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Original Article

VIRTUAL TARGET CONSTRUCTION FOR DISCOVERY OF HUMAN HISTAMINE H_4 RECEPTOR LIGANDS EMPLOYING A STRUCTURE-BASED VIRTUAL SCREENING APPROACH

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ABSTRACT

Objective: This study aimed to construct a virtual target to be used in structure-based virtual screening (SBVS) campaigns to discover ligands for human histamine receptor H_4 ($hHRH_4$).

Methods: The virtual targets construction was initiated by $hHRH_4$ homology modeling, followed by molecular docking of seliforant to the homolog model, and the virtual target candidate was constructed. The hHRH4 complexed to seliforant was subjected to molecular dynamics (MD) simulations in 100 ns. Finally, the pose with the least free energy of binding from the MD simulations was selected for further validation through re-docking simulations. All simulations were conducted by using the YASARA-Structure program package.

Results: This study resulted in one validated target for SBVS protocols development. All RMSD values in the internal validation in snapshot 519 molecular dynamics simulation results were less than 2 Å, and this hHRH4 homology model is valid as a virtual target in an SBVS protocol. Moreover, using the clusterization module on MD simulations analysis, ten different virtual targets were available for further utilization.

Conclusion: Virtual targets resulted from this study offer more possibilities to construct SBVS protocols to identify hHRH4 ligands. The validated virtual target and the ten different virtual targets resulted from clusterization can be accessed in the following GitHub repository: https://github.com/nugrahagerry/hHRH4.

Keywords: Histamine H_4, Seliforant, SBVS, Homology modeling, Molecular docking, Molecular dynamics

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INTRODUCTION

Human histamine receptor H_4 ($hHRH_4$) is the target for inflammation and allergic therapy [1], such as joints inflammation [2], atopic dermatitis [3], intestines inflammation and digestive allergy [4], also involved with chronic conjunctivitis allergy [5]. Furthermore, the $hHRH_4$ antagonist affects important regulation of lung inflammation allergy [6]. Therefore, the JNJ38518168 antagonist is under Phase II clinical examination as a drug candidate for asthma and rheumatoid arthritis treatment [7].

This receptor antagonist inhibits heart remodeling, maintains contractility, and increases lifetime [8]. Furthermore, the $hHRH_4$ is involved in pruritus pathogenesis that regulates microglia activity [9], giving a new target to inhibit Parkinson's disease (PD) development [10]. In addition, the histamine H_4 receptor inhibits cytokine being released in microglia cells [11], immune cells in the central nerves system related to various neurodegenerative diseases such as ischemic stroke and Alzheimer's disorder (AD) [12]. The receptor expresses a potential therapeutic target for inflammation and autoimmune diseases [13]. The $hHRH_4$ is essential in tumor development [14], became the target for cancer and immune cell treatments [15], and increases brain-derived neurotrophic factor (BDNF) in the primary cortical neuron [16].

Several $hHRH_4$ antagonists have reached clinical evaluation, but concerns about the potential for compound-specific toxicity cause premature termination of further studies [17]. Seliforant, a selective $hHRH_4$ antagonist, is well tolerated and binds highly to animal and human receptors. Seliforant has entered phase II clinical trials and is selective for $hHRH_4$ over histamine H_1, histamine H_2, and histamine H_3 receptors [18], providing preclinical support for pharmacokinetics/pharmacodynamics modeling and selection of clinically effective drug concentrations [19]. With its excellent safety profile, seliforant is the first compound accepted for daily oral dosing and the only one so far to enter clinical trials [17].

Considering the importance of $hHRH_4$, especially on inflammation diseases, rheumatoid arthritis, asthma, dermatitis, and psoriasis [20], it is relevant to explore the main aspects of $hHRH_4$. Exploring the receptor as a target for therapy in the future involves the receptor's active site, molecular modeling, and ligand exploration [21]. The main strategy and one of the effective methods in computer-aided drug discovery is structure-based virtual screening (SBVS) [22]. This approach efficiently designs and discovers bioactive compound optimization [23]. Furthermore, SBVS is able to generate direction for advanced drug development [24], accurate structural modeling, activity prediction [25], projecting ligand binding pose, and estimate its affinity towards the target receptor [26].

