IDENTIFICATION OF PROSPECTIVE NATURAL INHIBITORS AGAINST HUMAN HEPATOMA-DERIVED GROWTH FACTOR

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Article History: **Received:** 14.10.2023 **Revised:** 15.11.2023 **Accepted:** 14.12.2023

Abstract

Background: Hepatocellular carcinoma (HCC) poses a significant global health challenge, necessitating innovative therapeutic approaches. The human hepatoma-derived growth factor (hHDGF) has emerged as a crucial player in HCC progression, making it a potential target for inhibition. This study explores the inhibitory potential of various compounds against the hHDGF receptor complex, utilizing molecular docking simulations. **Methods:** A comprehensive in silico approach was employed, utilizing molecular docking simulations to assess the binding energies and interactions of compounds with the active site of hHDGF. In total of 17 ligands of natural compounds were selected based on their diverse chemical properties and structural characteristics. Comparative analyses were conducted against established compounds to identify potential lead candidates. **Results:** Rutin exhibited the most favorable binding energy within the active site of the hHDGF receptor complex, standing out as a lead candidate for inhibition. The superior binding energy indicates a robust interaction, suggesting rutin's potential as an effective hHDGF inhibitor. While rutin demonstrated the best binding energy, cautious interpretation is warranted, acknowledging the computational nature of molecular docking. Further experimental validations, including in vitro and in vivo studies, are essential to confirm rutin's inhibitory activity against hHDGF. **Conclusion:** The identification of rutin as a standout candidate underscores the significance of leveraging diverse natural compounds in drug discovery for HCC. Rutin's potential inhibitory activity against hHDGF opens avenues for further research, warranting detailed investigations into its mechanisms of action and therapeutic efficacy. The promising results of this molecular docking study pave the way for targeted experimental validations, advancing our understanding of rutin and its role as a potential inhibitor against hHDGF in the context of hepatocellular carcinoma.

Keywords: Hepatocellular carcinoma (HCC) ; hHDGF receptor complex ; molecular docking simulations ; rutin inhibition ; natural compounds

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DOI: 10.53555/ecb/2023.12.12.270

INTRODUCTION

Hepatocellular carcinoma (HCC) ranks among the most prevalent and lethal malignancies globally, representing a pressing public health challenge [1]. Despite advancements in therapeutic modalities, the limited efficacy of current treatments underscores the need for innovative approaches to combat this aggressive form of liver cancer [2, 3]. The human hepatoma-derived growth factor (hHDGF) has emerged as a significant contributor to HCC progression, presenting an attractive target for intervention [4].

The current treatment landscape for HCC includes surgical options, such as resection and liver transplantation, along with locoregional therapies like radiofrequency ablation and transarterial chemoembolization [5]. Systemic therapies, including tyrosine kinase inhibitors and immune checkpoint inhibitors, have also become integral components of HCC management [6]. However, the overall response rates and long-term outcomes remain limited, highlighting the urgency for novel therapeutic strategies.

The exploration and identification of natural inhibitors against hHDGF holds immense promise. Natural compounds, with their diverse and often multifaceted pharmacological properties, provide a rich source for potential therapeutic agents. Leveraging computational methodologies, particularly in silico approaches, offers a streamlined and efficient strategy for the identification of novel inhibitors, expediting the drug discovery process.

This study is driven by the imperative to enhance the current understanding of HCC therapeutics by focusing on the exploration of natural compounds as potential inhibitors against hHDGF. By employing in silico methods, we aim to elucidate the molecular interactions between bioactive

compounds and hHDGF, ultimately contributing to the identification of promising candidates for further experimental validation. Through this comprehensive approach, our study seeks to pave the way for the development of targeted and efficacious therapies to address the challenges posed by HCC and its associated molecular factors.

MATERIALS AND METHODS

Materials

The receptor complex of human hepatoma-derived growth factor (hHDGF) was obtained from the Protein Data Bank Repository (PDB) with the identifier: 5XSK [7]. The corresponding files, in .pdb format, were downloaded. Additionally, a 3D file conformer of the commercial drug sorafenib, MPD original ligand and 16 ligand files including: 10-hydroxydecanoic acid, apigenin, artepillin C, chrysin, daidzein, galangin, genistin, hydrogen peroxide, kaempferol, luteolin, methylglyoxal, naringenin, pinocembrin, quercetin, rutin were downloaded from PubChem [8]. These ligand files were in .sdf format.

