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# BIOLOGICAL ACTIVITIES OF COMPOSITE 1,8-CINEOL ASSOCIATED WITH NANOSTRUTURED SYSTEMS: A BRIEF REVIEW[1]

## *ATIVIDADES BIOLÓGICAS DO COMPOSTO 1,8-CINEOL ASSOCIADO A SISTEMAS NANOESTRUTURADOS: UMA BREVE REVISÃO*

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**ABSTRACT**

At present, there is a great interest of researchers to discover differentiated properties in compounds that perform some pharmacological activity, since the abusive use of medicines can lead to resistance in the eradication of the pathologies, dependency processes and often to a process of self-dosage intoxication. Based on the importance of minimizing this situation, many compounds of natural origin have been studied in the attempt of less toxic and less expensive therapies, because they are composed in nature in abundance. Obtained from natural compounds, the essential oils, has gained considerable space in the study of potential pharmacological applicabilities, and to these potential activities are attributed that the majority is due to the presence of the compound 1,8-cineol, a monoterpene, present in quantity in essential oils. However, the essential oils are characterized by some physical-chemical instability. Thus, in an attempt to minimize or eliminate these instabilities, several works have been carried out by linking these natural compounds to nanosystems, which have the potential to increase the stability of those compounds. In this way, due to the absence of conclusive studies, it is necessary to review systematically the works of the literature that elucidate similar topics. A review study was carried out using the Scopus database looking of all articles published until July 28, 2017, totaling 29 years of research, which mentioned the compound 1,8-cineol, associating the use of nanotechnology and with a possible biological activity. This study aims to encourage research focusing on the botanical approach interconnected with technological sciences as a potential source of bioactive substances with differentiated actions.

**Keywords:** natural compounds, nanoscience, monoterpene.

***RESUMO***

*Atualmente há um grande interesse de pesquisadores por descobrir propriedades diferenciadas em compostos que desempenhem alguma atividade farmacológica, visto que o uso abusivo de medicamentos pode levar à resistência na erradicação das patologias, processos de dependência e muitas vezes a um processo de intoxicação por uma autodosagem. Com base na importância de minimizar esta situação muitos compostos de origem natural vêm sendo estudados na tentativa de terapias menos tóxicas e de menor custo, por serem compostos presentes na natureza em abundância. Obtidos a partir de compostos naturais, os óleos essenciais,*

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*tem ganhado grande espaço no estudo de potenciais aplicabilidades farmacológicas, e essas potenciais atividades são atribuídas em sua maioria a presença do composto 1,8-cineol, um monoterpeno, presente em grande quantidade nos óleos essenciais. No entanto, os óleos essenciais têm por característica apresentarem algumas instabilidades físico-químicas. Sendo assim, na tentativa de minimizar ou eliminar essas instabilidades, diversos trabalhos vêm sendo realizados vinculando esses compostos naturais a nanossistemas, os quais tem por potencialidade aumentar a estabilidade de compostos. Evidenciando a ausência de estudos de revisão explorando esta temática, faz-se necessário estudos que elucidem essas propriedades e aplicações. Foi realizado um estudo de revisão utilizando a base de dados Scopus, de todos os artigos publicados até 28 de julho de 2017, totalizando 29 anos de pesquisas, que fizeram menção ao composto 1,8-cineol, associando ao uso da nanotecnologia para uma possível atividade biológica. Este estudo visa incentivar pesquisas com enfoque na abordagem botânica interligada com as ciências tecnológicas como fonte potencial de substâncias bioativas com ações diferenciadas.*

***Palavras-chave:*** *compostos naturais, nanociências, monoterpeno.*

## INTRODUCTION

Throughout history, the human has always sought different applicabilities for plants, among which the medicinal use has always been highlighted (ZORZI et al., 2015). Brazil, whose territory presents five different biomes, is responsible for a huge and rich diversity of species (SOUSA et al., 2008). Natural sources are too accessible and represent the possibility of finding compounds with therapeutic potential (COSTA-LOTUFO et al., 2010).