The development of structure-based drug design and discovery has been hampered by the lack of a crystal structure for the target protein. Meanwhile, information about the 3D structure of proteins is essential for understanding ligand-receptor interactions [27]. Due to the limitations of experimental data, homology modeling is currently the best choice for obtaining structural information. The purpose of homology modeling is to predict the structure of the sequence with the same accuracy as the results obtained experimentally [21]. Furthermore, advances in computational technology, the development of modeling software, and the increasing number of known protein structures have developed homology modeling methods rapidly and reliably to obtain 3D coordinates of proteins [27].

The crystal structure of $hHRH_4$ is not publicly available. Hence, homology modeling is required to generate virtual targets. Therefore, this study is aimed to generate virtual targets in order to develop a screening protocol for $hHRH_4$ ligand identification, started with hHRH4 homology modeling and then followed by molecular docking of seliforant to the homolog model, molecular dynamics (MD) simulations for 100 ns, and validation of the selected virtual target through re-docking simulations.

MATERIALS AND METHODS

Materials

The main instrument used in this study was a Dell Precision T7910 workstation with Ubuntu 20.04.1 LTS version as the operating system (OS) installed with YASARA-Structure 21.8.27 version as the main software [28]. All settings in the software were left as default. Materials being used are the crystal structure of human histamine H_1 (PDB ID: 3RZE) [29, 30], the lead compound seliforant [31], and the $hHRH_4$ sequence [32]. The simulations performed in this research required the development of some macro files, which could be accessed at github.com/nugrahagerry/hHRH4 [33].

Methods

The $hHRH_4$ homology modeling

The $hHRH_4$ sequence HRH4_HUMAN was obtained from Uniprot [32] in the FASTA format and saved as hHRH4. fasta. Homology modeling was then conducted using the menu *Options>Choose experiment>Homology modeling* in the YASARA-Structure program package. The H_1 histamine receptor from Protein Data Bank [29] was used as the protein template and the hHRH4. fasta file was used as the sequence. The output from homology modeling was a YASARA object hHRH4_Model. yob. Energy minimization was carried out to the output file using the menu *Options>Choose experiment>Energy minimization*.

Molecular docking of the lead compound towards the hHRH4 homolog receptor

The preparation of the molecular docking of the lead compound to the hHRH4_Model. yob was conducted with the YASARA-Structure program package by employing the target_prep. mcr command on the hHRH4_Model. yob file. The preparation resulted in the file hHRH4_receptor. sce consisting of the homolog model with a simulation cell for docking simulations. Subsequently, molecular docking simulations of seliforant towards hHRH4_receptor. sce were conducted by utilizing the dock_run. mcr command resulted in the hHRH4. yob file, which was the complex of seliforant-hHRH4.

Molecular dynamics simulations

Molecular dynamics simulations were conducted using YASARA-Structure by employing the md_runmembrane. mcr command. Molecular dynamics simulations were carried out with the following parameters AMBER14 as the force field at pH 7.4 with temperature 298K and pressure at 1 bar. Simulations were conducted until 100 ns, and the snapshots from the simulation were stored at 100 ps intervals [21].

Internal validation of the homology model

A snapshot of the most stable binding free energy pose resulting from the molecular dynamics was selected and then being validated internally. Firstly, energy minimization was carried out with the menu *Options>Choose experiment>Energy minimization*. The target_prep. mcr command was subjected to the minimized complex, which resulted in the following output files: hHRH4_receptor. sce, hHRH4_ligand. yob, and hHRH4_ligandref. yob. The validation was subsequently conducted by docking the hHRH4_ligan. yob towards hHRH4_receptor. sce for 1000 times utilizing the dock_run_1000. mcr command with hHRH4_(0001-1000). yob as the output files. The root-mean-square deviation (RMSD) values of the docked ligand poses were calculated by comparing the docked poses with hHRH4_liganref. yob by utilizing the rmsd_calculation. mcr command, which resulted in the hHRH4 (0001-1000). rmsd. log files.

