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In Silico Screening Inhibitors Histamine H_2 Chemical Compounds in Licorice Plants (*Glycyrrhiza glabra* L.) Using Autodock Vina

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Abstract
The inquiry about on in silico screening of chemical compounds of Histamine H_2 of Liquorice (Glycyrrhiza glabra L.*), aimed to get the potential bioactive compounds found in plants The Liquorice (Glycyrrhiza glabra* L.*) as a potential inhibitor Histamine H_2 with a screening in silico by Autodock Vina Docking process is carried out on enzyme Histamine H_2 as receptors and 105 chemical compounds in plants Liquorice (Glycyrrhiza glabra L.) as ligands using Autodock Vina program. ΔG_{bind} value and lowest RMSD of each compound that has been in the docking taken the value of the free energy change (ΔG) as a result of docking. Docking results showed that of the 105 chemical compounds of plant Liquorice (Glycyrrhiza glabra* L.*) are all potential as inhibitors Histamine H_2 with free energy change (ΔG) most low at Glabrene amounted to -9.6 kcal/mol, and the highest Isotachioside amounted to -4.5 kcal/mol.*

I. Introduction

Molecular docking is a computational technique used to investigate the binding interactions between small molecules (Jakhar *et al.*, 2020), such as compounds found in licorice root (*Glycyrrhiza glabra* L.), and specific target proteins, in this case, the H_2 receptors. The H_2 receptors are a type of histamine receptor found in the stomach, and they play a crucial role in regulating gastric acid secretion (Engevik, Kaji and Goldenring, 2020). Licorice root has been of interest for its potential as an H_2 receptor inhibitor, which could have applications in managing gastric conditions like acid reflux and ulcers (Roy *et al.*, 2023).

Glycyrrhizin is the primary bioactive compound in licorice root (Bell *et al.*, 2021). It is a triterpenoid saponin that has demonstrated anti-ulcer properties by inhibiting gastric acid secretion and protecting the gastric mucosa. Glycyrrhizin may interfere with the H_2 receptor's function, leading to reduced gastric acid production (Jain *et al.*, 2022). It is indeed possible that there are other compounds present in Licorice Root (*Glycyrrhiza glabra* L.) with similar inhibitory effects on H_2 receptors (de Lócio *et al.*, 2022). That's why research efforts are conducted, utilizing in silico methods, to explore the potential of such compounds.

In silico research involves computer-based simulations and computational modeling to analyze and predict the interactions between various molecules (Jabeen *et al.*, 2020), including those found in licorice root, and their target proteins, such as H_2 receptors. This approach allows researchers to efficiently screen a wide range of compounds and assess their potential for H_2 receptor inhibition without the need for extensive laboratory experiments (Wang *et al.*, 2023).

By employing in silico techniques like molecular docking and molecular dynamics simulations, scientists can identify promising candidate compounds within licorice root or even screen for potential compounds in other natural sources that may exhibit similar inhibitory effects on H_2 receptors (Donyapour, 2022). *In silico* research plays a crucial role in the exploration of licorice root's potential and the discovery of novel compounds that may have H_2 receptor inhibitory effects, furthering our understanding of the medicinal properties of this plant (Umashankar *et al.*, 2021). The goal is to expedite the discovery of new therapeutic agents or natural remedies for gastrointestinal disorders and related conditions.

II. Research Method

This research was conducted through an exploratory approach using the in silico method by performing docking using the Autodock Vina™ program. The materials used in this study were chemical compounds found in licorice root (*Glycyrrhiza glabra* L.), obtained from the "Jamu" KnapSack website, and the histamine H_2 enzyme

model with the code HRH2_HUMAN from the raptorx.uchicago.edu website in .PDB format. The tools used included free software VINA™, RaptorX website, HTML Takeout "Jamu" KnapSack, Asus® K43BY-VX039D Notebook with a 14-inch screen, AMD® E-series™ processor with E-450 CPU@1.6GHz, 2.00 GB RAM with 1333MHz memory speed (DDR3), ATI Radeon 1 GB graphics card, wireless type IEEE802.11b/g/n, and Windows 7 Ultimate operating system.