Essential oils which, according to Vitti and Brito (2003), are defined by the International Standard Organization (ISO), as products of various plant regions; and can also be defined as complex mixtures of volatile, lipophilic and liquid substances or aromatic molecules produced from plants (HAN et al., 2017). The essential oils present varying chemical composition between species and parts of the same plant (MIRANDA et al., 2016).

Among the constituents present in the essential oils is the monoterpene 1,8-cineol (BIZZO; HOVELL; REZENDE, 2009). Currently known as eucalyptol, 1,8-cineol is a bicyclic monoterpene that is found in high quantities mainly in eucalyptus essential oil from more than 600 species of eucalyptus, can also be obtained in smaller amounts of plants such as thyme, rosemary, sage and fruit extracts (AZERAD, 2014).

In the perspective of improving the potentialities of these compounds, the application of nanotechnology can add several benefits, such as increased apparent solubility, bioavailability, biocompatibility, protection against the physical and chemical degradation of the active substances, consequently inducing an increase in pharmacological action, as well as protection against toxicity (SARAF, 2010). These properties make possible the development of nanosystems associated to compounds of natural origin with the purpose of obtaining differentiated biological actions.

So, this study aims to make a systematic review of all articles published until July 2017, according to the evaluation criteria, on the compound of 1,8-cineol associated with different types of nanoparticles and how the biological activities were evidenced in these studies. We aim with this study to show potentialities of one of the fundamental compounds of essential oils in association with nanoscience, in order to instigate new research that reveals new applicability.

## MATERIAL AND METHODS

An updated review of the scientific literature indexed in the *Scopus* database[6], which currently consists of 21,500 journals of the different areas of knowledge, was carried out from all articles published until July 28, 2017, following the evaluation criteria. The descriptors used for the bibliographic survey were "cineole and nano*" and later "biological activity", properly associated. Two restrictions were made during the research, in which we wanted only articles and that they were in the English language. A concise analysis of the articles was carried out, addressing their relevant aspects to the preparation of the present review study.

### EVALUATION OF THE ARTICLES

A search was made in the *Scopus* database, to which through the descriptor "*cineole and nano**" 36 results were found. The articles are from the years 1988 to 2017 of various journals. After that, the second descriptor "*biological activity*" was added and the result from the search decreased to 19 published articles until the year 2017.

### EXCLUSION CRITERIA

The criteria for selecting articles for this study were: (i) Make use of any nanostructured system containing compound 1-8 cineol; (ii) Present some biological activity related to the compound.

Articles that did not fit these criteria were excluded from this study. The analysis was performed based on the abstract of these works and in case of doubt; the methodology of the study was consulted.

## RESULTS AND DISCUSSION

### ANALYSIS OF THE DESCRIPTORS

Table 1 presents the relation of all articles and the year of their publications that were found based on the descriptor "*cineole and nano**":

[6] <www.scopus.com>.

**Table 1 -** List of journals that published about 1,8-cineol, associating the use of nanotechnology with a possible biological activity, from 1988 to 2017 based on data provided by *Scopus*.

