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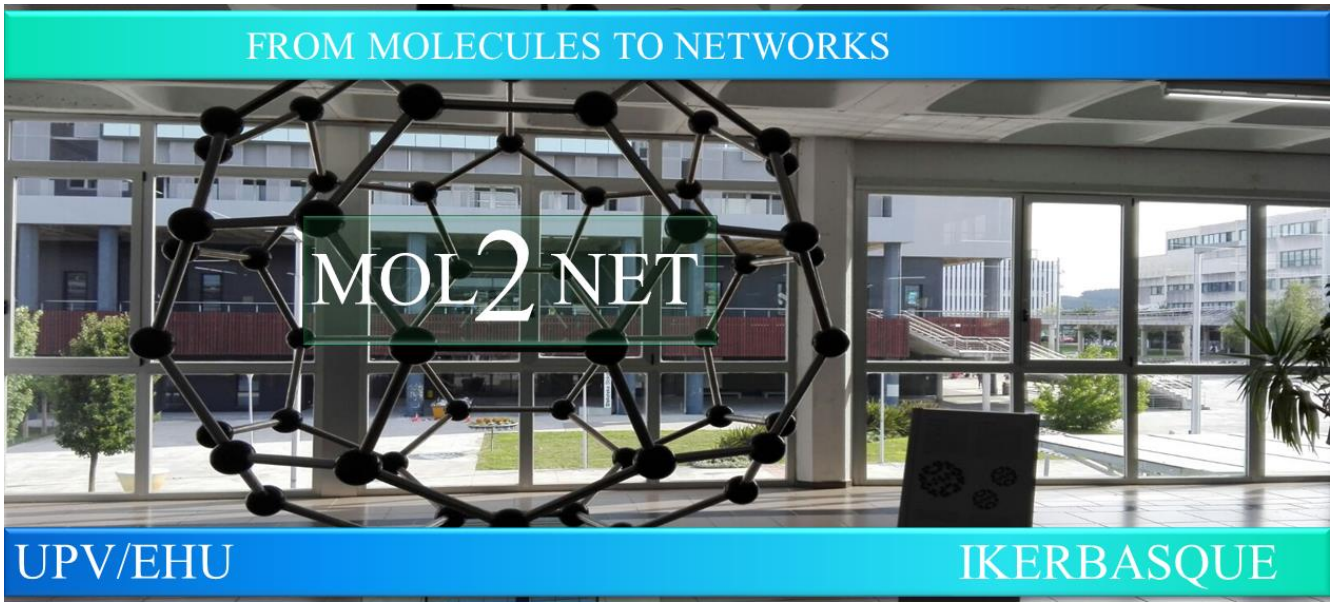

Prediction of antimalaria activity, cytotoxicity risks and molecular docking of constituents of rosemary essential oil (*Rosmarinus officinalis* L.) against *Plasmodium falciparum*.

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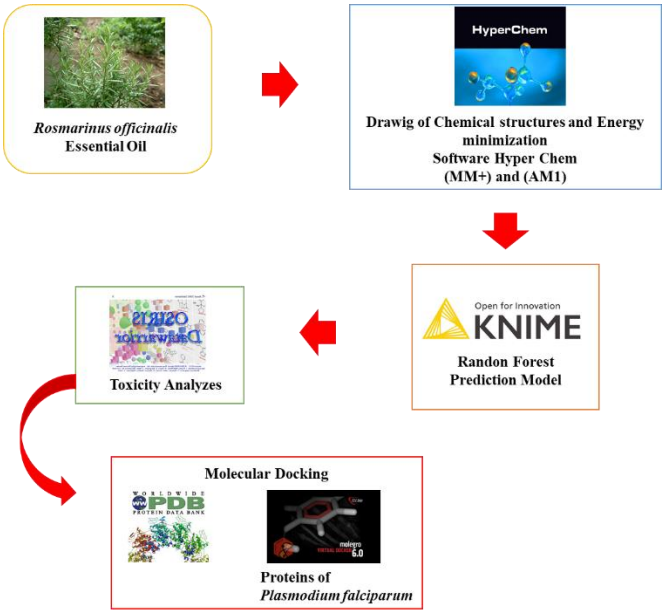
Graphical Abstract



Abstract.

