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Identification of Novel Competitive Antagonists for Histamine H1 Receptor in Malaysian Kelulut Honey

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ABSTRACT

Current breakthroughs in molecular docking approaches have significantly contributed to discovering novel antagonists that competitively bind to histamine H1 receptor (H1R), thereby inhibiting histamine-mediated reactions. A reliable antagonist must possess a superior binding affinity with H1R compared to histamine while having the ability to be efficiently absorbed and traverse the intestinal barrier for systemic circulation. The consideration of human intestinal absorption (HIA) provides an extension for comprehending ligands' bioavailability before engaging in docking studies. In this study, the Brain Or IntestinaL EstimateD permeation method (BOILED-Egg) model was utilized to predict the HIA of the ligands, followed by molecular docking to target the H1R with compounds presented in Malaysian Kelulut honey that are impenetrable to the blood-brain barrier (BBB-) by using a virtual screening tool, Pyrx. The findings highlighted the importance of specific residues, including ASP 107, TYR 108, SER 111, and TYR 431, in H1R, as they interact with histamine within the binding spaces, demonstrating strong intermolecular forces. Among 69 BBB- compounds, Polydatin (PD), Sophoflavescenol, and Dendrocandin B exhibited favorable results in docking studies with H1R, indicating their potential to be used as competitive antagonists in treating allergic symptoms. A more promising candidate can be nominated to develop optimal antagonists by addressing absorption properties and binding affinity perspectives.

Keywords: Antihistamine, histamine H1 receptor, human intestinal absorption, kelulut, molecular docking

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INTRODUCTION

The prevalence of allergies and inflammation has recently increased worldwide due to inadequate exposure to allergens such as environmental microorganisms and food allergens (Renz & Skevaki, 2021). Human mast cells degrade upon exposure due to elevated intracellular calcium ion levels and release inflammatory mediators, including histamine, into the cytoplasm. Histamine is then bound to the Histamine H1 Receptor, a G protein-coupled receptor, which can trigger various signaling pathways, including the Phospholipase C (PLC) and protein kinase pathways. It then results in intracellular calcium ion influx that triggers vascular permeability and physiological allergic reactions such as airway constriction and vasodilation (Zhou et al., 2024).

To date, antihistamines have been effective in mitigating histamine-mediated reactions. However, antihistamines can exhibit adverse reactions while relieving allergic symptoms. First-generation antihistamines can cause sedative effects due to their ability to penetrate the blood-brain barrier (BBB) and act on the central nervous system (CNS) (Ince & Ruether, 2021). Second and third-generation antihistamines were then developed to reduce the sedative effects by targeting the peripheral nervous system (PNS), nevertheless, they still result in adverse effects such as headache and dizziness when overdosed (Ince & Ruether, 2021). To minimize adverse effects associated with medications, natural food products such as honey have been considered as alternatives in treatment because they are rich in phytochemical compounds that are potentially useful to combat the disease.

Honey contains a variety of phytonutrients with pharmacological benefits, including antibacterial, anti-inflammatory, antioxidant, and wound-healing properties (Aspar et al., 2020). However, due to limited honey production, most studies have focused on manuka honey instead of Malaysian honey, particularly Kelulut honey (Tuksitha et al., 2018). Kelulut honey is a Malaysian polyfloral honey that possesses phytochemical compounds such as flavonoids and phenolic acids. These polyphenols are significant contributors to pharmacologic and therapeutic properties, including anti-inflammatory properties. Additionally, it is found that Kelulut honey consists of 69 BBB- compounds in a previous study of prediction of BBB permeability, showing that compounds in Kelulut honey can be potentially utilized in managing allergies with lesser side effects on CNS (Edros et al., 2023a).

Allergic symptoms and inflammation mostly involve smooth muscle due to the presence of Histamine H1 Receptor (H1R). A desired ligand must be able to passively absorb into the human gastrointestinal while impermeable to BBB to be transported to the affected area, particularly H1R in smooth muscle cells (Kikiowo et al., 2023). Thus, Human Intestinal Absorption (HIA) assessment is crucial to classify the Kelulut honey compounds into good intestinal absorption (HIA+) and poor intestinal absorption (HIA-) before molecular docking, demonstrating the ability of a ligand to be absorbed by the intestinal barrier into

the bloodstream. It is to ensure the bioavailability of the ligand, where it can be absorbed and delivered to the affected area through the bloodstream while not passing across the BBB, which could damage the brain due to toxicity and adverse effects (Zekri et al., 2023). Once absorbed, the ligand can mitigate histamine-mediated reactions by competitively binding to the H1R binding site (Wang et al., 2021).