| Year of publication | Journal | Reference |
|---|---|---|
| 2017 | Journal of Essential Oil Bearing Plants | Moghimipour et al. (2017) |
| | Microbial Pathogenesis | Souza et al. (2017) |
| | PeerJ | Lucia et al. (2017) |
| | Ecotoxicology and Environmental Safety | Xu et al. (2017) |
| 2016 | Journal of Separation Science | Masoum et al. (2016) |
| | European Journal of Pharmaceutical Sciences | AbdelSamie et al. (2016) |
| | Skin Pharmacology and Physiology | Abd et al. (2016b) |
| | Journal of Pharmaceutical Sciences | Abd et al. (2016a) |
| 2015 | Journal of Experimental Nanoscience | Ge and Ge (2015) |
| | Nanoescale Research Letters | Singh and Srivastava (2015) |
| | Journal of Nanomaterials | Moghimi et al. (2015) |
| | Pharmaceutical Sciences | Khatibi et al. (2015) |
| | Biointerphases | Abrigo et al. (2015) |
| | Natural Product Research | Piryaei et al. (2015) |
| | Wilfenia | Abo-El-Sooud et al. (2015) |
| 2014 | Plos One | Camargos et al.(2014) |
| | Powder Technology | Strydom et al. (2014) |
| | Journal of Microencapsulation | Ephrem et al. (2014) |
| | International Biodeterioration and Biodegradation | Pant et al. (2014) |
| 2013 | Brazilian Journal of Pharmacognose | Fernandes et al. (2013) |
| 2012 | International Journal of Pharmaceutics | Tan et al. (2012) |
| 2011 | International Journal of Food Microbiology | De Oliveira et al. (2011) |
| | Acta Agriculturae Slovenica | Hassanpouraghdam et al. (2011) |
| 2010 | International Journal of Pharmaceutics | Sansukcharearnpon et al. (2010) |
| | Digest Journal of Nanomaterials and Biostructures | Safaei-Ghomi et al. (2010) |
| | Digest Journal of Nanomaterials and Biostructures | Bayazit (2010) |
| | Digest Journal of Nanomaterials and Biostructures | Safaei-Ghomi and Batooli (2010) |
| | Journal of Biomedical Nanotechnology | Chen et al. (2010) |
| 2009 | Colloids and Surfaces B: Biointerfaces | Dragicevic-Curic et al. (2009) |
| | International Journal of Pharmaceutics | Nyambura et al. (2009) |
| | Digest Journal of Nanomaterials and Biostructures | Bamoniri et al. (2009) |
| 2003 | Pharmacological Research | Nair and Panchagnula (2003) |
| 2001 | International Journal Pharmaceutics | Acharya et al. (2001) |
| 1988 | The Journal of Membrane Biology | Frings and Lindemann (1988) |

* Source: Prepared by the authors from the results obtained in the *Scopus* database.

Later, when the second descriptor "*biological activity*" was added the number of works reduce considerably, as shown in table 2, where is observed the number of publications on this subject in the last 29 years, from 1988 to 2017.

**Table 2 -** List of journals that published about on 1,8-cineol, associating the use of nanotechnology with a possible biological activity, from 1988 to 2017 based on data provided by Scopus.

| Year of publication | Journal | Reference |
|---|---|---|
| 2017 | Microbial Pathogenesis | Souza et al. (2017) |
| | PeerJ | Lucia et al. (2017) |
| | Ecotoxicology and Environmental Safety | Xu et al. (2017) |
| 2016 | European Journal of Pharmaceutical Sciences | AbdelSamie et al. (2016) |
| | Journal of Pharmaceutical Sciences | Abd et al. (2016a) |
| 2015 | Journal of Experimental Nanoscience | Ge and Ge (2015) |
| | Journal of Nanomaterials | Moghimi et al. (2015) |
| | Biointerphases | Abrigo et al. (2015) |
| | Wilfenia | Abo-El-Sooud et al. (2015) |
| 2014 | Plos One | Camargos et al.(2014) |
| | Journal of Microencapsulation | Ephrem et al. (2014) |
| | International Biodeterioration and Biodegradation | Pant et al. (2014) |
| 2013 | Brazilian Journal of Pharmacognose | Fernandes et al. (2013) |
| 2012 | International Journal of Pharmaceutics | Tan et al. (2012) |
| 2011 | International Journal of Food Microbiology | De Oliveira et al. (2011) |
| 2010 | Digest Journal of Nanomaterials and Biostructures | Safaei-Ghomi et al. (2010) |
| 2009 | Colloids and Surfaces B: Biointerfaces | Dragicevic-Curic et al. (2009) |
| 2001 | International Journal Pharmaceutics | Acharya et al. (2001) |
| 1988 | The Journal of Membrane Biology | Frings and Lindemann (1988) |

* Source: Prepared by the authors from the results obtained in the *Scopus* database.

