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Prediction of antifungal activity, cytotoxicity risks and molecular docking against *Malassezia furfur* of constituents of citronella essential oil *(Cymbopogon winterianus)*

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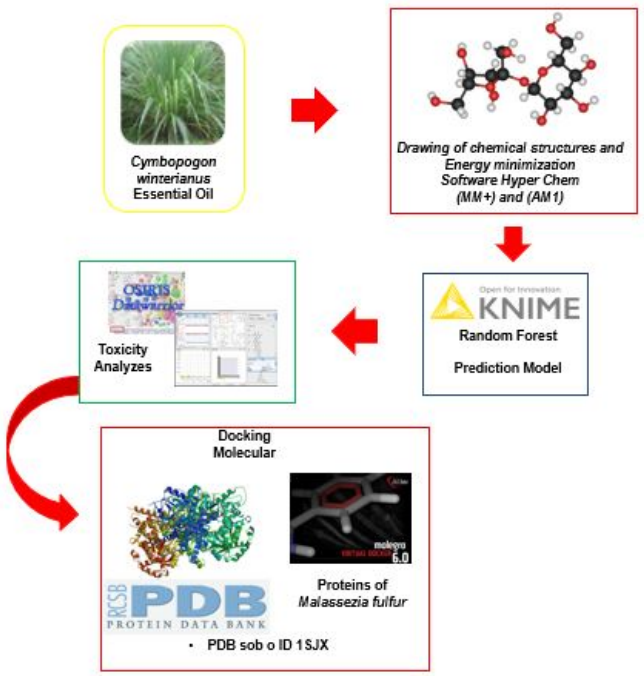
Graphical Abstract



Abstract

Malassezia furfur is a very common fungus classified as yeast and is able to proliferate on the scalp. Thus, it can cause superficial infections, dandruff and hair loss. The alopecia caused by this microorganism can be temporary or permanent, not only by M. furfur but also by M. globosa, reducing the quality of life of people, especially women who are affected. Malassezia can cause skin lesions, facilitating infection of bacteria such as Staphylococcus aureus. The aim of this study is an in silico analysis of citronella essential oil, aiming to identify possible constituents with fungicidal action against M. furfur.

Materials and Methods

Initially, 15 molecules were designed and optimized in software HyperChem 7.5 TM (RMS 0.1 kcal.Å-1.mol-1 in 800 cycles) [1] using molecular mechanics (MM +) and the semiempirical method (AM1). These molecules were then imported into a biological activity model developed in the free software KNIME Analytics Platform 3.7 [2,3], where RandomForest was used as a classifier and Weka 3.7 as a predictor. Consequently, the molecules were classified as active and inactive.

The active molecule was imported into free software OSIRIS DataWarrior 5.0 [4] to predict 4 toxicological parameters: mutagenicity, carcinogenicity, toxic effect on the reproductive system and tissue irritability. For a molecule to be considered toxic in this study, it must present risks in any of the parameters already mentioned.

After that, molecular docking was performed in the software Molegro Virtual Docker 6.0 (MVD) [5], using the crystallographic protein published in PDB with ID 1SJX [6], corresponding to the three-dimensional structure of a llama VHH domain OE7 binding the *M. furfur* cell wall protein.

Results and Discussion

After minimizing the energy of the 15 molecules under study using the software HyperChem, they were imported into a model of biological activity against the fungus *M. furfur.* Among the tested structures, only one compound showed activity according to the model: elemol (PubChem CID 92138, Figure 1).

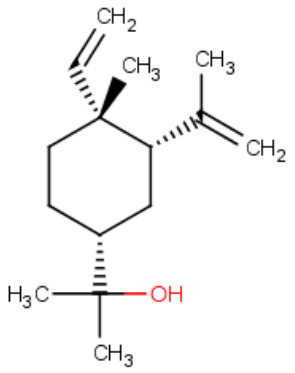


Figure 1. Elemol 2D structure.

As stated in the methodology, 4 cytotoxic parameters for elemol were analyzed: mutagenicity, carcinogenicity, toxic effect on the reproductive system and tissue irritability; where elemol presented no risk in any of the parameters. Thus, this compound was submitted to molecular docking to verify its interactions with the chosen protein.

Table 1. Molecular docking results.

Protein (PDB ID)	Name	Energy [kcal.mol^{-1}]	Interactions	
			Types	Residues
1SJX	Elemol	-65.70	H-bond	None
			Steric	Asp872, Thr877, Ile828, Ala824, Asn876, Thr852, Asn832 and Lys871
	Itraconazole	-9.10	H-bond	Asn873
			Steric	4(Ile831), 2(Thr877), 2(Asn873), Met834, 6(Ile828), 2(Asn876), Asp872, 2(Lys871), 2(Thr852), >6(Ser853) Arg900 and >6(Asn832)
	Miconazole	-59.19	H-bond	None
			Steric	2(Ile828), Ile831, 4(Asn876), Ala824, >4(Met834), 2(Asn832), 2(Ser853), 2(Lys871), 2(Thr877) and Asn873
	MPD	-31.88	H-bond	None
			Steric	None

According to the data presented in Table 1, it can be seen that elemol presented better ligand-receptor interaction energy (-65.70 kcal.mol-1) than the two controls used (itraconazole and miconazole), even better than the co-crystallized inhibitor (-31.88 kcal.mol-1). Also, it is noted that the elemol and the best energy control in molecular docking (miconazole) perform steric interactions with similar residues: Thr877, Ile828, Ala824, Asn876, Asn832 and Lys871.

Conclusions

Essential oils are widely used in trichology and cosmetic sciences for the treatment of fungal and bacterial diseases, being useful against alopecia and dermatitis. Thus, studies such as this one are important to analyze which essential oil compounds are responsible for the antifungal effect and if they present cytotoxicity risks, encouraging researchers to perform biological tests with these substances.

In this research, of the 15 essential oil constituents, only elemol showed good results: it had biological activity in the prediction model and did not show cytotoxicity. Therefore, it is concluded that elemol is a promising compound for the treatment of dandruff and superficial dermatitis caused by *M. furfur*.

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