Plasmodium falciparum is a protozoan that causes malaria in its most severe form in humans. Its transmission occurs through female mosquitoes of the genus Anopheles infected by Plasmodium, the most common symptoms are: high fever, chills, headaches, tachycardia and muscle pain. Cerebral malaria may even occur, responsible for most fatal cases of the disease. The objective of this study is an in silico analysis of rosemary essential oil, aiming to identify possible molecules with antimalarial action against Plasmodium falciparum.

Introduction

Malaria is a disease caused by the protozoan of the genus Plasmodium, transmitted by the bite of females of some species of the mosquito of the genus Anopheles. Out of 100 species, 4 of these protozoa infect humans, with *Plasmodium falciparum* being the one that leads to the most severe form of the disease, which can lead to death. The treatment of malaria is quite complicated, extensive and most of the time it is not effective due to reinfection. [1].

Chloroquine is part of the treatment plan for malaria, but *Plasmodium falciparum* over time has become resistant to this drug. Thus, the importance of the synthesis of new antimalarial drugs [2].

Rosmarinus officinalis is a plant known as rosemary and belongs to the Lamiaceae family, it is widely used in traditional medicine against diseases. Rosemary essential oil and extract are biologically active compounds with strong antioxidant activity, so these antioxidant molecules in rosemary essential oil demonstrate strong potential for the synthesis of new natural antimalarial drugs. [3].

Materials and Methods

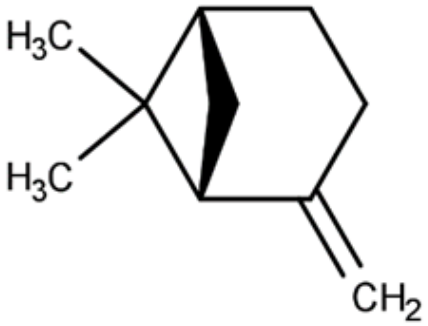
At first, 10 molecules of rosemary essential oil were optimized in the program HyperChem 7.5 TM (RMS 0.1kcal.Å-1.mol-1) using molecular mechanics MM+ and later the semi-empirical method AM1 was performed [4]. These molecules were selected for a biological activity prediction model in the KNIME Analytics Platform 3.7 software. The model calculated the parameters of precision, sensitivity, specificity, MCC, accuracy and ROC curve [5]. The molecules identified as active were selected for the OSIRIS DataWarrior 5.0 software to then verify the risks of cytotoxicity [6]. Soon

after, molecular docking was performed in Molegro Virtual Docker 6.0 software, where the following protein structures were used: Human S-adenosylhomocysteine hydrolase complexed with neplanocin (PDB ID: 1LI4) and Fluoro-neplanocin A in Human S-Adenosylhomocysteine Hydrolase (PDB ID: 3NJ4) [7].

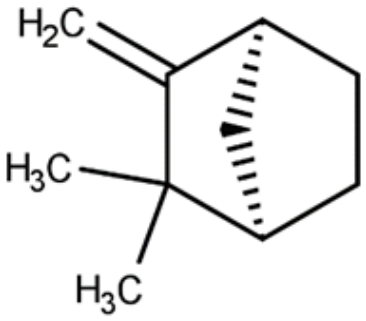
Results and Discussion

After analyzing 10 compounds of rosemary essential oil in the HyperChem software, they were evaluated in a model of biological activity against *Plasmodium falciparum.* Of all the molecules tested, three of them showed activity: beta-pinene (PubChem CID 10290825, Figure 1), camphene (PubChem CID 92221, Figure 1) and eucalyptol (PubChem CID 2758, Figure 1).

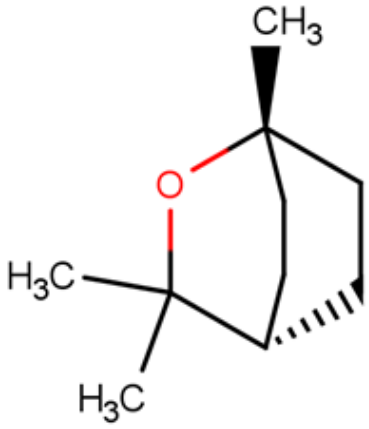
Figure 1. Chemical structures of the compounds selected in the in silico analysis