The sample preparation involved obtaining the HRH_2 protein structure from the Protein Data Bank (PDB) website using the keyword "HRH2" and then searching for "HRH2_HUMAN" with UniProt code P25021. After obtaining the sequence from UniProt, it was submitted to the RaptorX website for protein structure prediction. The resulting model was downloaded in .pdb format.

To prepare the protein for docking, water molecules and ligands were removed from the protein structure to eliminate interference during the docking process. This step was performed using the PMV (Python Molecule Viewer) software. The protein structure was then optimized using Autodocktools to adjust it to the docking environment. This optimization included adding or removing hydrogen atoms and setting grid box parameters for ligand binding (Najib *et al*., 2019).

The ligands were obtained from the "Jamu" KnapSack website in .mol format and were converted to .PDB files using the ArgusLab program. The optimization of ligands involved adding Gasteiger charges and setting the number of active torsions using Autodocktools in PMV.

The docking process was performed with Autodock Vina™, and a configuration file named 'conf.txt' was created to specify parameters such as the receptor, ligand, and grid box dimensions. The docking was executed through the Command Prompt. The process involved preparing protein and ligand structures, optimizing them for docking, and conducting the docking simulations using Autodock Vina™ (Tahir, Baharuddin and Najib, 2023).

The molecular docking analysis in this study includes the calculation of binding free energy (ΔGbind), Root Mean Square Deviation (RMSD), and ligand-protein residue interactions. The conformations of each docked ligand are ranked based on their ΔG_{bind} values, from the smallest to the largest. A lower ΔG_{bind} value indicates a more stable conformation, while a higher ΔG_{bind} value suggests less stability in the formed complex.

RMSD is a measure used to determine the success of binding mode predictions and is crucial for validating the docking program. A good RMSD value is typically ≤ 2 Å. Larger deviations indicate greater errors in predicting ligand-protein interactions. RMSD represents the difference between a ligand's conformation and its reference conformation. The RMSD values obtained for each ligand's docking in the best conformation are usually 0 because Vina compares each conformation to its own best conformation.

In addition to examining ΔG_{bind} values, interactions between the ligands and protein macromolecule residues are also analyzed. The identification of these interactions is performed using Autodocktools to visualize ligand-protein residue interactions and PyMOL to assess shape and volume compatibility between the ligand and the protein macromolecule. Protein residues are categorized into five types based on their amino acid structures: ionic, polar, aromatic, and hydrophobic. Ionic residues contribute the most to determining ΔG_{bind} values, followed by polar, aromatic, and hydrophobic residues, in that order.

III. Results and Discussion

Here is Table 1, which displays the docking results between chemical compounds from Licorice Root (*Glycyrrhiza glabra* L.) and Histamine H_2 receptor in kcal/mol.

Table 1. Docking results between chemical compounds from licorice root (*Glycyrrhiza glabra* L.) and histamine H_2 receptor

No.	Chemical Compounds	Free Energy (ΔG) (kcal/mol)	Note
1.	Glabrene C00009755	-9.6	(+)
2.	Shinpterocarpin C00018979	-9.6	(+)
3.	Glabrone (Euricarpin B) C00009434	-9.4	(+)
4.	[6",6"-Dimethylpyrano(2",3"-7,8)]-2'-hydroxy-4'-methoxy-3-arylcoumarin C00019376	-8.8	(+)
5.	Glyinflanin B C00007006	-8.8	(+)
6.	Kanzonol Y C00014617	-8.7	(+)
7.	Gancaonin H C00009923	-8.6	(+)
8.	Glycyrrhisoflavone C00020592	-8.6	(+)

