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"Unveiling the Dynamics: Interaction of 1NFK Receptor and Active Phytochemicals from BaelFruit"

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Abstract: The purpose of this work is to compare the hepatoprotective role of six active Phytochemicals of Bael—Marmelide, Marmenol, scoparone, 6,7-epoxyaurapetene, and Querectin catechin—as ligands. Techniques: using molecular docking to ascertain how a ligand interacts with its receptor. A lower docking score denotes a more stable protein binding. Findings: Through reacting with residues of amino acids HIS A64, Arg A56, GLY A66, ,ASN A136and HISA61 of the 1NFK receptor, marmelide, marmenol, scoparone, scopoletin, 6,7-epoxyaurapetene, and querectin catechin were found to have the potential to evolve as a heaptoprotective drug. Conclusions: HIS A64, Arg A56, GLY A66, ,ASN A136and HISA61 were amino acid residues implicated in ligand protein interactions according to molecular docking.

1. INTRODUCTION

The liver performs a staggering number of essential roles in the upkeep, operation, and control of the body's homeostasis. Nearly every metabolic process that leads to development, disease prevention, nutrition supply, energy production, and reproduction is impacted by it.[1] The metabolism of carbohydrates, proteins, and fats as well as detoxification, bile secretion, and vitamin storage are the liver's primary roles. Therefore, maintaining a functioning liver is essential to one's general health and wellbeing.[2] Hepatotoxicity is the term for liver damage caused by chemicals. Certain medications have the potential to harm an organ when used in excess or occasionally even when started within recommended dosage ranges. Hepatotoxicity can also be caused by other chemical agents, such as those employed in factories and labs, natural compounds (such microcystins), and herbal medicines.[4]

We refer to substances that harm the liver as hepatotoxins. Liver damage is the most frequent cause of drug withdrawals from the market, with over 900 medications linked to the condition. Subclinical liver damage caused by chemicals frequently only shows up as abnormal liver enzyme tests. Fifty percent of acute liver failures and five percent of hospital admissions are caused by drug-induced liver damage. Over 75% of idiosyncratic drug reaction cases end in liver transplantation or even death.[5]

These are Fruits of Bael's active ingredients [6-8]. It has been reported that marmelide effectively blocks the production of Hepatic processes

2. Material and Methods

2.1. lignd Preparation

The PubChem Database provided the ligands that were utilized in this investigation. Open Babel was used to convert six test compounds of Bael fruit and standard control compound structures (Silymarin) that were downloaded in the SDF format to the PDB format. Supplementary Figure 1 provides the ligands and their SDF structures (see supplementary information). The Auto Dock Tool was then used to assign the rotatable bonds and Gasteiger charges to the PDB ligands [9]. Every rotatable bond had unrestricted movement.

2.1.1. Preparation of protein structure

Based on the review of the literature, eight protein X-ray crystal structures were retrieved from the Protein Data Bank. Table 1 provides the proteins, their PDB structure identifiers, and the active site (see supplementary material). Co-crystallized ligands (X-ray ligand) were present in the binding sites of all the proteins. Each protein structure's ligand was taken out of the binding location and stored to a

different file. Swiss PDB was used to find and replace any missing atoms in each protein structure [10]. Next, the AutoDockTool was used to add the solvation term and the Gasteiger charges to the protein structure. Additionally, the objective functions that let us evaluate and select the most likely tautomer as well as the three-dimensional configurations of the ligand in the proper protonation state [11]. The Marmelide Docking simulation ligands included marmenol scoparone scopoletin 6,7-epoxyaurapetene, and querectin catechin.

2.1.2. **Protein-Ligand Docking:** AutoDock Tool was used to construct each protein's grid parameter file. A grid-box was made big enough to cover the entire protein binding site and allow all ligands to move freely in it. The number of grid points in the x, y, and z-axes was set to 20×20×20. The distance between two connecting grid points was 0.375 Å. For protein structures without ligands in the binding site, the center of the active binding site was determined from the structure and utilized as the grid-box's center. The center of the ligand in the X-ray crystal structure served as the grid-box's centre.

