2020;20(1):1-8. Disponível em: https://link.springer.com/article/10.1186/s12879-020-05534-1.
7. Usui M, Onizuka S, Sato T, Kokabu S, Ariyoshi W, Nakashima K. Mechanism of alveolar bone destruction in periodontitis - Periodontal bacteria and inflammation. Jpn Dent Sci Ver [Internet]. 2021 [cited 2022 May 21];57:201-08. Available from: https://www.sciencedirect.com/science/article/pii/S1882761621000272. doi: 10.1016/j.jdsr.2021.09.005.
8. Berto C, Wirth F, Barth N, Hermes DM. Bases of antifungal resistance: a commented review. Uningá Journal [Internet]. 2018 [cited 2022 May 21];55(3):52-71. Available from: http://revista.uninga.br/index.php/uninga/article/view/773.
9. Teixeira AR, Figueiredo AF, França RF. Bacterial resistance related to indiscriminate use of antibiotics. Health Focus. 2019;11: 853-75. Available at: https://portal.unisepe.com.br/unifia/wp-content/uploads/sites/10001/2019/09/077_RESIST%C3%8ANCIA-BACTERIANA-RELACIONADA-AO-USO-INDISCRIMINADO-DE-ANTIBI%C3%93TICOS.pdf.
10. Sting SK, Butzge J, Mezzomo L, Calil LN, Apel M, Mezzari A, *et al.* Antifungal activity of essential oils against Candida spp. Brazilian Journal of Health Review. 2020;3(1):100-113. Available at: https://brazilianjournals.com/index.php/BJHR/article/view/5915.
11. Rojas GC, Ulate LA. Resistencia antimicrobiana: microorganismos más resistentes y antibioticos con menor actividad. Rev Med Cos Cen. 2016;73(621):757-763. Available at: https://www.medigraphic.com/cgi-bin/new/resumenI.cgi?IDARTICULO=69870.
12. Esteves CO, Rodrigues RM, Martins AL, De Almeida Vieira R, Barbosa JL, Vilela JB. Medicamentos fitoterápicos: prevalência, vantagens e desvantagens de uso na prática clínica e perfil e avaliação dos usuários. Rev Med (São Paulo) [Internet]. December 10, 2020 [cited May 21, 2022];99(5):463-72. Available from: https://www.revistas.usp.br/revistadc/article/view/160705.
13. Macedo WL. Use of herbal medicine in the treatment of chronic noncommunicable diseases: integrative review. ReBIS [Internet]. 2019[cited 2022 May 21];1(3):36-43. Available from: https://revistarebis.rebis.com.br/index.php/rebis/article/view/42/39.
14. Rigodanzo C. Diabete mellitus type 2: medicinal plants and phytotherapeutics as therapeutic alternatives for disease control [Course Conclusion Paper]. Ijuí: Universidade Regional do Noroeste do Estado do Rio Grande do Sul - UNIJUÍ; 2019. 29 p. Available from: https://bibliodigital.unijui.edu.br:8443/xmlui/handle/123456789/5536.
15. Da Silva IA, Mendes DP, Abreu CR. Therapeutic and pharmacological aspects in the use of *Chenopodium ambrosioides* L. Revista JRG [Internet]. 2020 [cited May 21, 2022];3(7):427-36. Available from: http://www.revistajrg.com/index.php/jrg/article/view/73.
16. Fernandes VD, Ribeiro AB, De Holanda FR, De Oliveira VF, Dos Anjos RM, Alves MA, *et al. In silico* evaluation of monoterpene ascaridol's antiprotozoal activity. Res Soc Deve [Internet]. 2020 [cited 2022May21];9(9):e202996891. Available from: https://rsdjournal.org/index.php/rsd/article/view/6891.

17. Ribeiro AB, Fernandes VD, De Souza Alencar JA, Medeiros JP, De Souza LD, De Oliveira OL, *et al*. *In silico* evaluation of the anthelmintic activity of Ascaridol monoterpene. Res Soc Dev [Internet]. 2020 [cited 2022May21];9(7):e757974944. Available from: https://rsdjournal.org/index.php/rsd/article/view/4944.
18. Santana MT, Gomes LL, Batista FB, Dos Santos TA, Matias LB, De Oliveira HM, *et al*. Antiviral activity of the monoterpene thymol: an *in silico* study. J Med Health Promot [Internet]. 2018 [cited May 21, 2022];3(2):994-99. Available from: https://jmhp.fiponline.edu.br/pdf/cliente=13-e705c9196e6aae5248cb2d44447ef77f.pdf.
19. Caceres AI, Liu B, Jabba SV, Achanta S, Morris JB, Jordt SE. Transient receptor potential cation channel subfamily M member 8 channels mediate the anti-inflammatory effects of eucalyptol. Br J Pharmacol. 2017;174(9):867-79. Available at: https://bpspubs.onlinelibrary.wiley.com/doi/full/10.1111/bph.13760.