For a ligand to exhibit competitive antagonism, it should possess a structural analog while demonstrating higher binding affinity and better conformation compared to histamine when it interacts with active residues in the H1R active site (Conrad et al., 2023). Virtual screening was commonly utilized to investigate small molecules via structure-based screening, especially the molecular docking technique. Structure-based docking can provide valuable insights into the binding pattern of Kelulut Honey ligands at the H1R active site, identifying the potential antagonist that competitively interacts with the active residue that histamine did.

In this work, PyRx, a virtual screening tool, was utilized for molecular docking between H1R and BBB- compounds in Kelulut honey. BBB- ligands present in Kelulut honey were extracted from BBB permeability prediction in a previous study to identify their potential as an H1R antagonist via molecular docking (Edros et al., 2023a). The structure of the H1R was extracted from the protein data bank (PDB) and refined using PyMol to obtain the most robust structure, followed by HIA prediction using the BOILED-Egg model to obtain HIA+ ligands for docking (Daina & Zoete, 2016). Once protein and ligands were prepared, grid generation was performed to set the H1R binding site as docking space, and molecular docking could be started. The result of binding affinity was extracted, whereas the output of binding conformation was visualized in Biovia Discovery Studio Visualizer to analyze the interaction of H1R-ligand complexes. By correlating and comparing the binding affinity and interaction, potential antagonists among ligands in Kelulut honey were identified.

METHODS

Protein Preparation

The crystal structure of H1R (PDB ID: 3RZE) was retrieved from the Protein Data Bank (https://www.rcsb.org/) with a resolution of 3.10Å, determined by x-ray diffraction. The H1R-doxepin complex was preprocessed by using PyMol version 3.0.2 (The PyMOL Molecular Graphics System, Version 3.0 Schrödinger, LLC) to remove doxepin, water molecules, and the phosphate group, extracting the H1R structure without the presence of antagonists (Akram et al., 2024). Then, hydrogen atoms were added to demonstrate the hydrogen bond interaction with ligands, producing an H1R structure for molecular docking.

Ligands Preparation

BBB-compounds present in Kelulut honey from previous studies regarding BBB permeability prediction were used as ligands to identify their potential as an H1R antagonist via molecular docking (Edros et al., 2023b; Feng et al., 2024; Mohd et al., 2020). The structure of ligands was extracted from PubChem (https://pubchem.ncbi.nlm.nih.gov/) to ensure the availability of 3D structure. Before initializing the ligands for docking, gastrointestinal absorption of ligands was predicted by using the BOILED-Egg model based on topological polar surface area (TPSA) and water-octanol partition coefficient (Log P) (Daina & Zoete, 2016). HIA+ ligands that can be passively absorbed into the GI tract barrier were then prepared by inputting ligands structure in .pdb format into Open Babel in PyRx version 0.8 (https://pyrx.sourceforge.io/) for energy minimization with energy difference cutoff of 0.1 in 200 steps using Universal Force Field (uff) (Dallakyan & Olson, 2015).

Molecular Docking

After the optimization, a grid was generated specifically at the binding site of histamine with 30Å (X=15.98, Y=34.95, Z=22.47) to comparatively analyze the binding affinity and conformation between ligands and histamine. Molecular docking was performed using Autodock Vina integrated with PyRx with an exhaustiveness of eight, representing eight initial random runs for ligand conformation search within the space of the H1R binding site (Dallakyan & Olson, 2015).

Post Docking Analysis

Post-docking analysis involves binding affinities ranking among ligands and histamine, binding conformation with root mean square deviation (RMSD), and binding interaction between ligands and residues. This study generated and extracted the binding affinity and RMSD in a .csv file. H1R-ligands complexes were visualized in two-dimensional (2D) and three-dimensional (3D) views using PyMol and Biovia Discovery Studio Visualizer (version 21.1.0.20298, San Diego). It analyzes the binding conformation and interaction, including intermolecular and covalent forces between active residue and ligands (Ahmed et al., 2021). All results were organized and curated for correlation analysis to identify the potential H1R competitive antagonist among Kelulut honey ligands.