9.	Glabrocoumarin C00031814	-8.5	(+)
10.	Licoagrochalcone B C00014469	-8.5	(+)
11.	Glabridin C00002529	-8.4	(+)
12.	Isoglabranin C00008171	-8.4	(+)
13.	3, 4 - Didehydroglabridin C00035925	-8.3	(+)
14.	Glyzaglabranin C00009399	-8.3	(+)
15.	Hispaglabridin B C00009735	-8.3	(+)
16.	Licoisoflavone A C00002542	-8.3	(+)
17.	Glyinflanin A C00007007	-8.2	(+)
18.	Phaseol C00010051	-8.2	(+)
19.	8-Prenyl-phaseollinisoflavan C00019389	-8.1	(+)
20.	Isovitexin C00001059	-8.1	(+)
21.	Licocoumarin A C00019315	-8.1	(+)
22.	4'-O-Methylglabridin C00009726	-8.0	(+)
23.	Licoagrodin C00014716	-8.0	(+)
24.	Liqoflavanone C00008451	-8.0	(+)
25.	Glycyrol Neoglycyrol C00009777	-7.9	(+)
26.	Hydroxywighteone C00009892	-7.9	(+)
27.	Kanzonol D C00004091	-7.9	(+)
28.	Licoricidin C00009739	-7.9	(+)
29.	Wighteone C00002586	-7.9	(+)
30.	Kanzonol V C00019466	-7.8	(+)
31.	Pinocembroside C00014304	-7.7	(+)
32.	Kanzonol W C00019316	-7.6	(+)
33.	Licochalcone A C00007057	-7.6	(+)
34.	Odoratin C00009407	-7.5	(+)
35.	Pinocembrin C00000992	-7.5	(+)
36.	Echinatin C00006922	-7.4	(+)
37.	Gancaonin G C00009888	-7.4	(+)
38.	Glycycoumarin C00010040	-7.4	(+)
39.	Licochalcone B C00006938	-7.4	(+)
40.	Licoisoflavone C00009557	-7.4	(+)
41.	Tachiogroside B C00019031	-7.4	(+)
42.	Glabranin C00000965	-7.3	(+)
43.	Glyinflanin G C00007097	-7.3	(+)
44.	Isoliuiritigenin C00006925	-7.3	(+)
45.	Genistein C00002526	-7.2	(+)
46.	Isomucronulatol C00009714	-7.2	(+)
47.	Kanzonol X C00019467	-7.2	(+)
48.	Licochalcone C C00007056	-7.2	(+)
49.	Galangin C00004533	-7.1	(+)
50.	Liquiritin C00008193	-7.1	(+)
51.	Ononin C00002553	-7.1	(+)
52.	Prunetin C00002564	-7.1	(+)
53.	7-Methoxy-2-methylisoflavone C00009381	-7.0	(+)
54.	Calycousin 7-O-Glucoside C00010087	-7.0	(+)
55.	Genkwanin C00001043	-7.0	(+)
56.	Glyzarin C00009396	-7.0	(+)

57.	Kanzonol Z C00014393	-7.0	(+)
58.	7-Hydroxy-2-methylisoflavone C00009379	-6.9	(+)
59.	Prunasin C00001454	-6.9	(+)
60.	3-Methyl-2-butenyl 6-O-alpha-L-arabinopyranosyl-beta-D-glucopyranoside C00019032	-6.8	(+)
61.	Glabrol C00008459	-6.8	(+)
62.	Folerogenin C00020493	-6.7	(+)
63.	Liquiritigenin C00000977	-6.7	(+)
64.	Shinflavanone C00014227	-6.7	(+)
65.	Hispaglabridin A C00002534	-6.6	(+)
66.	Tachioside C00019029	-6.6	(+)
67.	3-Hydroxyglabralol C00008611	-6.5	(+)
68.	Glabroisoflavone A C00031815	-6.5	(+)
69.	Naringenin C00000982	-6.5	(+)
70.	Glabroisoflavone B C00031816	-6.4	(+)
71.	Isoglycycoumarin C00010041	-6.4	(+)
72.	Kanzonol U C00019465	-6.4	(+)
73.	Tephrinone C00008177	-6.4	(+)
74.	3,2',4'-Trihydroxy-6",6"-dimethyl-3'-prenylpyrano[2",3"-4,5]chalcone C00007096	-6.3	(+)
75.	Glycyrrhitinic acid C00003521	-6.2	(+)
76.	Kanzonol T C00019474	-6.2	(+)
77.	Licoagrocarpin C00049208	-6.1	(+)
78.	Lycopyranocoumarin C00010042	-6.1	(+)
79.	3' Methoxyglabridin C00009730	-6.0	(+)
80.	7-Acetyloxy-2-methylisoflavone C00009395	-6.0	(+)
81.	Licoagroaurone C00014650	-6.0	(+)
82.	Licoagrochalcone A C00014456	-6.0	(+)
83.	Glycyrrhizin C00003522	-5.9	(+)
84.	Licoagrochalcone D C00014470	-5.9	(+)
85.	Licoisoflavone B C00009497	-5.9	(+)
86.	Formononetin C00002525	-5.8	(+)
87.	Kanzonol R C00019330	-5.7	(+)
88.	Licoagrochalcone C C00014487	-5.7	(+)
89.	Afrormosin C00002507	-5.6	(+)
90.	Licoagrone C00014673	-5.6	(+)
91.	Neoisoliquiritigenin (Neoisoliquiritin) C00007185	-5.4	(+)
92.	Afrormosin 7-O-(6'-malonylglucoside C00010169	-5.3	(+)
93.	Afrormosin 7-O-glucoside (Wistin) C00010093	-5.3	(+)
94.	Glyasperin M C00019475	-5.3	(+)
95.	Isoliquiritin C00007184	-5.3	(+)
96.	Isoschaftoside C00006381	-5.3	(+)
97.	Liquiritigenin 7-glucoside-4'-apiosyl-(1--2)-glucoside C00014309	-5.3	(+)
98.	Liquiritin apioside C00008195	-5.3	(+)
99.	Hirsutrin C00005373	-5.1	(+)
100.	Licoagroside A C00019028	-4.9	(+)
101.	Shaftoside C00006177	-4.9	(+)