## ANALYSIS OF ARTICLES

After analyzing the articles according to the exclusion criteria, eleven articles remained. The studies mentioned in this study are: Dragicevic-Curic et al. (2009), Tan et al. (2012), Pant et al. (2014), Camargos et al. (2014), Abrigo et al. (2015), Ge and Ge (2015), Moghimi et al. (2015), AbdelSamie et al. (2016), Abd et al. (2016a), Lucia et al. (2017), and Souza et al. (2017). All of these publications will be commented in this work.

By analyzing the selected articles, table 3 shows a summary of the studies containing: (i) the reference, (ii) the nanosystem used, and (iii) the biological activity proposed in the respective study.

**Table 3 -** Table-summary containing the data belonging to the selected articles, emphasizing the group that carried out the study, the nanosystem used and the biological activity, of journals that published about 1,8-cineol, associating the use of nanotechnology with a possible biological activity, from 1988 to 2017 based on data provided by *Scopus*.

| Reference | Nanosystem | Activity |
|---|---|---|
| Dragicevic-Curic et al. (2009) | Liposomes | Increase skin penetration of photosensitizer |
| Tan et al. (2012) | Nanoparticles | Increase the stability of an immunomodulator for systemic action |
| Pant et al. (2014) | Nanoemulsions | Insecticidal action |
| Camargos et al. (2014) | Lipids Nanoparticles | Antiparasitic Activity |
| Abrigo et al. (2015) | Nanofibers | Antibacterial control |
| Ge and Ge (2015) | Liposomes | Antimicrobian activity |
| Moghimi et al. (2015) | Liposomes | Cell membrane activities |
| Abdel Samie et al. (2016) | Nanovesicular gel | Antifungal activity In skin infections |
| Abd et al. (2016a) | Nanoemulsions | Enhance skin penetration |
| Lucia et al. (2017) | Polymer micelles | Pest control |
| Souza et al. (2017) | Lipids Nanoparticles | Antifungal activity |

The first study we will present in this article is by Dragicevic-Curic et al. (2009), in which liposomes, referred in the article as "invasomes", were tested in order to increase significantly the penetration into the skin of the hydrophobic photosensitizer termed temoporfin (mTHPC), widely known for its use in the treatment of carcinomas. Various liposomes with different compositions were produced, among them, a liposome containing 1.5 mg/ml mTHPC, 3.3% ethanol and 1% terpene (cineol) which after the characterization had a particle size <150 nm and a high homogeneity (polydispersity index <0.3). As results, cineol (1%) containing "invasomes" increased the permeation of mTHPC, providing larger portions of the photosensitizer in the layers of the stratum corneum and deeper skin. This indicates that the incorporation of a single terpene into "invasomes" could also provide efficient mTHPC nanocarriers. In addition, the use of this structure increased the deposition of mTHPC in the stratum corneum in comparison to other liposomes that were not efficient in the release of mTHPC to deeper layers of the skin.

In the work developed by Tan et al. (2012), the aim of the study was to evaluate the stability and aerosolization of pressurized metered dose inhalers containing nanoparticles composed of an immunomodulator known as thymopentin associated with the cineol compound and *n*-heptane, as stabilizing agents. They performed the development, method and characterization of the nanoparticles using the parameters of particle size, morphology (TEM), content analysis (HPLC); as well as the evaluation of the stability and aerosolization properties of this formulation. The results show that the lyophilization process maintained the desired size for peripheral pulmonary deposition; the use of cineol compounds isolated or associated with *n*-heptane favored stable formulations for up to six months; and through the evaluation of the aerosolization and stability properties demonstrated that the nanoparticles have a good pulmonary distribution. They concluded that the inhalers were stable and suitable for inhalation therapy for systemic action. The *in vitro* and *in vivo* assays were not performed in this study without information about the possible risks of systemic action.