RESULTS AND DISCUSSION

H1R Active Site

In protein preparation, H1R embedded in the phospholipid bilayer consists of 12 receptor cavities and six active sites, as illustrated in Figure 1. Out of six active sites, it is found that histamine interacts with an active site containing residues including ASP107, TYR108,

SER111, THR112, TRP158, ASN198, TRP428, TYR431, PHE432, PHE435, and TYR458 in transmembrane (TM) 3, 5, and 6 of H1R (Feng et al., 2013; Xia et al., 2021). These residues are located in three extracellular loops that are extended from the hydrophobic TM and interact with the hydrophobic core of the phospholipid bilayer, making H1R an integral protein, as illustrated in Figure 1(A). Therefore, this binding site is accessible through extracellular domains, triggering the signaling transduction to the GCPR protein via intracellular domains (Kok et al., 2022).

Specifically, ASP107 and TYR431 form hydrogen bonds with protonated amine groups in histamine. At the same time, THR112 and TYR431 interact with 3-position nitrogen atom (N^{τ}) and 1-position nitrogen atom (N^{π}) in the imidazole ring, respectively. These hydrogen bonds stabilize the binding between histamine and the binding site (Riza et al., 2019). Not forgetting aromatic residues, including TRP428, PHE432, PHE435, and TRP158, which interact with histamine through hydrophobic interaction (Mehta et al., 2021). Contacts between hydrophobic surfaces of protein and ligands expel the water molecules from the binding spaces, resulting in the increment of entropy that contributes to the binding stability and specificity. Additionally, π-π stacking contributed by TYR108 and TRP158 in the upper aromatic region of the imidazole ring also anchored histamine in position, enhancing the stability and binding affinity (Xia et al., 2021). Therefore, the grid was generated based on this specific active site to identify ligands that potentially modulate H1R activities upon binding. Figures 1(B) illustrate the active site involved in molecular docking and the active residues interacting with histamine within the binding site.

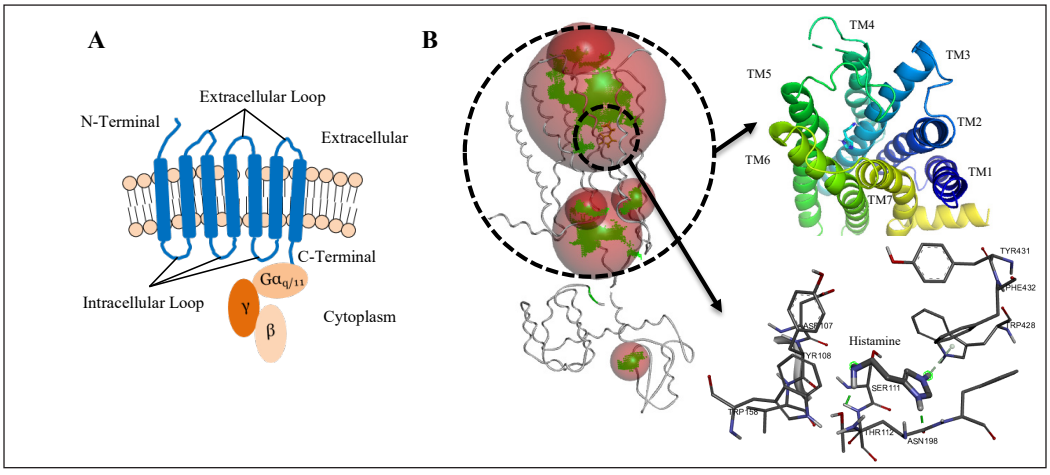

Figure 1. (A) Structure of H1R as an integral protein in the phospholipid bilayer and (B) Six binding sites are visualized by a red sphere along with the visualization of the H1R structure indicating seven TM involved in the binding site and active residue involved in the interaction between the H1R active site and histamine

HIA Assessment

In bioavailability assessment, HIA is one of the critical properties in Absorption, Distribution, Metabolism, and Excretion (ADME) to identify the ligands that can be passively absorbed by the human gastrointestinal (GI) tract (Laskar et al., 2023). HIA+ ligands are more likely to be absorbed by the GI tract after administration than HIA- ligands. A high absorption rate indicates that HIA+ ligands can effectively reach therapeutic concentrations in the systemic circulation (Zhang et al., 2020). Subsequently, the efficacy and consistency of HIA+ ligands in H1R inhibition can be enhanced. Among 69 BBB- ligands, 10 were predicted as HIA+ out of 50, as highlighted in Figure 2. The rationale for using BBB- ligands instead of ligands that are permeable to BBB (BBB+) is to minimize the potential adverse reactions in the CNS, like first-generation antihistamines. In contrast to first-generation antihistamines that may cause sedation, a second and third-generation antihistamine targets H1R in the PNS, thus causing fewer adverse reactions (Cevikbas & Lerner, 2020).