2.1.3. Simulation Docking

The active ingredients, marmelide, marmenol, scoparone, scopoletin, 6,7-epoxyaurapetene, and querectin catechin, were docked with the protein. You will see seven alternative ligand conformations that attach to the one NFK at varying energies once the docking process is complete. Ten conformations with the lowest score were selected for review and interpretation of the docking outcome data.

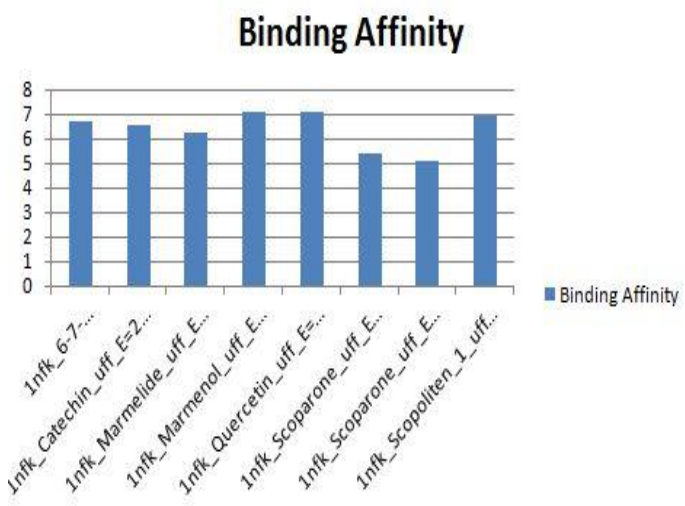


Figure 1: Docking score comparison of ligands on one NFK and test of ligand molecules. Please take note that the docking score displayed is the result of using the ligand binding protein with the lowest energy

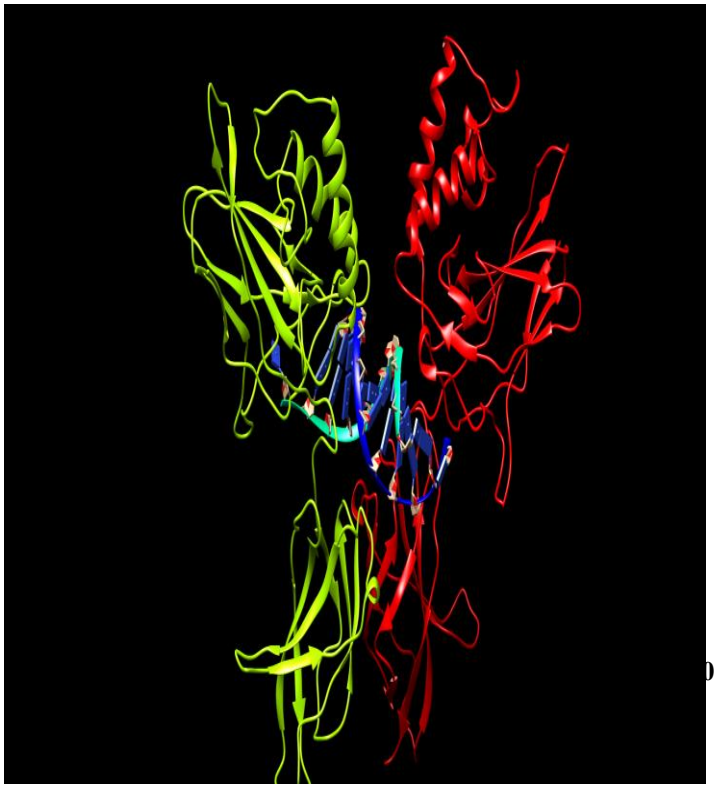


Figure 2: Basic Structure of 1NFK ligand-molecule interactions seen with the GLY A66, ASN A136, HISA61, Arg A56, and HIS A64 amino acid residues of the 1NFK receptor