Beta-pineno 2D structure



Camphene 2D structure



Eucalyptol 2D structure

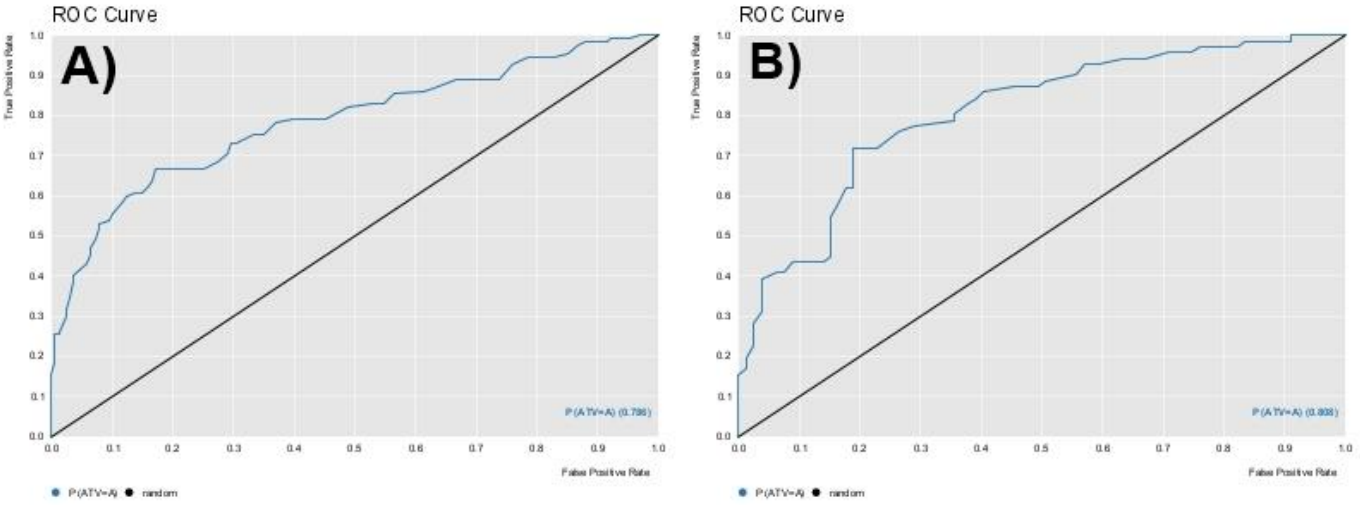
In the KNIME software, the reliability of the models was verified through parameters such as: specificity, sensitivity, precision, accuracy, precision, ROC curve and MCC. Table 1 shows the results of each statistical parameter for the activity prediction model against Plasmodium falciparum.

Table 1. Statistical parameter values obtained for all models.

Parameters	Test	Cross
Precision	0.76	0.65
Sensitivity	0.70	0.68
Specificity	0.81	0.72
Accuracy	0.76	0.70
MCC	0.51	0.40
Curva ROC	80.78	78.62

In Table 1, the values of the parameters obtained were: 0.76 and 0.65 for precision, 0.70 and 0.68 for sensitivity, 0.81 and 0.72 for specificity, 0.76 and 0 .70 for accuracy and 0.51 and 0.40 for MCC. In addition, the models were also observed through the graphs of the ROC curve, in figure 2.

Figure 2: ROC curves of the models. A) Cross; B) Test



The risks of toxicity were verified, analyzing the parameters for beta-pinene, camphene and eucalyptol: carcinogenicity, mutagenicity, tissue irritability and toxic effect on the reproductive system. Therefore, molecular docking was used to analyze the interactions between the proteins chosen with these 3 compounds.

According to Table 2, the three compounds obtained good energy of ligand-receptor interaction: eucalyptol (-55.497), beta-pinene (-51.1448) and camphene (-61.7987). Camphene had the lowest binding energy of the 3 compounds, indicating that it has a better affinity for the protein. Regarding interactions with amino acid residues of the protein, it was seen that the three molecules and the co-crystallized inhibitor performed identical steric interactions with amino acid residues (Figure 3). Camphene and the co-crystallized inhibitor performed steric interactions with Val138, while eucalyptol and the inhibitor co-crystallized with Thr97, Thr101, and beta-pinene and the inhibitor co-crystallized with Asn140.

Table 2. Molecular docking results.

