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Unveiling the Potency of *Coriandrum sativum* as Repellent for Antimalarial: *In silico* Study

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Abstract: This study identified the potency of 2-Decenoic acid and Cyclododecanol from *C. sativum* as a repellent agent for antimalarial with in silico approach. The 3D structures of 2-Decenoic (CID5282724) and Cyclododecanol (CID15595) were downloaded from the PubChem database. Bioactive compounds were docked with macromolecule AgamOBP-1 (3N7H) from the PDB database using Molegro Virtual Docker 5. Docking results were visualized and analyzed by Pymol and Discovery studio 4.1. Visualization was done as 2D and 3D form. The result showed that 2-decenoic acid and cyclododecanol were performed binding to the active sites odorant binding protein of *Anopheles* mosquito. Several residues of AgamOBP-1 protein was identified both of cyclododecanol and 2-decenoic acid of *C. sativum*, which were LEU96, MET89, HIS77, ALA88, and LEU76. Those residues has a pivotal region of AgamOBP-1 protein. Besides that, those residues also found as DEET active sites, indicating the same mechanism action of cyclododecanol and 2-decenoic acid. The inhibition of AgamOBP-1 prevent mosquitoes from taking blood from the host. In summary, in silico study suggested that cyclododecanol and 2-decenoic acid of *C. sativum* were potentially preventing malaria by AgamOBP1 inhibition. Further study needed to establish the plant product as an oil for an antimalarial agent.

Keywords: antimalarial, 2-Decenoic acid, Coriandrum sativum, Cyclododecanol, in silico.

Introduction

Mosquito-borne diseases are the major cause of death in the world. Nearly half of the global population is highly at risk of malaria transmission. (Nyasa *et al*., 2021; Adugna *et al*., 2022). Specifically, Indonesia had approximately 130 million people living in high-risk regions. In 2022, 68.3% of districts and municipalities of Indonesia reported being free of malaria. However, some areas in Indonesia have relatively high malaria cases (Sugiarto *et al*., 2022). Some alternatives to prevent malaria are being developed. The potential target to prevent malaria is the olfactory system, which triggers behavioral responses. The key protein that is involved in the detection of pheromones is odorant-binding proteins (OBPs). It is located on the olfactory neurons in the olfactory system (Archunan, 2018).

The olfactory system of the *A. gambiae* primarily consists of antennae and maxillary palps. The third chemosensory organ, labella, located on the head, might detect low volatile odorants. A sensillum covers each organ as sensory hair. Each sensillum contains olfactory sensory neurons that may have chemoreceptors (Carey & Carlson, 2011; Saveer *et al*., 2018). Repellent designed to inhibit OBP prevented humans from being bitten by mosquitoes. The most used synthetic chemical repellent is DEET. It played a critical role in insect management (Alayo *et al*., 2015). However, synthetic chemical repellents are found unsafe for public health. It causes toxic reactions, such as skin allergies, neurological effects, and cardiovascular properties (Sanghong *et al*., 2015; Afify *et al*., 2019). Besides, synthetic chemicals disrupt the ecosystem by making them mosquito-resistant. Thus, it is crucial to find an alternative repellent (Govindarajan *et al*., 2016; Asadollahi *et al*., 2019).

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Plant-based repellent has been established as it contains abundant bioactive phytochemicals. Importantly, plant-based repellent is safe and biodegradable. Many studies have reported that plants have a repellency effect, such as bioactive compounds in citronella, lavender, camphor, jasmine, eucalyptus, lemongrass, chamomile, cajeput, and rosemary (Ansari *et al*., 2005; Govindarajan *et al*., 2011; Afify *et al*., 2019). Most of the plants used for repellent had a strong smell (Asadollahi et al., 2019). Essential oil from eucalyptus can protect against mosquitoes with protection time ranging from 1.7 h to 11 h. The 20% compounds from rosemary oil was reported effectively protect from *A. stephensi* for 8 h.

This study proposed cilantro or coriander (*Coriandrum sativum* L.) as a plant-based repellent. The leaves of *C. sativum* are often called cilantro. The leaves are rich in 2-decanoic acid and cyclododecanol in the essential oil. The most distinctive character of cilantro is the smell. It has a strong odor and is oftenly used to add flavor to food and hide the unpleasant smell of certain materials in dishes (Kohara *et al*., 2006). Moreover, *C. sativum* has been known to have insecticidal activity. The essential oil is significantly toxic against larvae of *Aedes aegypty* and it is assumed could harmful to *Anopheles* spp. Considering the potency of *C. sativum*, this study aims to predict the potency of 2-decanoic acid and cyclododecanol of *C. sativum* as a repellent agent for antimalarial by *in silico* study (Laribi et al., 2015; Chahal et al., 2017).