3. RESULTS AND DISSCUSSION

The docking procedure utilized in this stage is similar to the validation step of the docking protocol; it involves docking each of the seven ligand conformations and performing a ligand comparison test on the previously generated protein. The following outcomes are displayed in (Figure), which was achieved by docking Marmelide Marmenol scoparone scopoletin 6,7-epoxyaurapetene Querectin catechin onto the 1 NFK receptor based on the docking score

According to the visualization results (Figures 2 and 3), the ligands (Marmelide, Marmenol, scoparone, scopoletin, 6,7-epoxyaurapetene, Querectin catechin) may interact with the histamine H1 receptor's amino acid residues HIS A64, Arg A56, GLY A66, ,ASN A136and HISA61 . They may also have distinct bond distances between each of these residues. Van der Waals forces and the formation of hydrogen bonds were anticipated based on those interactions. Figure 2 illustrates which amino acid residues—found in helices III, V, and VI—dominately participate in receptor-ligand interactions. HIS A64 and ARG A56are two amino acids that are critical for both GPCR activation and NFK receptor binding as antagonists, according to Shimamura et al. (2011) and Rahim (2010) [12, 13]. When comparing native ligands, ligands, and ligands to Asp107 and Trp428 at the distance of amino acid interaction, the natural ligand and ligand comparison had tighter bond distances (lower energy).Marmelide was found to be a highly effective inhibitor of hepatic process by suppression of Ca2+ absorption in a previous investigation[14]. Marmelide was also effective to prevent RBL-2H3 cells' extracellular Ca2+ influx and reduced hepatic process by more than 70% when compared to the control [15-16]. HIS A64, Arg A56, GLY A66, ASN A136, and HISA61 were the amino acid residues implicated in ligand protein interactions, according to molecular docking.

The docking studies suggested that low docking score have more potential regarding heaptoprotective activity[17]. According to Nugroho et al. (2011), marmelide functions as a competitive agonist for the 1NFK receptor. These findings demonstrated that marmelide.

Particularly when it comes to the INFK receptor, marmenol, scoparone, scopoletin 6,7-epoxyaurapetene, and querectin catechin have the potential to develop as heapatic relife activity [18].One of the most often used medications to treat hepatotoxicity is silymarin[19]. Moreover, it functions at the histamine H1 receptor as an inverse agonist [20]. Hepatoprotective effects are seen when drugs interact with Aegle Marmelos Correa's active ingredients.

The protein 1 NFK receptor's amino acids and ligand were shown to interact by virtual screening [21]. Although the 1 NFK receptor can bind a wide variety of amino acids, only a few specific amino acids— HIS A64, Arg

A56, GLY A66,ASN A136 and HISA61 —contribute to its hepatoprotective effects. HIS 64 and glya66 showed closer proximity distances to Marmelide than to (E, R)-Marmelide, according to the bond distance computation. On amino acids HIS A64, Arg A56, GLY A66,ASN A136 and HISA61.Marmelide had a distance of 1.72 angstrom, 3:36 angstrom, and 3:26 angstrom, respectively. On the other hand, the distances of (E, R)-Marmelide are 2.69, 3.85, and 4.97 angstroms, respectively.

The highest level of intrinsic activity was seen in the ligand that was most closely aligned with the receptor. Marmelide's proximity result shows that it required less energy (-109.4690) to bind to the histamine-1 receptor active site than did (E, R)-Marmelide (-102.2860). Marmenol, however, continued to exhibit more hepatoprotective efficacy than auraptene, scoparone, and skimmianine (E, R). These outcomes took into account both the docking score and the interaction distance between the ligand and the protein's active site. The reason for this was that the distances of histamine, auraptene, and skimmianine were greater than those of(E,R)-Marmelide

