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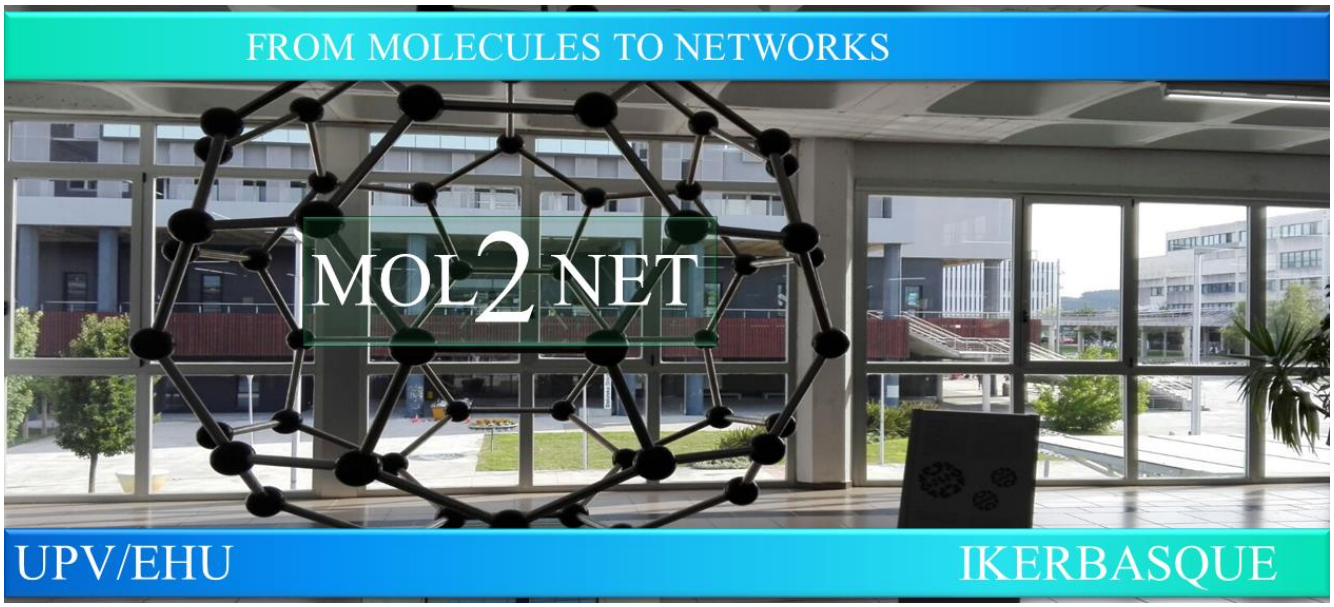
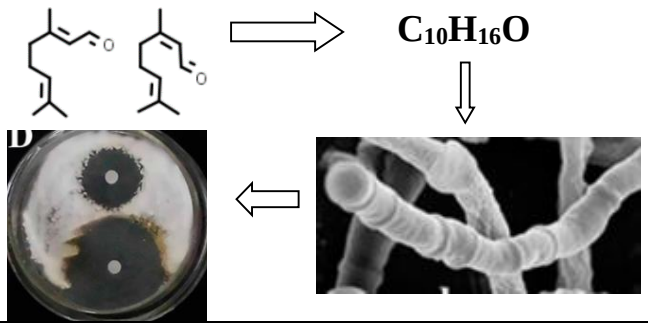


Physicochemical differences and antifungal activity of citral isomers: neral and geranial

Teresa Carolliny Moreira Lustoza Rodrigues[a], Aline Matilde Ferreira dos Santos[b], Jéssica Paiva de Moura [a], Jeremias Justo Emídio [a], Paulo Sérgio da Silva Pereira [a], Igor Mikael Alves de Araujo[a], Nikole Durand Trigueiro[a], Ana Karoline Silva de Aquino Vital[a], Marcus Tullius Scotti[a], Luciana Scotti[a], Alex France Messias Monteiro[a].

[a] Postgraduate Program in Natural Products and Synthetics Bioactive, Federal University of Paraíba, Health Science Center. Campus I, 50670-910, João Pessoa, PB, Brazil;
[b] Postgraduate Program in Neuroscience, Federal University of Paraíba, Health Science Center. Campus I, 50670-910, João Pessoa, PB, Brazil;

Graphical Abstract



Abstract.

The citral is a monoterpene composed of two isomers: neral and geranial. These molecules have several pharmacological activities, such as antioxidant, anti-inflammatory, and antifungal. Therefore, this work analyzed the physicochemical differences of the citral isomers and a case study of their antifungal activity.

Introduction

Medicinal plants have been used for centuries to treat diseases empirically. These vegetables contain many secondary metabolites such as phenols, terpenes, and aromatic components. With the need for new pharmacological treatments, essential oils (EO) gains space in the market due to their easy obtainment and numerous biological activities.