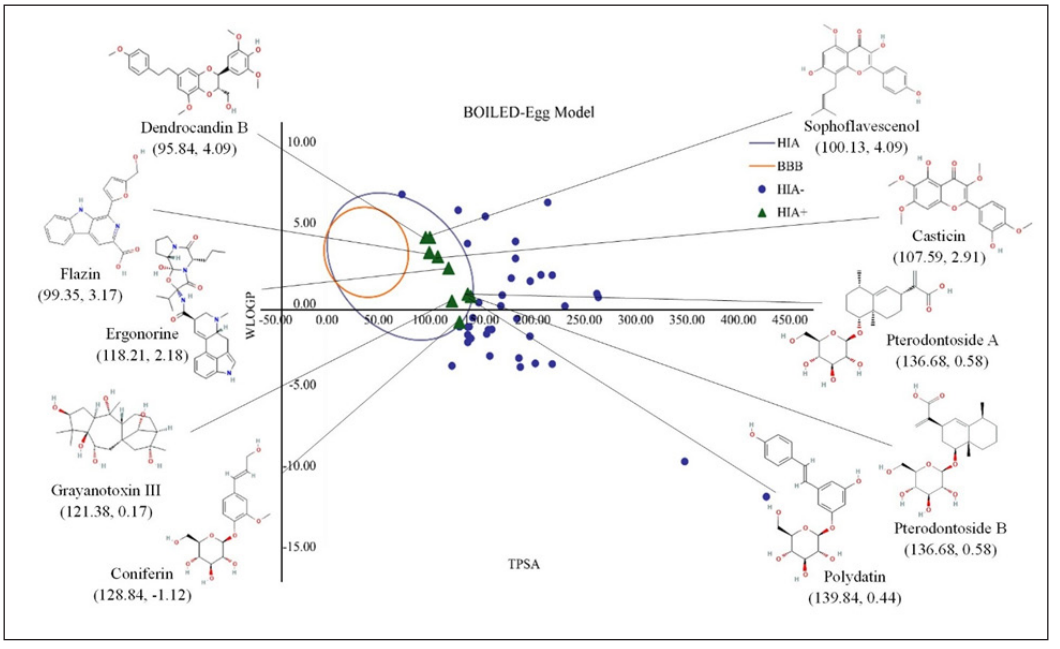

Figure 2. BOILED-Egg model was employed for HIA prediction and 2D structures of 10 HIA+ ligands at two sides of the model. A scatter plot shows the relationship between TPSA and Log P values for HIA+ and HIA- ligands, which are represented as triangle-shaped and bullet-shaped points, respectively. TPSA (x-axis) and WLOGP (y-axis) values for 10 HIA+ ligands are shown as coordinates beneath their respective structures

From the result, the TPSA of 10 ligands ranged from 95.84 to 139.84, whereas Log P ranged from -1.12 to 4.09. TPSA represents the surface of ligands that can interact with

the water molecules by forming hydrogen bonds, whereas Log P indicates the lipophilicity of a ligand. According to the findings, low TPSA and moderate Log P are preferred for a ligand to exhibit optimal intestinal membrane penetration (Ramirez et al., 2021). A lower TPSA value correlates with less interaction with the intestinal barrier, thus providing better membrane permeability and absorption across the phospholipid bilayer of the GI tract. From the perspective of lipophilicity, a moderate Log P value indicates that ligands that reach a balance between hydrophilicity and hydrophobicity are accessible to passive diffusion through the intestinal phospholipid bilayer and able to be soluble in the bloodstream after absorption (Chmiel et al., 2019).