RESULTS AND DISCUSSION

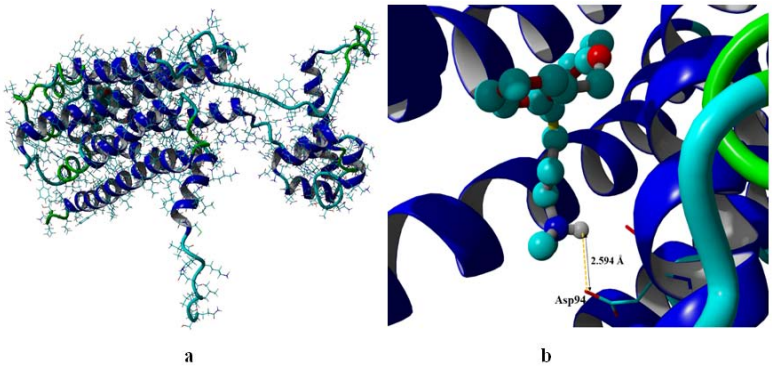
According to the Z-score parameter, five homologous models have been generated and sorted in the homology modeling (table 1). YASARA-Structure combined the models to obtain a hybrid model with an accuracy exceeding each contributor's (table 2). The visual assessment of hHRH4_Model. yob output (fig. 1a) as a hybrid model protein structure resulted from homology modeling showed the interaction of the native ligand with the active site of the receptor (fig. 1b).

Table 1: Structural model of homology modeling results

Rank	Z-score	Model ID	Original number	Comment
1	-0.764	3RZE_p05	5	Good
2	-0.777	3RZE_p03	3	Good
3	-0.894	3RZE_p02	2	Good
4	-0.971	3RZE_p01	1	Good
5	-1.034	3RZE_p04	4	Good

Table 2: Hybrid model of homology modeling results

Check type	Quality Z-score	Comment
Dihedrals	-0.156	Good
Packing 1D	0.201	Optimal
Packing 3D	-1.076	Satisfactory
Overall	-0.445	Good



a b

Fig. 1: The homology results structure of the hHRH4 hybrid model (a) and the hybrid model interaction of the ligand-hHRH4 (b)

Docking simulations of seliforant to the hHRH4 model with 25 iterations resulted in 3 proposed conformations (table 3). The visual assessment showed that confirmation number 3 formed a vital hydrogen bond between seliforant and Asp94 with a hydrogen bond distance of 2.06 Å (fig. 2). The free energy of binding of the complex was-6.7270 kcal/mol.

Table 3: Molecular docking results

Run	Binding energy [kcal/mol]	Contacting receptor residues
001	-6.9150	Asp94 Tyr95 Cys98 Thr99 Val102 Val146 Pro149 Phe168 Leu175 Thr178 Ser179 Glu182 Phe183
002	-6.8537	Trp316 Tyr319 Ser320 Thr323 Gln347
003	-6.7270	

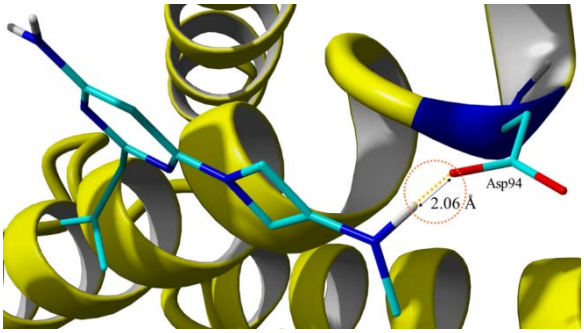


Fig. 2: Seliforant-Asp94 bond pose from docking simulation number 3

The MD simulations showed that the RMSD value remained constant after 2 ns. (fig. 3). The delta RMSD values were calculated at every 5 ns, and the data showed that most of the delta RMSD values are less than 1 (fig. 4). The free energy of binding calculation recognized the most stable system at the picosecond 519 (fig. 5), with the free binding energy of-8.430 kcal/mol. The energy minimization experiment was completed after 501 steps, and the final energy was-13681.901 kJ/mol. This system, therefore, was selected and further analyzed as a virtual target for validation.

