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Letter to the Editor

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Insights on essential oils opportunities in the therapy of multidrug resistant Fungi

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Essential oils: definitions and chemical complexity

Essential oils (EOs), sometimes referred to as volatile oils, essences, etheric oils, or aetheroleum, are derived from various parts of plants, including flowers, leaves, stems, roots, and seeds. They contain highly concentrated volatile compounds and are utilized for a range of purposes such as aromatherapy, massage, skincare, and as natural remedies for different health problems. The composition of EOs can vary based on the plant species and the part of the plant from which it is extracted. Some popular types of essential oils include lavender, peppermint, eucalyptus, lemon, and tea tree oil. (Gentile et al., 2020; Zuzarte and Salgueir 2015). According to the AFNOR NT 75-006 standard (February 2006): "An essential oil is a product obtained from plant row-material, either by steam distillation or by mechanical processes from epicarp of lemons, either by dry distillation, and which is separated from the aqueous phase by physical processes. The most frequent method for obtaining essential oils is through distillation, however, other techniques such as enfleurage (using fat for extraction), maceration, solvent extraction, and mechanical pressing are employed for specific products. EOs complexity includes thousands of biomolecules as secondary metabolites with a major role of attracting pollinators, deterring predators and protecting plants from harmful pathogens. Essential oils are primarily made up of terpenes produced through the mevalonate pathway, including monoterpenes (monoterpene hydrocarbons and oxygenated monoterpenes), and sesquiterpenes (sesquiterpene hydrocarbons and oxygenated sesquiterpenes). Additionally, they contain phenolic compounds that are derived from the shikimate pathway. Due to their chemical composition, essential oils possess a range of biological activities, including antioxidant, anti-inflammatory, antimicrobial, antifungal, among others, which make them of significant interest in the food and cosmetic industries and for human health applications.

Multidrug resistant Fungi and Essential oils

Multidrug-resistant fungi (MDR fungi) are fungal pathogens that have developed tolerance to a range of drugs. The recent emergence of these pathogens resistant to multiple classes of antifungal drug is a serious concern. Ergosterol is a type of lipid that plays a crucial role in maintaining the fluidity and permeability of fungal cell membranes, as well as ensuring the proper function of integral membrane proteins. It is also necessary for the survival of fungal cells. (Leber et al., 2003; Tatsumi et al., 2013; Song et al., 2016; Scorzoni et al. 2017).
Ergosterol is a potential target for the development of antifungal agents against multi resistant fungi (e.g: *Candida* spp.; *Aspergillus fumigatus*) either by inhibiting its biosynthesis or by

binding to it, causing formation of pores in the membrane (Scorzoni et al. 2017). Mechanisms of resistance to clinically relevant classes of antifungal drugs include the Ergosterol sequestration (Polyene's drug class), the Inhibition of ergosterol biosynthesis (Azole's drug class) and Inhibition of β-1,3-glucan synthase (Echinocandins's drug class) (Berman and Krysan., 2020). It is important to note that multidrug resistance fungal strains is a growing public health concern and new treatments are needed to combat these infections. Some of the most common multidrug-resistant fungal species include, among others: *Candida* spp., *Aspergillus fumigatus*, *Cryptococcus neoformans*, (Fernandes et al., 2022; Marquez and Quave., 2020).

Antifungal activity of essential oils against multi resistant antifungal pathogens is well documented (Nazzaro et al., 2017; Singh and Pulikkal., 2022; Yadav et al., 2022). The toxic effect of essential oils and their components regarding fungal cells is attributed to their capability causing harmful effects to the cell walls and membranes, triggering the damage to cellular organelles, the coagulation of cytoplasm and leakage of macromolecules (Burt 2004; Hyldgaard et al. 2012). The oils' ability to dissolve in fats as lipophilic components, allows them to penetrate the cell wall and harm the layers composed of polysaccharides, fatty acids, and phospholipids, making the cells more permeable (Helal et al. 2006; Rammanee and Hongpattarakere 2011; Dwivedy et al. 2016).

In our opinion, investigations on the effect of essential oils against multi resistant fungi should be conducted in an intense way .Moreover, a multidisciplinary approach including the effect of selected essential oils, pure phytochemicals isolated from essential oils, the combination between different essential oils and/or pure phytochemicals with the known used antifungal drugs as well as the correlation between the inter-reactions of those oils and/or phytochemicals with fungal biological molecules in the fungal cell wall and cell membrane (Ergosterol, Chitin....) could understand in the depth and in detailed manner the mode of action and therefore valorise adequately their effect on multi resistant fungi.

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