Docking Analysis

In molecular docking, 10 HIA+ ligands were docked with H1R to obtain their binding affinities and binding conformation. The docking results with 0 in RMSD were tabulated in Table 1. During docking, it was observed that Polydatin (PD) has the highest binding affinity of -8.1 kcal/mol, followed by Sophoflavescenol with -7.9 kcal/mol. The binding affinity of Dendrocandin B and Flazin was recorded as -7.6 kcal/mol. The lowest binding affinity was -5.8 kcal/mol and -6.1 kcal/mol recorded by Pterodontoside A, Grayanotoxin III, and Pterodontoside B, respectively, as their binding site are not within the cavity. Other ligands also show good binding energy against H1R, suggesting their potential to be H1R antagonists. This work analyzed three ligands with the highest binding affinities based on their binding conformation, as visualized in Figure 3.

Table 1
Binding affinities of HIA ligands from the lowest to the highest binding energy

HIA+ ligands	Binding affinities (kcal/mol)
Polydatin	-8.1
Sophoflavescenol	-7.9
Dendrocandin B	-7.6
Flazin	-7.6
Coniferin	-7.4
Casticin	-7.1
Ergonorine	-6.2
Pterodontoside B	-6.1
Grayanotoxin III	-6.1
Pterodontoside A	-5.8

PD demonstrated the highest binding affinity among tested ligands, forming 11 interactions with H1R. These interactions included one unfavorable donor-donor interaction, one π-Anion, one π-Alkyl bond, three π-π T-shaped bonds, and five hydrogen bonds. Three hydrogen bonds were established between the hydroxyl group of phenol and ASN198, TYR458, and ILE454 with distances of 1.77Å, 2.76Å, and 2.80Å The cumulative effect of multiple hydrogen bonds bound to phenol contributes to structure stability because hydrogen bonds reinforce each other in the interaction (Shukla & Tripathi, 2020). The other two hydrogen bonds were found between terminal oxygen and LYS179 with distances of 1.78Å and 2.79Å. Lysine residue consists of a positively charged side chain, which can interact with negatively charged terminal oxygen, inducing a strong electrostatic force