Protein (PDB ID)	Name	Energy [Kcal.$^{mol-1}$]	Interactions	
			Types	Residues
1LI4	Camphene	-61.7987	H-bonds	None
			Steric	Val138
	Eucalyptol	-55.497	H-bonds	None
			Steric	Thr97, Thr101
	Beta- pineno	-51.1448	H-bonds	None
			Steric	Asn140
	Cloroquina	-121.774	H-bonds	None
			Steric	Gly27, Asp53
	NAI	-266.145	H-bonds	Try85, Asp53, Gly99, Asn140, Leu163, Val138, His195 Phe100,
			Steric	Ile31, Met30 Asn140, Val138, Thr97, Thr101

Figure 3: Interactions of rosemary essential oil and control molecules with 1LI4

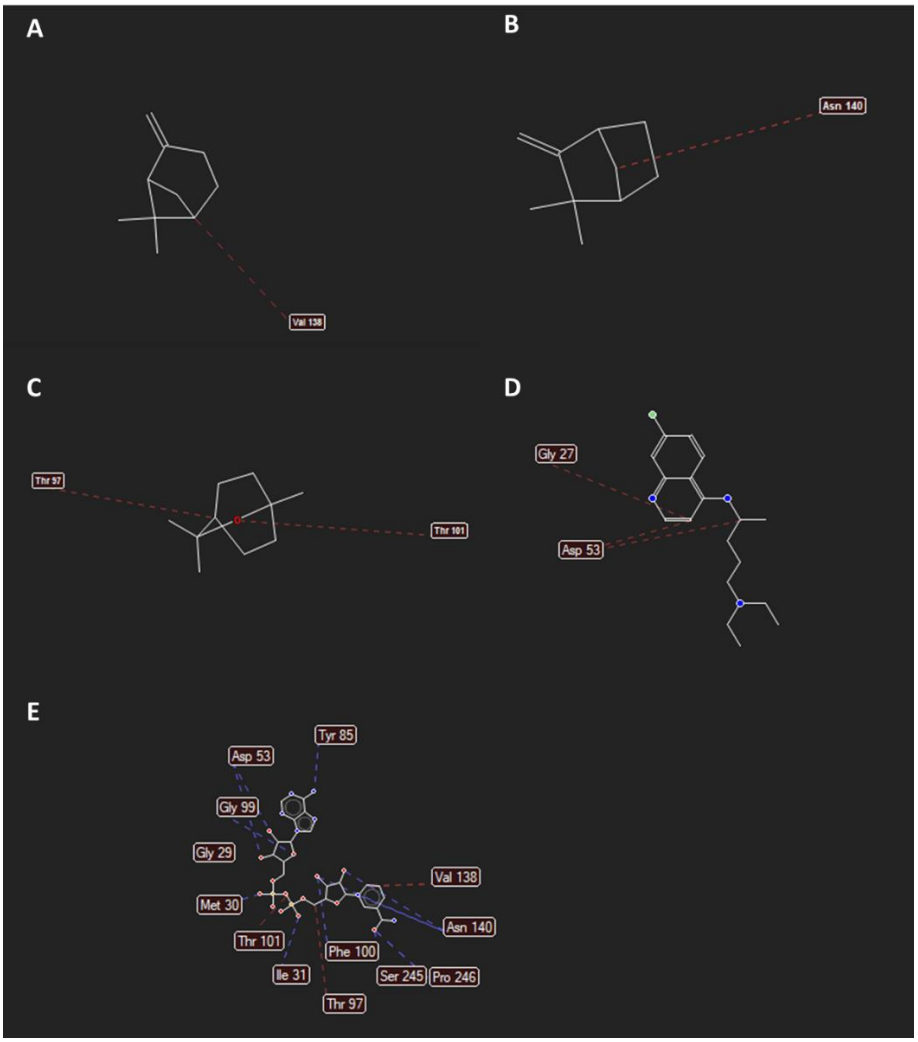
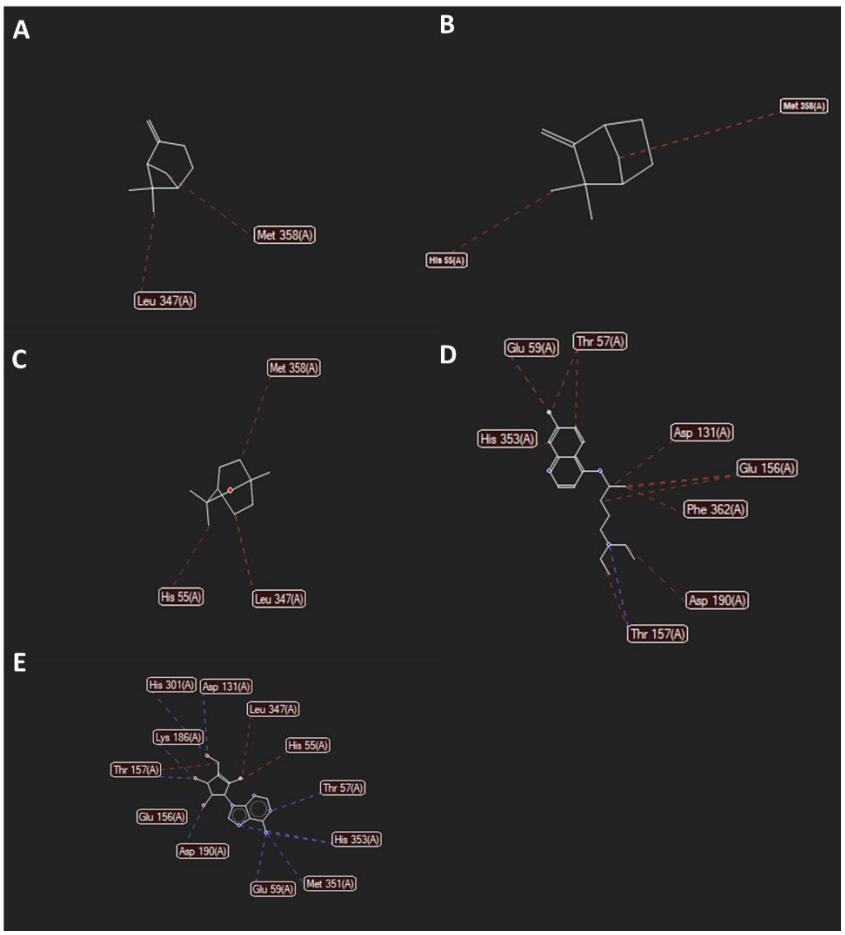