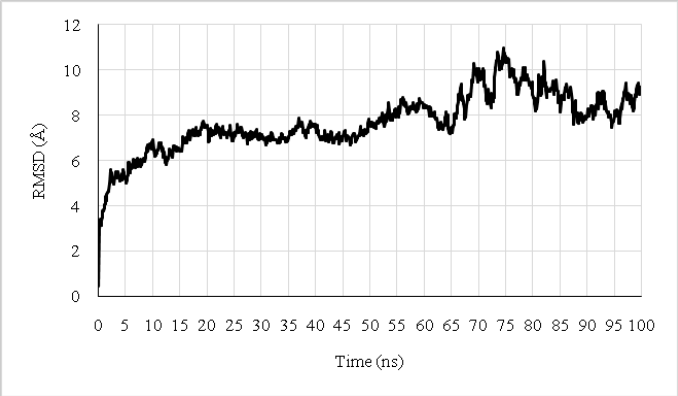


Fig. 3: RMSD (Å) vs. time (ns) graph

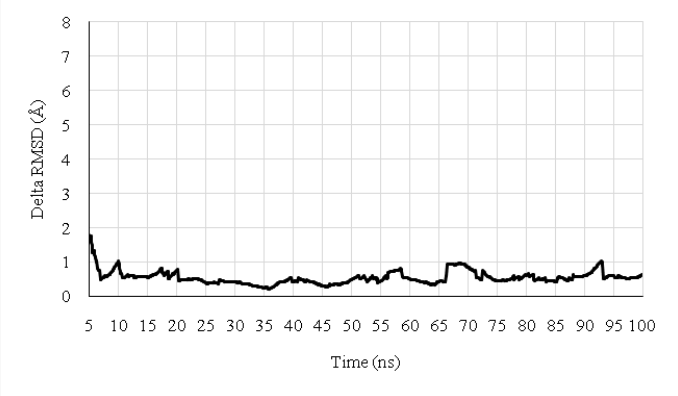


Fig. 4: Delta RMSD (Å) vs. time (ns) graph

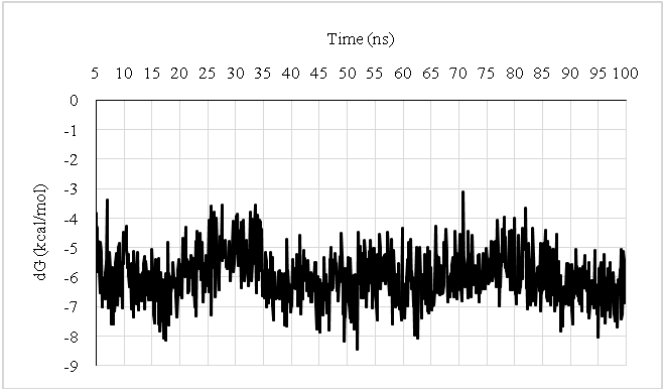


Fig. 5: The free binding energy (kcal/mol) vs. time (ns) graph

Internal validation with ligand-receptor re-docking 1000 times with 25 iterations resulted in 1000 data with RMSD values below 2 Å. Clustering of the molecular dynamics simulation resulted by setting the minimum RMSD value between clusters of 5 Å provided 10 clusters with an output of hHRH4_(cluster01-cluster10). yob.

The hHRH4 homology modeling

The 3D structure of the human histamine H1 receptor (hHRH1) consisting of 428 residues was used as the template because hHRH1 was the only receptor of the GPCR group (hHRH1-hHRH4) with the crystal structure publicly available. As a result, 319 of the 390 target residues (81.8%) were aligned with the template residues, resulting in 25.4% sequence identity and 48.9% sequence similarity. The level of sequence similarity with>25% similarity between the target and template indicates an excellent quality of homology results [34].

The homologous model ranking was adjusted for the Z-score parameter (table 1). The standard deviation of the model quality was compared with the 3D structure of the high-resolution X-ray results. The best parts of all homologous models were combined to obtain a hybrid model (fig. 1a), with the accuracy exceeding the individual contributors. From table. 2, it is known that the overall Z-score value is-0.319, indicating a good quality of the homology model result. The corresponding Z-score parameter is between-2 and 2. The structural section is considered poor if this parameter is not met because the geometry of the protein backbone deviates from what it should be [35]. The hydrogen bond distance between the native ligand and the amino acid Asp94 is 2.594 Å (fig. 1b). Thus, aspartic acid number 94 in hHRH4 is significant for histamine binding and is an essential anchor for ligands [36].