Protein Preparation and Virtual Screening

After utilizing Discovery Studio Visualizer [10] to eliminate initial ligands and water molecules, the protein's .pdb files undergo a series of essential steps to facilitate molecular docking with PyRx [9]. These steps encompass acquiring the protein structure in a suitable format, importing it into PyRx, excluding water molecules, supplementing missing residues as needed, introducing hydrogen atoms, assigning atom types, optimizing the structure, and ultimately saving the meticulously prepared protein structure. Adhering to this procedural framework ensures that researchers adequately ready their protein structures for precise and dependable docking simulations.

Molecular Docking

The PyRx Tools software was utilized to prepare both the protein and ligand, converting them into .pdbqt format. To This analysis employed Pyrx's gridbox tool to define the receptor docking region for molecular docking. Figure 2 depicted the binding energy and 3D interactions between the human hepatoma-derived growth factor (hHDGF) and the investigated ligand inhibitors. gypsogenin emerged as the compound with the most favorable binding affinity among the initiate molecular docking simulations, follow these steps: Commence by acquiring the protein structure from a database such as the Protein Data Bank (PDB) and import it into PyRx. Prepare the protein by eliminating water molecules, addressing missing residues, and introducing hydrogen atoms. Optionally, assign atom types and optimize the structure for heightened accuracy. Save the meticulously prepared protein structure in either PDB or PDBQT format. Subsequently, procure the ligand structure from a chemical database or generate it computationally, ensuring compatibility with PDB or SDF formats. Import the ligand into PyRx, add hydrogen atoms if necessary, assign atom types, and convert it to PDBQT format if required. Save the prepared ligand structure also in pdbqt format. The binding energy (ΔG) value was employed to quantify the intensity of interaction between the ligand and the target in the process of molecular docking. The calculation of inhibition constants (Ki) entailed assessing the strength of binding between a ligand and a target receptor. This assessment was accomplished through the utilization of the formula:

$$Ki = e^{-RT/\Delta G}$$

Protein and Ligand Interaction

The generation of docking data for both the protein and ligand was conducted in accordance with .pdb files. The PyRx program was utilized to seamlessly integrate the data, ensuring a uniform and cohesive representation for subsequent analyses. Additionally, PyMOL was employed for a systematic 3D visualization, facilitating a detailed examination of spatial arrangements, binding interfaces, and conformational changes [10].

RESULTS

Protein and Ligand Interaction

In total of 19 compounds were tested, demonstrating promising potential for further investigation. Notably, the docking process was validated using the original ligand (ligand EVR) obtained from the protein-ligand complex 3D structure, confirming the accuracy of the simulations (Figure 1).

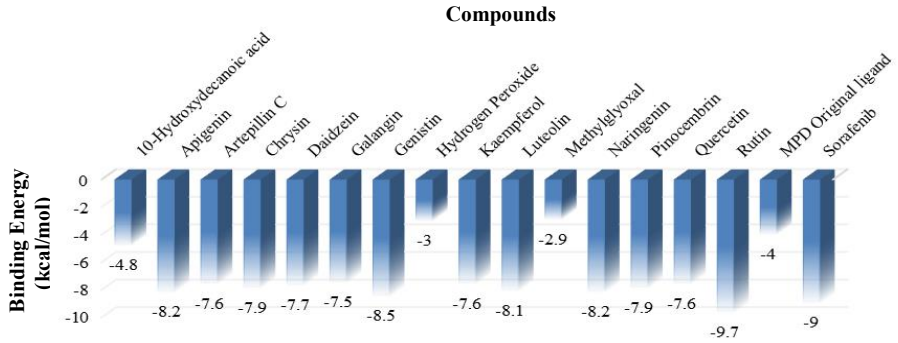

Figure 1: Binding energy between natural compounds and human hepatoma-derived growth factor (hHDGF).