Materials and Methods

Protein and ligands preparation

The 3D structure of *An. gambiae* OBP-1 protein, AgamOBP-1 (3N7H), was downloaded from PDB. Protein was prepared by Discovery Studio 4.1 by removing natural ligand bounds and water molecules. Ligands from C. sativum, 2-Decenoic acid (CID5282724) and Cyclododecanol (CID15595), and N,N-diethyl-3-methylbenzamide (DEET) as a repellent control (CID) were downloaded from PubChem as SDF format. PyRx prepared ligands by minimizing the energy (Krisnamurti *et al*., 2021).

Molecular docking and visualization

All ligands were docked to protein by Molegro Virtual Docker 5 (Bitencourt-Ferreira *et al*., 2019). Docking was performed to the protein active sites with the grid as follows, X=12.63; Y=9.59; Z=13.41; radius 11. The 2D and 3D visualization were performed by PyMol and Discovery Studio 4.1 Protein-ligands binding energy of ligands was analyzed with the formulation ΔG = Moldock Score + Moldock Grid Score + Rerank score.

Results and Discussion

Antimalarial properties of Cyclododecanol from *C. sativum*

The antimalarial property of Cyclododecanol and 2-Decenoic acid was identified by comparing the binding interaction of AgamOBP-1 to DEET. The result in Figure 1 showed the interaction of AgamOBP-1 and DEET binding. DEET posed binding to AgamOBP-1 through Gly92, Met89, His77, Ala88, Leu96, Leu7, Leu80, Met91, and Trp114. The binding involved in the AgamOBP-1 and DEET interaction were hydrogen bond and hydrophobic interaction. DEET was bound to the receptor by spending -266.448 kJ/mol binding energy (Table 1).

Binding of Cyclododecanol to AgamOBP-1 (Figure 2; Table 1) was performed through Leu96, Met89, and His77 with hydrophobic interaction. The binding energy of AgamOBP-1 and Cyclododecanol was -252.045 kJ/mol. As the highlight, the amino acid residues involved in the AgamOBP-1 and Cyclododecanol binding were similar with amino acid residues in AgamOBP-1 and DEET binding. From the 3D visualization (Figure 2a), Cyclododecanol were posed binding to AgamOBP-1 similarly to AgamOBP-1 and DEET binding (Figure 1). The Leu96, Met89, and His77 amino acid residues of AgamOBP-1 and Cyclododecanol were involved in AgamOBP-1 and DEET binding. It indicated that Cyclododecanol has potency as antimalarial through inhibiting olfactory binding protein. Inhibition of *A. gambiae* olfactory binding protein could prevent malaria because inhibiting the receptor could result in the

failure of *A. gambiae* physiological and behavioral response.

Table 1. Interaction of cyclododecanol and 2-decenoic acid of *C. sativum*

Interaction	Name	Category	Types
AgamOBP-1 and DEET (control) **(-266.448 kJ/mol)**	GLY92	Hydrogen Bond	Carbon Hydrogen Bond
	MET89	Other; Hydrophobic	Pi-Sulfur; Pi-Alkyl
	HIS77	Hydrophobic	Pi-Pi Stacked; Pi-Alkyl
	ALA88	Hydrophobic	Alkyl
	LEU96	Hydrophobic	Alkyl; Pi-Alkyl
	LEU76	Hydrophobic	Alkyl
	LEU80	Hydrophobic	Alkyl
	MET91	Hydrophobic	Alkyl
	TRP114	Hydrophobic	Pi-Alkyl
AgamOBP-1 and Cyclododecanol **(-252.045 kJ/mol)**	LEU96	Hydrophobic	Alkyl
	MET89	Hydrophobic	Alkyl
	HIS77	Hydrophobic	Pi-Alkyl
AgamOBP-1 and 2-Decenoic acid **(-273.536 kJ/mol)**	ARG94	Hydrogen Bond	Conventional Hydrogen Bond
	LEU73	Hydrogen Bond	Conventional Hydrogen Bond
	ALA88	Hydrophobic	Alkyl
	LEU76	Hydrophobic	Alkyl
	HIS77	Hydrophobic	Pi-Alkyl

Note: Blue color represent the amino acid residues that are involved in the AgamOBP-1 and DEET binding

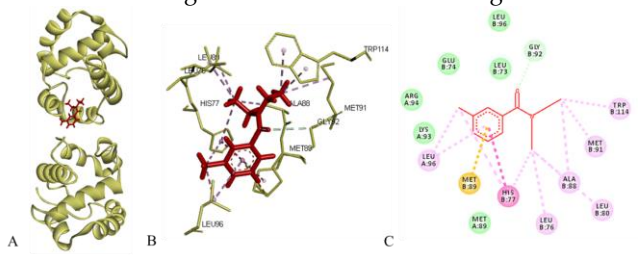

Figure 1. Binding of DEET to AgamOBP-1: A-B. 3D visualization, C. 2D visualization