EO can be obtained by several extraction methods: steam distillation, hydrodistillation, and supercritical solvents and fluids (1,2). As they are lipophilic compounds, among the methods above, the most used are steam distillation and hydrodistillation (3).

Citral, a compound present in some essential oils, is widely used in the perfume and cosmetics, aromatherapy, and food industries (4,5) and is much investigated for its therapeutic characteristics by the pharmaceutical industry (6), due to different activities, some of them are anxiolytic (7), antibacterial (8), antioxidant (9), analgesic (10) e antiepileptic (11).

Results and Discussion

Citral is a monoterpene with the formula $C_{10}H_{16}O$ (3,7-dimethyl-2,6-octadienal). It appears as a light yellow liquid with a citric odor similar to that of lemon. As for its composition, it is the result of two geometric isomers: trans-geranial (E; Figure 1.a) and cis-neral (Z; Figure 1.b) (12).

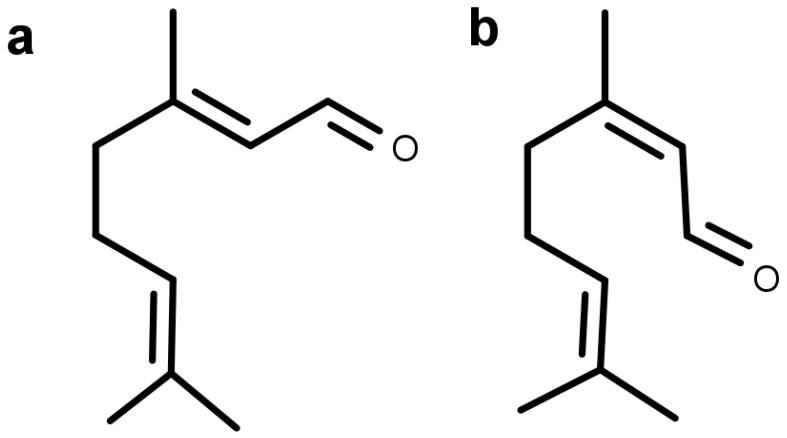


Figure 1. a: 2D structure of geranial ((2E)-3,7-dimethylocta-2,6-dienal); b: 2D structure of neral ((2Z)-3,7-dimethylocta-2,6-dienal).

Both isomers are insoluble in water and have a density equal to 0.891-0.897 at 15 °C (13). Thus, due to their geometric differences, they present different LogP among several physicochemical characteristics (Table 1). The LogP consists of a partition coefficient and is a parameter used to evaluate the lipophilicity of compounds. This characteristic evaluates the ability of these molecules to cross

biological membranes (14). Some small structural changes alter the LogP, common to isomeric compounds, such as E-resveratrol equal to geranial have higher lipophilicity compared to Z isomers (15).

Table 1. Physicochemical characteristics of neral and geranial

Properties	Neral	Geranial
Molecular Weight	152.23	152.23
Boiling point	228.00 °C	228 °C
Solubility (at 25 °C)	84.71 mg/L	84.71 mg/L
LogP	3.170	3.450

Source: The Good Scents Company Information System (16,17)

In the study by Zheng *et al.* (2021) (18), they evaluated the antifungal activity of the isomers, geranial e neral. They performed a test to identify the minimum inhibitory concentration (MIC) and minimum fungicidal concentration (MFC). This test was performed using a broth macrodilution assay. Inhibitory actions were analyzed on 3 types of fungi *Aspergillus flavus*, *Candida albicans*, and *Trichophyton rubrum*. The results obtained determined that geranial presented better performance compared to neral when analyzing the antifungal action for all fungi, mainly *T. rubrum*. This work was corroborated by the study by Miranda-Cadena et al. (2022) (19), who analyzed the citral compound in some types of *Candida* including *C. albicans*. Furthermore, another study demonstrated that *Litsea cubeba* oil, which has citral as the major compound, has antifungal activity against *A. flavus* (20).

In another test performed by the researchers, inhibition halos were observed in the disk diffusion assay with the fungus *T. rubrum*. The geranial proved to be a more potent substance than neral, but both showed inhibitory activity (18). Miron *et al.* (2014) (21), evaluated the inhibitory activity not only of citral but also of the isomers against the same fungus and concluded that geranial had the best results among the isomers, however, the citral compound showed the best performance, thus both isomers acted synergistically. This synergistic activity of the isomers makes it possible for the citral compound to present good results in the treatment of various diseases.

A few studies investigate the activities of the isomers separately, another study investigated the anti-inflammatory activity of neral and geranial, which concluded that neral, in addition to having anti-inflammatory activity, is responsible for the antioxidant activity of the citral compound, while geranial demonstrated oxidizing activity (22).

Conclusions

Thus, it concludes that the geometric isomers neral and geranial have the physical-chemical difference regarding LogP and have antifungal activity. However, geranial is the most potent molecule. Finally, further studies analyzing the isomers and citral are needed.

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