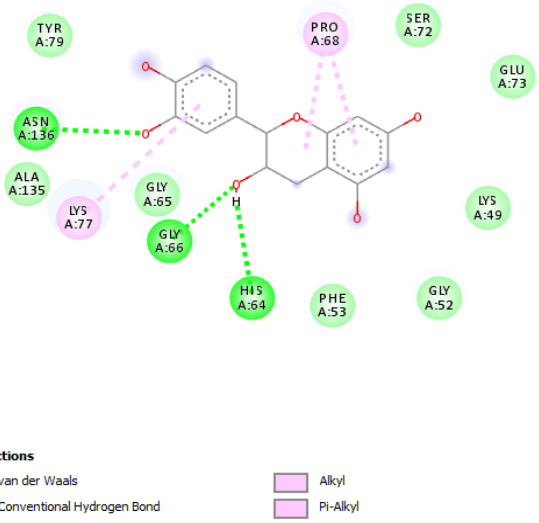
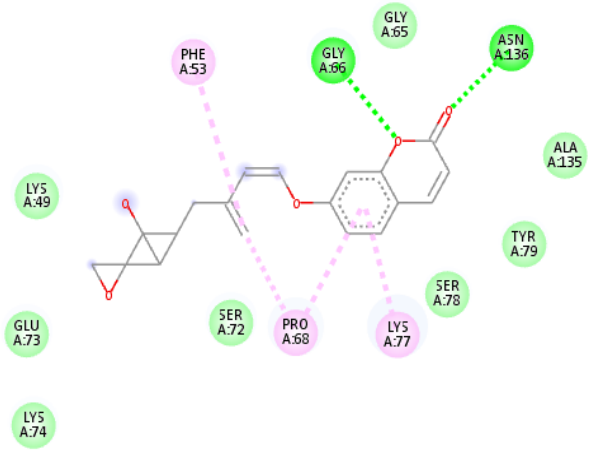
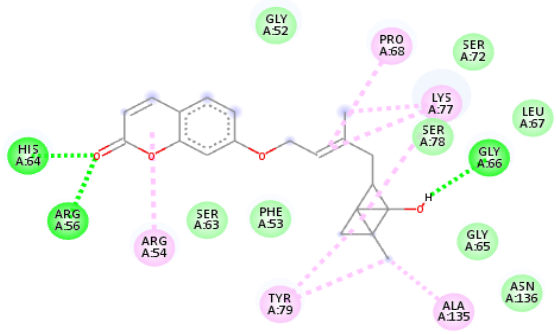


Fig. three compounds having maximum interaction





Ligand	Binding Affinity
1nfk_6-7-Epoxyaraptene_uff_E=3946.44	6.7
1nfk_Catechin_uff_E=203.65	6.5
1nfk_Marmelide_uff_E=372.01	6.2
1nfk_Marmenol_uff_E=4320.67	7.1
1nfk_Quercetin_uff_E=2214.99	7.1
1nfk_Scoparone_uff_E=132.36	5.4
1nfk_Scoparone_uff_E=132.36	5.1
1nfk_Scopoliten_1_uff_E=2122283315.16	6.9

4. CONCLUSION

Through their interactions with the 1NFK receptor, six active phytochemicals from Bael fruit—marmelide, marmenol, scoparone, scopoletin, 6,7-epoxyaurapetene, and quercetin catechin—have been shown in this study to have hepatoprotective potential. We discovered important amino acid residues (HIS A64, Arg A56, GLY A66, ASN A136, and HISA61) that are essential in the binding interactions between these phytochemicals and the 1NFK receptor by using molecular docking approaches. These interactions imply that these substances may help to stabilize the receptor, which may be a factor in their hepatoprotective benefits.

According to the docking experiments, ligands with lower docking scores had more persistent interactions and larger binding affinities, suggesting that they may be useful for hepatoprotection. Specifically, marmelide showed a strong suppression of hepatic processes, supporting earlier research on its ability to lower extracellular Ca2+ influx in hepatic cells.

Marmelide's medicinal potential was further highlighted by the binding affinity and proximity data, which indicated that it took less energy to bind to the active site than other compounds

The results, taken together, provide credence to the possible hepatoprotective properties of these powerful phytochemicals, particularly marmelide. Their potential to lessen hepatotoxicity is demonstrated by their capacity to bind with particular amino acid residues in the 1NFK receptor in an efficient manner. In order to verify their effectiveness and safety in human applications, future research should concentrate on in vivo studies and clinical trials

5. CONFLICT OF INTREST

The Authors declare no conflict of intrest finicial or otherwise.

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