102.	Rutin C00005413g	-4.8	(+)
103.	Vicenin 2 C00006229	-4.8	(+)
104.	Licuroside C00007186	-4.7	(+)
105.	Isotachioside C00019030	-4.5	(+)

Description: (-): Not active as an inhibitor of Histamine H_2; (+): Active as an inhibitor of Histamine H_2

The table provided (Table 1) presents the docking results between chemical compounds derived from Licorice Root (*Glycyrrhiza glabra* L.) and the Histamine H_2 receptor, measured in kcal/mol. Each row corresponds to a specific chemical compound, and the "Free Energy (ΔG)" column represents the binding energy of the compound with the receptor.

The docking results reveal the potential interactions between various chemical compounds found in Licorice Root and the Histamine H2 receptor. These interactions are crucial in understanding the inhibitory effects of these compounds on the receptor. Here are some key observations and discussions regarding the data; Binding Energies (ΔG):The binding energies, represented as ΔG values, indicate the strength of the interaction between each chemical compound and the Histamine H_2 receptor. A lower ΔG value suggests a more stable and favorable binding interaction. In this table, we observe a range of ΔG values, with the most negative values indicating stronger binding affinities. Active Compounds: Compounds with a "(+)" in the note column are considered active inhibitors of the Histamine H2 receptor. These compounds exhibit favorable binding interactions, as indicated by their low and negative ΔG values. Notable examples of active compounds include Glabrene, Shinpterocarpin, and Glabrone.

Variability in Binding Affinities: The data show that Licorice Root contains a diverse range of chemical compounds with varying binding affinities for the Histamine H2 receptor. Some compounds, such as Glabrene and Shinpterocarpin, exhibit strong binding interactions with ΔG values as low as -9.6 kcal/mol, suggesting their potential as effective inhibitors. On the other hand, compounds with less negative ΔG values may have weaker binding affinities.

Structural Diversity; Licorice Root contains a wide variety of chemical compounds, including flavonoids, coumarins, and isoflavones (Wahab *et al.,* 2021). The structural diversity of these compounds may contribute to differences in their binding affinities with the Histamine H_2 receptor.

Further Exploration: To gain a comprehensive understanding of the inhibitory potential of these compounds, it is essential to consider factors beyond binding energy, such as toxicity, bioavailability, and in vivo efficacy. Additionally, experimental validation is necessary to confirm the inhibitory effects of these compounds on the Histamine H_2 receptor. The docking results provide valuable insights into the potential of Licorice Root compounds as inhibitors of the Histamine H_2 receptor. Further research and experimental studies are needed to validate these findings and explore their therapeutic applications in treating conditions associated with Histamine H_2 receptor activation.

IV. Conclusions

The results of the docking analysis demonstrated that every one of the 105 chemical compounds found in Licorice (*Glycyrrhiza glabra* L.) can act as an inhibitor of Histamine H_2. Glabrene had the most favorable free energy change (ΔG) at -9.6 kcal/mol, while Isotachioside had the highest at -4.5 kcal/mol.

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