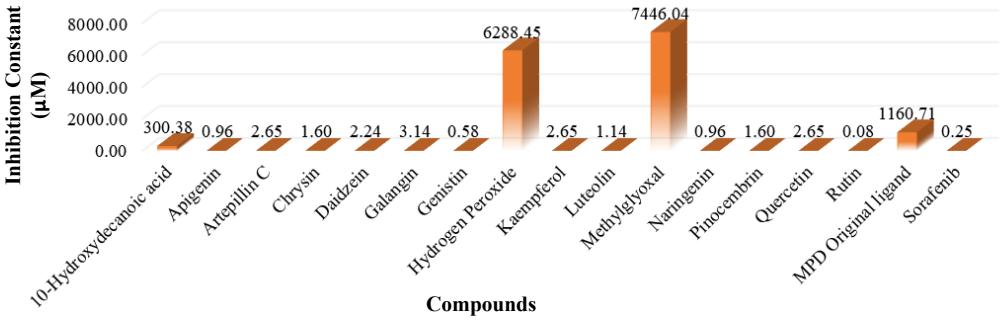

Figure 2: Inhibition constant of natural compounds towards human hepatoma-derived growth factor (hHDGF).

Figures 3 and 4 provided a comprehensive 2D and 3D visualizations, respectively of the interaction complex involving human hepatoma-derived growth factor (hHDGF) and two distinct compounds: rutin and sorafenib, in comparison to the original ligand. The figure serves as a visual representation of the molecular interactions at a detailed level, shedding light on the binding patterns and structural nuances of these interactions. In Figures 3A and 4A, the interaction between hHDGF and Rutin was depicted, showcasing the spatial arrangement and bonding between the two entities. The visualization helps elucidate how rutin interacts with specific binding sites on hHDGF, offering insights into the potential pharmacological implications of this interaction. Figures 3B and 4B performed the interaction between hHDGF and sorafenib, a known pharmaceutical drug. This visualization provides a comparative analysis of the binding characteristics between Sorafenib and hHDGF in relation to Rutin, highlighting any differences or similarities in their binding profiles. Understanding these interactions is crucial for assessing the potential therapeutic impact of Sorafenib on hHDGF. Lastly, in Figures 3C and 4C, the figure includes the interaction between hHDGF and the original ligand. This serves as a reference point, allowing for a comparison with the interactions observed with Rutin and Sorafenib. By visualizing the original ligand binding, researchers can discern any deviations or enhancements in the binding patterns introduced by rutin or sorafenib.

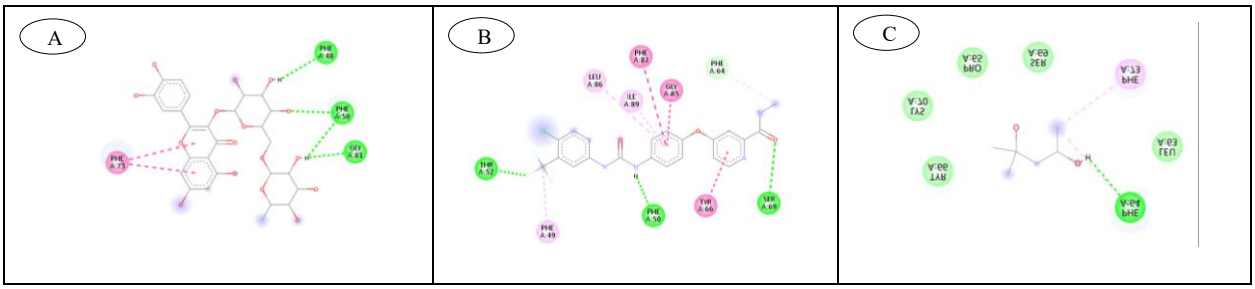

Figure 3: The 2D visualization of interactions complex between: A human hepatoma-derived growth factor (hHDGF) and Rutin; B. hHDGF and Sorafenib drug; hHDGF and the original ligand.

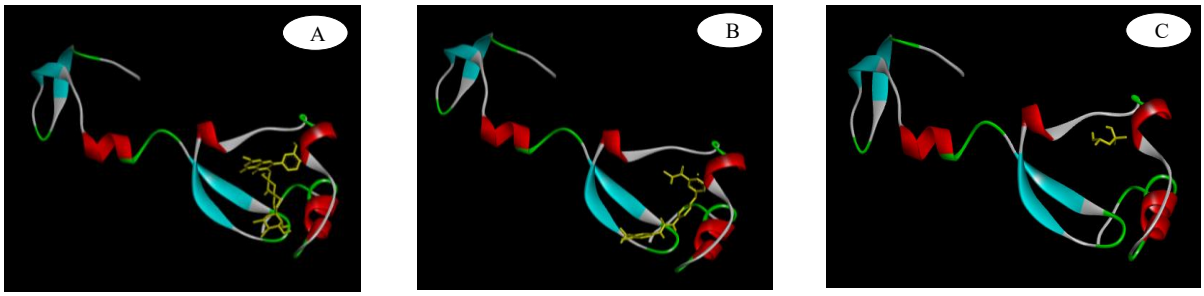

Figure 4: The 3D visualization of interactions complex between: A human hepatoma-derived growth factor (hHDGF) and Rutin; B. hHDGF and Sorafenib drug; hHDGF and the original ligand.