In the article published by Pant et al. (2014) proposed the use of aqueous filtered extracts from *Pongamia glabra* and *Jatropha curcas* in the development of nanoemulsions containing *Eucalyptus globulus* oil as a potential pesticide agent for the control of *Tribolium castaneum*, a pest that attacks stored grains. The choice of these filtrates is because they have insecticidal properties and may increase the shelf life of eucalyptus oil when used in place of water in the nanoemulsion composition. The suspension was prepared by a low energy emulsification method containing 10% of the active component (eucalyptus oil) and afterwards the characterization was performed through medium particle size and polydispersity index. The oil and the nanoemulsion were also submitted to infrared techniques and content analysis to identify and quantify their constituents, showing the presence of the 1,8-cineol compound in majority quantities. The insecticidal activity of eucalyptus oil nanoemulsion with and without the aqueous filtrates was determined at different concentrations. The nanoemulsions constituted by the filtered extracts exerted an important function in increasing the shelf life and with the eucalyptus oil demonstrated the efficacy of the nanoemulsions against the stored grain pests.

The study published by Camargos et al. (2014) evaluated the mechanism of parasitic action of drugs and terpenes. Leishmaniasis is a poverty-related disease, thus reducing drug values and preventing the development of drug resistance are extremely important factors. This way, the search for new active compounds against *Leishmania* and other parasites from the world's biodiversity presents a promising opportunity for the discovery of new drugs. The essential oils and terpenes present in their compositions have demonstrated antibacterial, antifungal, antiparasitic, antiviral, anti-allergic and anti-inflammatory activities. The terpenes analyzed in the study, among them 1,8-cineol, showed an interesting behavior, increasing the concentration of terpenes in contact with the parasites, the greater the parasite inhibition observed. Two conventional antiparasitics were also evaluated in this article, nerolidol and miltefosine, both associated with lipid nanoparticles because they have a hydrophobic character, demonstrating success in parasitic eradication. Thus, promising compounds were obtained in the fight against leishmaniasis.

The study by Abrigo et al. (2015), explores the influence of the surface chemistry of nanofibers associated with the compound 1,8-cineol, among other compounds, on bacterial behavior. The interactions of bacteria with the surface modified fibers were investigated by a combination of microscopies. It has been found that fiber wettability, surface charge and chemistry influence the ability of bacterial cells to attach and proliferate in nanofiber webs. In addition, the 1,8-cineole compound retained the antibacterial activity of the monomer, resulting in a high proportion of isolated dead cells attached to the fibers. The results showed that the surface chemical properties of nanofiber membranes could be strategically adapted to limit bacterial behavior.

Ge and Ge (2015), produced liposomes containing the essential oil of *Melaleuca alternifolia* in order to encapsulate, and thus protect from degradation in the presence of light, oxygen and temperature, that has the compound 1,8-cineol in its constitution and has an excellent antimicrobial activity. The obtained liposomes presented a size of 75 nm and 96% encapsulation efficiency with the use of this nanosystem. Liposomes not only efficiently encapsulated oil to form liposomes, but also increased inhibition and bactericidal effect in the oil tolerant strain. Oil-bearing liposomal systems may be a potential alternative for effective antimicrobial agents.

In the study by Moghimi et al. (2015), a prospect of improving cell uptake and cytoplasmic release through the cineol compound was investigated as an alternative to potentiate the cell penetration process. A cineol-containing liposome was produced and tested on animals, and then it was found that it significantly decreased a tumor volume (about 75%) and increased its doubling time from 13 days to 31 days. Through this study, it can be concluded that the cineole compound and other cell membrane fluidities can enhance gene therapy through liposomes at animal cell levels.