20. Gomes LL, De Araújo Neto AP, De Medeiros FL, Santana MT, Dos Santos TA, De Oliveira HM, *et al.* Evaluation *in silico* of eucalyptol monoterpene toxicity. RSD [Internet]. 2020 Apr. 1 [cited 2022 May 21];9(5):e158953092. Available from: https://rsdjournal.org/index.php/rsd/article/view/3092.
21. Marinho TO, De Lucena HL, De Sousa AP, Da Silva FA, De Medeiros TK, De Souza OF, *et al*. Antiviral activity of 1,8-cineole monoterpene: *in silico* study. Res Soc Dev [Internet]. 2022Mar.19 [cited 2022May21]; 11(4):e31011427363. Available from: https://rsdjournal.org/index.php/rsd/article/view/27363.
22. Pino JA, Moncayo-Molina L, Spengler I, Pérez JC. Chemical composition and antibacterial activity of the leaf essential oil of *Eucalyptus globulus* Labill. from two highs of the canton Cañar, Ecuador. Rev CENIC Cienc Quim [Internet]. 2021[cited May 21, 2022];52(1):26-33. Available from: https://www.redalyc.org/articulo.oa?id=181669387001.
23. Turato, ER. The question of complementarity and differences between quantitative and qualitative research methods: a necessary epistemological discussion. In: Grubits S, Noriega JA, organizators. Método qualitativo: epistemologia,complementariedade e campos de aplicação. São Paulo: Vetor; 2004. p. 17-51.
24. Srinivas N, Sandeep KS, Anusha Y, Devendra BN. *In vitro* cytotoxic evaluation and detoxification of monocrotaline (Mct) alkaloid: an *in silico* approach. Int Inv J Biochem Bioinform.2014;2(3): 20-29. Available at: https://www.researchgate.net/profile/Dr-Sandeep-Kusuma/publication/262182857_*In_Vitro*_Cytotoxic_Evaluation_and_Detoxification_of_Monocrotaline_Mct_Alkaloid_An_*In_Silico*_Approach/links/00463536e089219384000000/*In-Vitro*-Cytotoxic-Evaluation-and-Detoxification-of-Monocrotaline-Mct-Alkaloid-An-In-Silico-Approach.pdf.
25. Moo CL, Yang SK, Osman MA, Yuswan MH, Loh JY, Lim WM, Lim SHE, Lai KS. Antibacterial activity and mode of action of ÿ-caryophyllene on *Bacillus cereus*. Pol. J. Microbiol [Internet]. 2020 [Cited March 18, 2022];69(1):1-6. Available from: https://doi.org/10.33073/pjm-2020-007 DOI 10.33073/pjm-2020-007.
26. Brown, SK, Garver, WS, Orlando, RA. 1,8-cineole: An underestimated anti-inflammatory therapeutic. J. Biomol. Res. Ter [Internet]. 2017 [Cited March 19, 2022];6(1):2-6. Available from: https://doi.org/10.4172/2167-7956.1000154 DOI 10.4172/2167-7956.1000154.
27. Dhakad AK, Pandey VV, Beg S, Rawat JM, Singh A. Biological, medicinal and toxicological significance of Eucalyptus leaf essential oil: a review. J Sci Food Agric [Internet]. 2018 [Cited March 20, 2022];98(3):833-848. Available from: https://doi.org/10.1002/jsfa.8600 DOI 10.1002/jsfa.8600.
28. Sudhoff H, Klenke C, Greiner JF, Müller J, Brotzmann V, Ebmeyer J, Kaltschmidt B, Kaltschmidt C. 1,8-Cineol Reduces Mucus-Production in a Novel Human *Ex Vivo* Model of Late Rhinosinusitis. PLoS One [Internet]. 2015 [Cited March 23, 2022]24;10(7):e0133040. Available from: https://doi.org/10.1371/journal.pone.0133040 DOI 10.1371/journal.pone.0133040.
29. Perveen, S. Introductory chapter: Terpenes and terpenoids. In: Perveen, S., Al-taweel, A., organizers. In Terpenes and terpenoids. United Kingdom: Intech Open; 2012. p. 1-12.
30. Yang SK, Yusoff K, Thomas W, Akseer R, Alhosani MS, Abushelaibi A, Lim SHE, Lai KS. Lavender essential oil induces oxidative stress that modifies bacterial membrane permeability of carbapenase-producing *Klebsiella pneumoniae*. Sci. Rep [Internet]. 2020 [Cited March 25, 2022]10(1):1-14. Available from: https://doi.org/10.1038/s41598-019-55601-0 DOI 10.1038/s41598-019-55601-0.