Table 3. Molecular docking results.

Protein (PDB ID)	Name	Energy [Kcal.mol^{-1}]	Interactions	
			Types	Residues
3NJ4	Camphene	-58.9217	H-bonds	None
			Steric	His55, Met358
	Eucalyptol	-47.3896	H-bonds	None
			Steric	Met358, His55, Leu347
	Beta-pineno	-41.837	H-bonds	None
			Steric	Met358, Leu347
	Cloroquina	-103.02	H-bonds	Thr157
			Steric	Asp190, Phe362, Glu156, Asp131, Thr57, Glu59, His353
	AFX	-151.498	H-bonds	His301, Asp131, Lys186, Thr157 Asp190, Glu59, Met351, His353, Thr57
			Steric	Leu347, His55, Thr157

Figure 4: Interactions of rosemary essential oil and control molecules with 3NJ4



According to Table 3, the three compounds obtained good energy of ligand-receptor interaction: eucalyptol (-47.3896), beta-pinene (-41.837) and camphene (-58.9217). Camphene demonstrated the best binding energy of the 3 molecules tested. Analysis of interactions with amino acid residues of the protein, it was seen that the three molecules and the co-crystallized inhibitor performed identical steric interactions with amino acid residues (Figure 4). Camphene and the co-crystallized inhibitor performed steric interactions with His55, while eucalyptol and the inhibitor co-crystallized with His55 and Leu347, and beta-pinene and the inhibitor co-crystallized with leu347.

Conclusions

In this study, of the 10 essential oil constituents, only eucalyptol, beta-pinene and camphene obtained excellent results: having biological activity in the prediction model and not presenting cytotoxicity risks. The camphene compound stood out with a lower binding energy value than the other compounds tested, indicating that camphene has a better affinity for the protein.

Therefore, it is concluded that eucalyptol, beta-pinene and camphene are promising molecules for the treatment of malaria caused by *Plasmodium falciparum*, but further studies are needed to verify the activity of these compounds.

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