Molecular docking of seliforant to the hHRH4 homolog

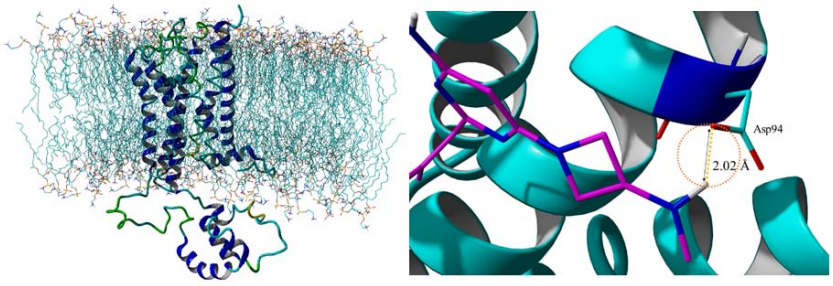
Seliforant docking was required to predict the structure of the ligand-receptor complex since molecular docking simulations could visualize the drug candidate's binding orientation with their target proteins, looking for possible affinities and activities [37]. The ranking on the docking simulations output of seliforant-hHRH4 was determined based on the best free binding energy, as shown in the table. 3. Visual assessment was necessary to confirm the formation of a vital bond between seliforant and the active receptor site, especially to the amino acid Asp94. Vital binding to Asp94 must be formed to generate a therapeutic effect as a histamine H4 antagonist [36]. Therefore, docking number 3 was chosen because it creates a bond with Asp 94. As a result, the binding free energy of the complex is-6.7270 kcal/mol. The Binding free energy value indicates the strength of the ligand-receptor interaction [38].

Molecular dynamics simulation of the seliforant-hHRH4 complex

Molecular dynamics simulation results were analyzed to obtain the RMSD and the free binding energy values. The obtained data show a stable system with the delta of the RMSD values of less than 2.0 Å during the production run [39]. Therefore, molecular dynamics simulation is acceptable if it generates an RMSD value less than 2.0 Å [40]. Therefore, this value is used to measure the stability of the structure during the simulation.

The analysis of the most stable system was carried out to examine the ligand-receptor binding mode. The free binding energy value calculation was required to evaluate the system's stability at a certain time interval. The most stable system was formed at 519 picosecond time intervals with the free energy of binding value-8.430 kcal/mol (fig. 6a). Thermodynamically, the interaction of ligands with receptors can occur if the resulted ligand-receptor complex has lower potential energy [41].

A hydrogen bond was formed between N atom number 6134 in the seliforant ligand and Asp94 residue based on visual observation. The bond distance between the atoms formed was 2.02 Å (fig. 6b). It is well known that hydrogen bonds can be formed if the distance between the donor and acceptor is ≤3.5 [40]. Energy minimization is required so that the structure resulting from MD simulation reaches its local minimum. The incorrect atomic geometry positions can be corrected, and the lowest potential energy was obtained for the system to make the confirmation of the system more stable.



a b

Fig. 6: a) The most stable system at the 519 picosecond time interval, b) Visual observation of the interaction between seliforant and Asp94

Internal validation hHRH4

The system in snapshot 519 was separated from the receptor structure and its ligand. Internal validation was carried out by re-docking the receptor-ligand 1000 times with 25 iterations. A total of 25,000 simulations were carried out. The re-docking ligand poses were compared with the reference ligand poses to see the reproducibility of the resulting virtual targets [42] by examining the RMSD values. All RMSD values in the re-docking simulations were less than 2 Å. Therefore, this hHRH4 homology model is valid as a virtual target in an SBVS protocol. This value represents the first step in developing a high-quality structure-based virtual screening protocol [42]. Furthermore, 10 more complexes are available from the clustering of molecular dynamics simulations to provide more virtual targets to develop structure-based screening campaigns further to discover hHRH4 ligands. Validated models and the clustered models can be accessed at https://github.com/nugrahagerry/hHRH4.

CONCLUSION

Homology modeling studies followed by molecular docking simulations and 100 ns molecular dynamics simulations resulted in a structure of human receptor histamine H4 complexed with seliforant as the ligand. This study's internal validated virtual target has offered a valid target to be employed in SBVS protocols to rapidly and accurately identify hHRH4 ligands. Additionally, by employing the clustering module of the results from MD simulations, ten different virtual targets are also available for further uses.

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Nil

AUTHORS CONTRIBUTIONS

G. N., M. M., and H. D. P. conceptualized the project; E. P. I. was in charge of software; G. N. was in charge of hardware and simulations; G. N. completed the original draft preparation of the manuscript; E. P. I., M. M., and H. D. P. reviewed and edited the manuscript. All authors have read and agreed to the published version of the manuscript.

CONFLICT OF INTERESTS

The authors declare no conflict of interest, financial or otherwise.

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