31. MOO, Chew-Li *et al.* Atividade antimicrobiana e modo de acção do 1,8-cineol contra *Klebsiella pneumoniae* produtora de carbapenemase. Relat. Cient [Internet]. 2021 [Citado em 27 de março de 2022]11(1):1-13. Disponível a partir de: https://doi.org/10.1038/s41598-021-00249-y DOI 10.1038/s41598-021-00249-y.
32. Yang SK, Yusoff K, Ajat M, Thomas W, Abushelaibi A, Akseer R, Lim SHE, Lai KS. Perturbação da membrana de *Klebsiella pneumoniae* produtora de KPC por indução de stress oxidativo por casca de canela (*Cinnamomum verum* J. Presl) óleo essencial. PLoS ONE [Internet]. 2019 [Citado em 30 de março de 2022]14(4):e0214326. Disponível a partir de: https://doi.org/10.1371/journal.pone.0214326 DOI 10.1371/journal.pone.0214326.
33. Vading M, Nauclér P, Kalin M, Giske CG. A infecção invasiva causada por *Klebsiella pneumoniae* é uma doença que afecta doentes com elevada comorbidade e associada a uma elevada mortalidade a longo prazo. PLoS One [Internet]. 2018 [Citado em 01 de abril de 2022]13(4):e0195258. Disponível a partir de: https://doi.org/10.1371/journal.pone.0195258 DOI: 10.1371/journal.pone.0195258.
34. Yoro T, Alioune D, Abdoulaye D, Jean C, Saad Bouh CB, Alassane W, Julien P. Óleo essencial de Eucalyptus albaL. Cultivo na Zona Salina de Fatick (Senegal) como Fonte de 1,8 Cineole e da sua Actividade Antibacteriana. J. Deliv. de Drogas. Ter [Internet]. 2022 [Citado 02 de abril de 2022]10(1-s):140-143. Disponível a partir de: https://doi.org/10.22270/jddt.v10i1-s.3918 DOI 10.22270/jddt.v10i1-s.3918
35. Li, L.; Li, ZW; Yin, ZQ; Wei, Q.; Jia, RY; Zhou, LJ; Xu, J.; Canção, X.; Zhou, Y.; Du, YH; *et al.* Atividade antibacteriana de óleos essenciais foliares e seus constituintes de *Cinnamomum longpaniculatum*. Int. J. Clin. Exp. Med. 2014, 7, 1721-1727.
36. Bongomin F, Gago S, Oladele RO, Denning DW. Prevalência Global e Multi-Nacional de Doenças Fúngicas - Estimativa de Precisão. J Fungos (Basileia) [Internet]. 2017 [Citado em 03 de abril de 2022]3(4):57. Disponível a partir de: https://doi.org/10.3390/jof3040057 DOI: 10.3390/jof3040057.
37. Liu S, Hou Y, Chen X, Gao Y, Li H, Sun S. Combinação de fluconazol com agentes não antifúngicos: uma abordagem promissora para lidar com infecções resistentes de Candida albicans e uma visão sobre a descoberta de novos agentes antifúngicos. Int J Agentes Antimicrobianos [Internet]. 2014 [Citado em 05 de abril de 2022]43(5):395-402. Disponível a partir de https://doi.org/10.1016/j.ijantimicag.2013.12.009 DOI: 10.1016/j.ijantimicag.2013.12.009.
38. Marak MB, Dhanashree B. Antifungal Susceptibility and Biofilm Production of Candida spp. Isolated from Clinical Samples. Int J Microbiol [Internet]. 2018 [Citado em 18 de abril de 2022]2018(7495218):2-5. Disponível a partir de: https://doi.org/10.1155/2018/7495218 DOI: 10.1155/2018/7495218.
39. Karpiński TM. Óleos Essenciais de Plantas da Família Lamiaceae como Antifúngicos. Biomol [Internet]. 2020 [Citado em 20 de abril de 2022]10(1):103. Disponível a partir de: https://doi.org/10.3390/biom10010103 DOI: 10.3390/biom10010103.
40. Müller-Sepúlveda A, Chevecich CC, Jara JA, Belmar C, Sandoval P, Meyer RS, Quijada R, Moura S, López-Muñoz R, Díaz-Dosque M, Molina-Berríos A. Caracterização Química do Óleo Essencial de Lavandula dentata Cultivado no Chile e o seu Efeito Antibiofilme contra Candida albicans. Planta Med [Internet]. 2020 [Citado em 01 de maio de 2022]86(16):1225-1234. Disponível a partir de https://doi.org/10.1055/a-1201-3375 DOI: 10.1055/a-1201-3375.
41. Adwan G, Salameh Y, Adwan K, Barakat A. Avaliação da actividade antifúngica das pastas de dentes à base de plantas e convencionais contra isolados clínicos de Candida albicans. Asian Pac J Trop Biomed [Internet]. 2012 [Citado em 10 de maio de 2022]2(5):375-9. Disponível a partir de: https://doi.org/10.1016/S2221-1691(12)60059-8 doi: 10.1016/S2221-1691(12)60059-8.