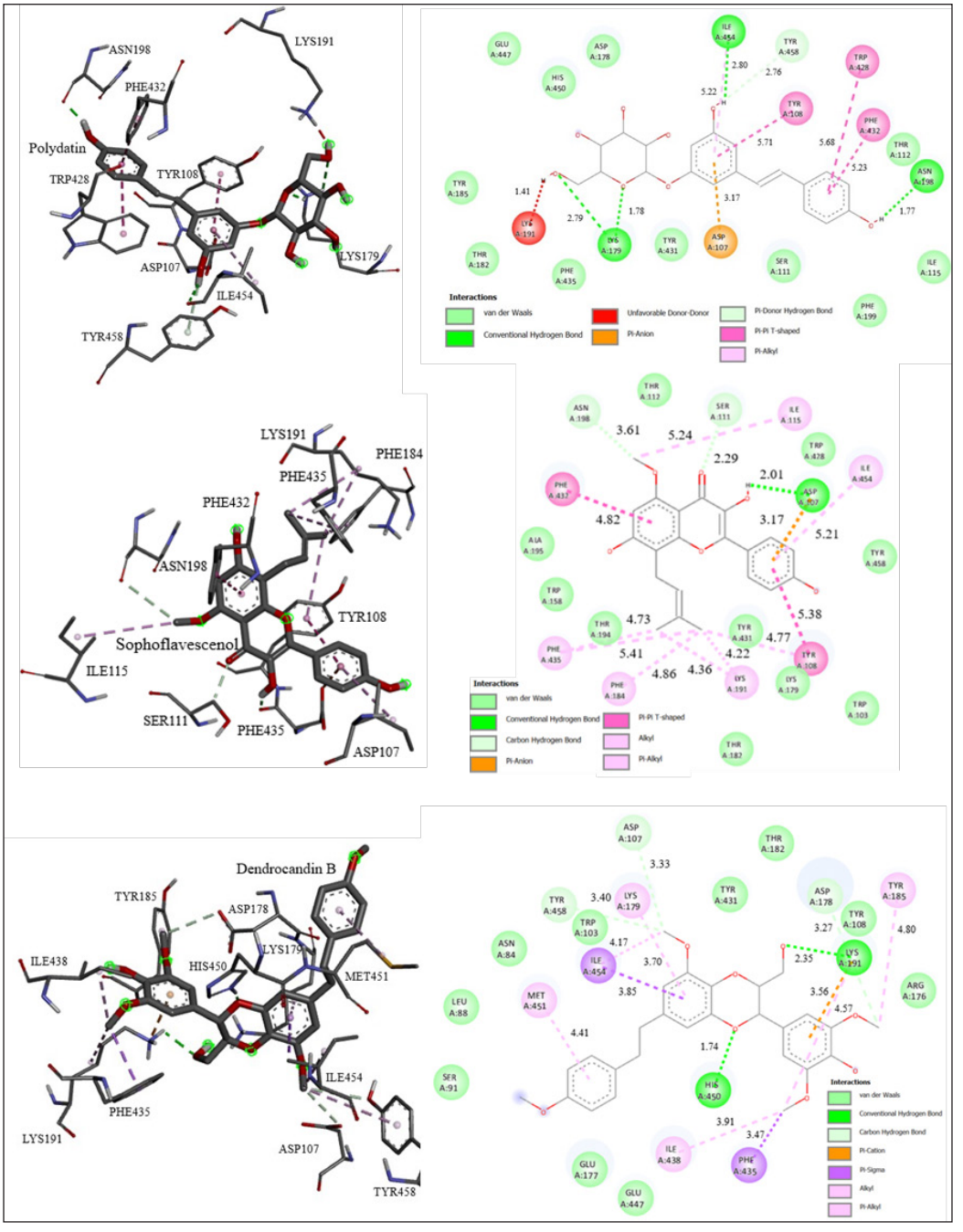

Figure 3. 3D and 2D view of H1R-ligand interaction for Polydatin (top), Sophoflavescenol (middle), and Dendrocandin B (bottom)

with a short bond distance (Dereka et al., 2021). π-π T-shaped interaction was observed between two phenol rings when approaching the H1R active site, interacting with TYR108, TRP428, and PHE432. Each distance was 5.23Å, 5.68Å, and 5.71Å, respectively. Other than π-π interaction, the phenol ring in the middle also interacts with the active site via the electrostatic bond, π-Anion with ASP107, and hydrophobic bond, π-Alkyl, yielding distances within 3.17Å and 5.22Å, respectively.

Previous studies have highlighted that PD, a resveratrol derivative with enhanced bioavailability, demonstrates its potential as a mast cell stabilizer. Unlike antihistamines, PD works as a mast cell stabilizer to inhibit the IgE-mediated allergic reaction. Depressing calcium influx in the mast cell can prevent degranulation, resulting in minimizing histamine release upon mast cell activation (Karami et al., 2022). This study suggest that PD can also function as an H1R antagonist as it exhibits the highest binding affinity amongst BBB-ligands in Kelulut Honey while interacting with prominent residues involved in the H1R histamine binding pattern. Additionally, PD has demonstrated anti-inflammatory properties that reduce inflammation. It makes PD an interesting candidate for a dual mechanism of action similar to a second-generation antihistamine, olopatadine, which acts as a mast cell stabilizer and selectively antagonizes H1R (Kaliner et al., 2010; Tamura et al., 2004). In short, PD has the potential for a dual mechanism of action, which allows it to stabilize most cells and block the binding of histamine in H1R.

The docking of Sophoflavescenol and H1R with the binding affinity of -7.9 kcal/mol showed 14 interactions, including 11 non-bond interactions and three hydrogen bonds. Among non-bond interactions, four π-alkyl were found in the terminal aliphatic chain and one within a benzene ring. Other than hydrophobic interaction, π-Anion also formed between ASP107 and the benzene ring. As the structure of Sophoflavescenol consists of two aromatic rings, π-π T-shaped is formed between two benzene rings with TYR108 and PHE432, respectively. The longest distance of these non-bond interactions was 5.41Å, whereas the shortest distance was 3.17Å. Nevertheless, the strongest interactions were contributed by hydrogen bonds between ligands with ASP107, SER111, and ASN198 at the distances 2.01Å, 2.29Å, and 3.61Å, respectively.

