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INHIBITORY POTENTIAL OF ISOPRENOID BIOSYNTHESIS IN *TOXOPLASMA GONDII* BY LIMONENE: AN *IN SILICO* STUDY

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Abstract

Toxoplasmosis is a pathology caused by the apicomplexan *Toxoplasma gondii*, and in pregnant women or immunocompromised individuals, it can cause severe symptoms, including mental confusion, lack of coordination and seizures. Protein prenylation is a ubiquitous covalent post-translational modification found in all eukaryotic cells, comprising the attachment of a farnesyl or a geranylgeranyl isoprenoid. It is essential for the proper cellular activity of numerous proteins in apicomplexans. Considering the inhibition of prenylation already documented for *Plasmodium* sp. by the monoterpene limonene, the present study aimed to determine the inhibitory potential of this terpene also on the activity of the farnesyl/geranylgeranyl diphosphate synthase of *T. gondii* through modeling of this protein and subsequent docking procedures. The modeling of the protein of interest was performed in the *AlphaFold 2* software, a program for modeling protein structures based on artificial intelligence available in Colab. The entire amino acid sequence provided in the ToxoDB database (identifier: TGME49_224490) was used for structural prediction. After modeling, the model was refined in the YASARA server and used for simulations (in triplicate), with magnesium divalent cations (*MIB2*); and with small molecules in the SwissDock server (*Autodock Vina*): dimethylallyl diphosphate (DMAPP), DMAPP+isopentenyl diphosphate (IPP), limonene, and DMAPP+limonene. The conformations most similar to the 1rqi model and stable were subsequently analyzed. The 2D interaction diagram generated by the *Discovery Studio* software shows that the stability of the DMAPP+limonene model (-5.278 kcal/mol) is quite similar to that of DMAPP+IPP (-5.550 kcal/mol), which may indicate an inhibitory potential due to competition at this binding site. Future *in vitro* results should further clarify the mechanism associated with the effect of limonene on isoprenoid synthesis in *T. gondii*.

Keywords: Toxoplasmosis, Prenylation, Inhibition.