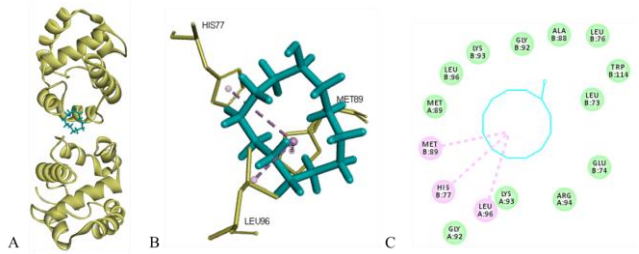

Figure 2. Binding of Cyclododecanol to AgamOBP-1: A-B. 3D visualization, C. 2D visualization

Antimalarial properties of 2-decenoic acid from *C. sativum*

Similar to Cyclododecanol, other bioactive compounds of *C. sativum* named 2-Decenoic acid were also able to perform binding to AgamOBP-1 active sites (Table 1). 2-Decenoic acid was bound to AgamOBP-1 through Arg94, Leu73, Ala88, Leu76, and His77 amino acid residues (Figure 3). Those amino acid residues were bound through 2-Decenoic acid by hydrogen bond and hydrophobic interaction. Moreover, these following amino acid residues, Ala88, Leu76, and His77 amino acid residues were also involved in AgamOBP-1 and DEET binding (Figure 1).

Interestingly, 2-Decenoic acid posed binding to AgamOBP-1 (-273.536 kJ/mol) with a stronger binding energy than AgamOBP-1 and DEET binding. The presence of hydrogen bonds in AgamOBP-1 and 2-Decenoic acid assumed could increase the binding efficiency, resulting in strong binding. The strong binding indicated better inhibition.

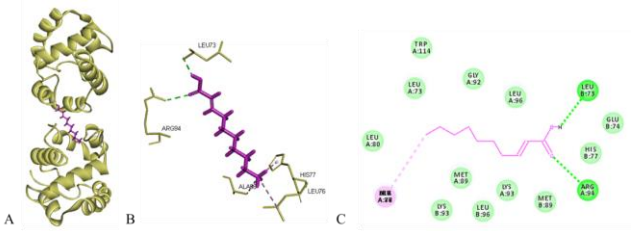

Figure 3. Binding of 2-Decenoic acid to AgamOBP-1: A-B. 3D visualization, C. 2D visualization

Discussion

The olfactory system is essential in guiding insect behaviors (Xu *et al*., 2010). The major protein involved in olfaction is OBP. It involves odor recognition, solubilizing, and delivering odorant molecules to odorant receptors. Besides, it is essential to guide insects for host-seeking and oviposition (Leal, 2007; Leite *et al*., 2009; McMeniman *et al*., 2014). Targeting OBP is a prospective strategy to prevent malaria, such as N,N-diethyl-3-methylbenzamide (DEET), which is a potential agent to inhibit OBP (Alayo *et al*., 2015). However, the toxicity of DEET led to discovery of other repellent agents. Potential repellent agents must have a similar mechanism with commercial repellent, such as DEET. Interestingly, this study found bioactive compounds of *C. sativum*, Cyclododecanol and 2-Decenoic acid, able to perform an inhibition at the specific sites of DEET - AgamOBP-1 binding. It is possible that Cyclododecanol and 2-Decenoic acid performed the same mechanism to AgamOBP-1 similarly with DEET mechanism to AgamOBP-1.

Being the first protein to interact with the odor, OBP is the protein involved in determining odorant preference in *A. gambiae*. OBP function to transport odorants from cuticular pores to odorant receptors on the dendritic membranes of olfactory neurons (Biessmann *et al*., 2010). Inhibition of OBP leads to signal transmission failure to the neuronal

components (Pelosi *et al*., 2018). Bioactive compounds of *C. sativum* predicted could interfere with the transmission process of odorants to olfactory neurons by inhibiting AgamOBP-1. Thus, it automatically prevents the behavioral responses of *An. gambiae* (Laribi *et al*., 2015; Afify *et al*., 2019).

Based on previous findings, it has been demonstrated that plant extracts are potentially repellent. Plant-based repellent performed protection to *Anopheles spp.* at least four hours of protection, the longest being 11.5 hours (Asadollahi *et al*., 2019). Interestingly, previous study showed the preference of using natural repellents (i.e. lemongrass oil and eucalyptus) (Pappenberger *et al*., 1996; Ansari *et al*., 2005; Amer and Mehlhorn, 2006; Auysawasdi *et al*., 2016). Here, Cyclododecanol and 2-Decenoic acid binding to AgamOBP-1 in this study is expected to exhibit repellency activity against *A. gambiae*. Both cyclododecanol and 2-decanoic acid binding to AgamOBP-1 were identical with DEET and AgamOBP-1.

Conclusions

In conclusion, cyclododecanol and 2-decenoic acid of *C. sativum* are predicted to have activity similar to DEET to AgamOBP-1. It indicated that *C. sativum* has potency as a repellent agent to prevent malaria.

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