Sophoflavescenol is a flavonoid consisting of two aromatic rings connected by a heterocyclic ring, which is known for diverse pharmacological properties, including antioxidant and anti-inflammatory activities (Hamad, 2023). Previous studies indicate that flavonoids exhibit the potential to inhibit histamine release. For instance, quercetin and luteolin demonstrate the advantage of suppressing the release of pro-inflammatory mediators, including histamine, from human mast cells instead of inhibiting H1R because of low binding affinity compared to known antihistamines (Rakha et al., 2022). Thereby, it is reasonable to hypothesize that Sophoflavescenol can suppress the mast cell from releasing histamine due to structural similarity. From the perspective of binding interaction, unlike

other flavonoids, the presence of hydrophobic interactions towards terminal aliphatic chains in Sophoflavescenol contributes to the efficient packing of the structure within the binding site. Empty spaces between aliphatic chains and aromatic rings within the binding site were minimized to stabilize the structural conformation (Xiao & Woods, 2023). With that, the conformational flexibility of the structure can be minimized to become more specific and stable in the interaction, highlighting the possibility of Sophoflavescenol comparatively inhibiting H1R.

The interaction between Dendrocandin B and the H1R active site was recorded as -7.6 kcal/mol with 14 interactions. ASP107, ASP178, LYS191, HIS450, and TYR458 contributed five hydrogen bonds. Each distance from the longest to the shortest was 3.40Å, 3.33Å, 3.27Å, 2.35Å, and 1.74Å. Furthermore, nine non-bond interactions were observed during molecular docking. One electrostatic bond was recorded as a π-Cation interaction between LYS191 and the benzene ring. Meanwhile, four π-alkyl hydrophobic bonds were observed, and the distance ranged from 3.70Å to 4.80Å. Unlike PD and Sophoflavescenol, Dendrocandin B consists of two π-Sigma interactions with residue PHE435 and ILE454 at 3.47Å and 3.85Å, respectively, instead of π-π T-shaped, which have slightly stronger interactions in terms of binding distances. Dendrocandin B is a bibenzyl derivative commonly extracted from the *Dendrobium* species. Previous studies indicate that compounds extracted from *Dendrobium* species possess anti-inflammatory and anti-allergic properties (Wu et al., 2014). Nonetheless, there is a lack of studies that have directly examined the anti-allergic activity of Dendrocandin B on H1R. Since the interactions with H1R highlight the high binding affinity towards H1R among BBB-ligands, extensive studies are necessary to investigate the pharmacological activities, particularly anti-allergic properties, of Dendrocandin B.

Based on docking results, Sophoflavescenol and Dendrocandin B bind to prominent residues in extracellular domains extending from TM, demonstrating their potential to block histamine binding and inhibit histamine-mediated reactions. In summary, this study identifies Polydatin, Sophoflavescenol, and Dendrocandin B as potential natural H1R antagonists with strong binding affinity, with Polydatin and Sophoflavescenol also showing potential dual action as mast cell stabilizers to inhibit histamine release (Ye et al., 2017). Most observed bonding was non-covalent, involving interactions requiring lower energy. However, the combination of various non-covalent bonds, such as hydrogen bonds, electrostatic interactions, hydrophobic forces, and van der Waals forces, plays a significant role in determining the strength and stability of the interaction between ligands and the protein (Adhav & Saikrishnan, 2023; Chaubah et al., 2019). It enables the ligands to occupy binding sites within the active site, preventing histamine from binding and triggering signaling pathways that lead to allergic reactions. These findings suggest a natural alternative from Kelulut honey to synthetic antihistamines in allergy treatments.

CONCLUSION

This study employed a comprehensive approach involving molecular docking and the BOILED-Egg model for HIA prediction to identify potential H1R competitive antagonists from the ligands presented in Malaysian Kelulut Honey. Among 69 BBB- compounds, Polydatin, Sophoflavescenol, and Dendrocandin B exhibit the highest binding affinity with the optimal bioavailability profile. The docking results revealed the interactions between identified ligands and critical residues, including ASP107, TYR108, ASN198, PHE435, and TYR458, with the H1R active site. These ligands formed multiple non-covalent interactions such as hydrogen bonds, ionic bonds, π interactions, and van der Waals interactions, suggesting their capabilities to competitively bind to the identified active site.

However, further studies are required prior to the *in-vitro* and *in-vivo* assessment to ensure the efficacy and effectiveness of these ligands to discover the ligands with optimal antagonist profiles and minimum adverse reaction when having antagonism interactions with H1R. It is recommended that machine learning techniques be implemented to identify H1R antagonists and address the gap in this study. By employing an automated workflow of machine learning, the time taken for analyzing protein-ligand interactions can be reduced by training the machine learning model using a dataset. In addition, consideration of physicochemical properties, including Lipinski's rule of five in predicting the binding affinity, can significantly improve the accuracy of the docking analysis.

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