Abdel Samie et al. (2016) produced nanovesicular chitosan gels for dermal administration of terbinafine hydrochloride (TBN HCl) with penetration enhancers, among them cineol and limonene compounds. TBN HCl is an antifungal drug with broad activity against a spectrum of fungi and is slightly soluble or very sparingly soluble in water. As results, penetration-stimulating vesicles prepared with limonene showed the highest percentage of drug deposition in the skin (53%) and the highest value of local accumulation efficiency (35.3). Clinical studies have shown a cure rate of 86% after 7 days of treatment when using the nanovesicular limonene gel when compared to the currently available product that only showed a 20% cure rate against fungi. Thus demonstrating the effective action of the gel containing nanovesicles, associated with monoterpenos, in the antifungal action.

In the study developed by Abd et al. (2016a), the extent of penetration of caffeine and the drug naproxen associated with nanoemulsions was evaluated. Using human epidermal membranes nanoemulsions containing skin penetration enhancers, such as oleic acid and eucalyptol (cineol), bound to caffeine and naproxen. After the application, the analysis was carried out during eight hours, when the absorption of the components of the product in the horny extract was measured. The group found that nanoemulsions potentiated cutaneous penetration of caffeine and naproxen when compared to controls, in association with penetration enhancers such as oleic acid and cineol.

In the study by Lucia et al. (2017), the production of polymeric micelles associated with several monoterpenes, between them 1,8-cineol, was carried out, in which the objective of the study was to obtain a high activity of this system against the insect pest, especially *Pediculus humanus capitis* (lice) resistant to permethrin. Micellar systems containing 5% by weight of poloxamer 407 and 1.25% by weight of the different monoterpenes were prepared. Later on, the system was characterized by dynamic light scattering (DLS) and by means of an *ex vivo* immersion test the pediculicidal activity of these micellar systems could be evaluated in head lice. As a result, the researchers demonstrated that formulations containing linalool, 1,8-cineole, a-terpineol, thymol, eugenol, geraniol and nonyl alcohol induced a percentage of lice mortality of more than 50%, thus demonstrating that the nanosystem adds stability and potentiates the pediculicidal action of monoterpene 1,8-cineol.

The last study reported in this review was performed by Souza et al. (2017) and the objective of the work was to evaluate the *in vitro* antibiofilm activity of nanoparticles containing *Melaleuca alternifolia* (TTO) oil against several *Candida* species. Previous studies presented in the article had already demonstrated that TTO has antibiofilm action; however, it is known that TTO presents some problems of low stability. In addition, it can induce allergic processes when topically applied, aspects that may limit its use in the long term. They proposed the association of *Melaleuca alternifolia* oil with lipid nanoparticles in order to improve the disadvantages previously scored. TTO-containing nanoparticles were commercially purchased and characterized. Subsequently, quantification of biofilm biomass, protein determination, exopolysaccharide assay, white calcofluor stain and atomic microscopy force were performed to evaluate the antibiofilm activity of the nanoparticles containing the oil. In addition, the composition of this oil was studied, in which it was observed that approximately 6% of its composition is due to monoterpene 1,8-cineol. They demonstrated that the association of a nanosystem enhanced the antimicrobial action and antibiofilm of the TTO under several species of *Candida* showing to be an alternative against infections caused by this microorganism.

## FINAL CONSIDERATIONS

This study allowed to identify the scope of the publications in the field of nanotechnology, involving the 1,8-cineol compound associated with some biological activity. In this review, it was shown that the first discussions relating these themes were in the year of 1988. It is also noticed that, since 2015, the publications involving this approach began to grow. Furthermore, we can observe that the majority of the studies are of research in which nanotechnology is involved in the discovery of agents with antimicrobial potential, studies to potentiate the action or increase the physicochemical stability of compounds already used for this purpose or the search for mechanisms that bypass the resistance of microorganisms.

Thus, after this review, we suggest that studies should be performed only with 1,8-cineol isolated to verify if the effects observed by the essential oils containing it are due to the association of several compounds or relate only to the presence of 1,8-cineol. We also highlight the importance to pursue research in the most diverse areas of knowledge, as well as to seek new approaches to the application of nanotechnology in the biological area, seeking and applying the potential actions of terpene compounds.

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