DISCUSSION

The molecular docking results of the compounds against the receptor complex of human hepatoma-derived growth factor (hHDGF) have provided valuable insights into their potential as inhibitors. The hHDGF receptor complex, retrieved from the Protein Data Bank (PDB) with the identifier 5XSK, served as the structural foundation for this investigation [11]. The molecular docking analysis included a diverse set of ligands, ranging from a 3D conformer of the commercial drug sorafenib to natural compounds such as 10-hydroxydecanoic acid, apigenin, artepillin C, chrysin, daidzein, galangin, genistin, hydrogen peroxide, kaempferol, luteolin, methylglyoxal, naringenin, pinocembrin, quercetin, and rutin. Each ligand was downloaded from PubChem in .sdf format.

Among the tested compounds, rutin emerged as a standout candidate, exhibiting the most favorable binding energy within the active site of the hHDGF receptor complex. The superior binding energy of rutin suggests a robust interaction with the receptor, indicating its potential as an effective inhibitor against hHDGF. This finding is particularly noteworthy, as it highlights rutin's capacity to form stable and favorable molecular interactions within the binding pocket of the receptor, which is crucial for its inhibitory activity.

While rutin demonstrated the best binding energy, it is essential to interpret these results with caution. Molecular docking is a computational technique that provides valuable predictions but necessitates further experimental validation to confirm the actual inhibitory activity of rutin against hHDGF. In-depth in vitro and in vivo studies will be essential to corroborate the computational findings and assess the translational potential of rutin as a therapeutic agent for hepatocellular carcinoma.

Rutin, a flavonoid widely found in various plants, possesses several potential bioactive effects that have garnered interest in the field of health and medicine [11].

Rutin is recognized for its potent antioxidant properties. It scavenges free radicals and reactive oxygen species, thereby helping to protect cells from oxidative stress [12]. This antioxidant activity contributes to the prevention of cellular damage and may play a role in reducing the risk of chronic diseases associated with oxidative stress. Rutin has demonstrated anti-inflammatory effects by modulating various inflammatory pathways. It may inhibit the production of inflammatory mediators, potentially providing relief in conditions characterized by chronic inflammation. Rutin has been associated with cardiovascular health benefits. It may help in maintaining healthy blood vessels, reducing the risk of cardiovascular diseases [13]. Rutin's potential to lower blood pressure and improve circulation contributes to its cardioprotective effects [14]. Some studies suggest that rutin may have anticancer properties [15, 16]. It has demonstrated inhibitory effects on the growth of certain cancer cells and may induce apoptosis (programmed cell death) in cancer cells [17]. However, further research is needed to fully understand its efficacy and potential applications in cancer treatment. Rutin has shown promise in protecting the nervous system. It may have neuroprotective effects by scavenging free radicals, reducing inflammation, and promoting neuronal survival [18]. These properties suggest a potential role in the prevention or management of neurodegenerative diseases. Rutin exhibits antimicrobial properties, demonstrating inhibitory effects against various pathogens, including bacteria and fungi [19]. This antimicrobial activity suggests potential applications in combating microbial infections. Rutin may have beneficial effects in managing diabetes. It has been reported to improve insulin sensitivity, regulate blood glucose levels, and reduce complications associated with diabetes [20]. These effects contribute to its potential role in diabetes management.

The identification of rutin as a lead candidate underscores the significance of employing diverse natural compounds in drug discovery endeavors. Rutin's potential inhibitory activity against hHDGF opens avenues for further research, warranting detailed investigations into its mechanisms of action and therapeutic efficacy. The promising results of this molecular docking study pave the way for targeted experimental validations, advancing our understanding of rutin and its role as a potential inhibitor against hHDGF in particular hepatocellular carcinoma.

CONCLUSION

In conclusion, the molecular docking analysis of various compounds against the receptor complex of human hepatoma-derived growth factor (hHDGF) has provided valuable insights into their potential as inhibitors. Utilizing the hHDGF receptor complex obtained from the Protein Data Bank (PDB), this study encompassed a diverse range of ligands, including both a 3D conformer of the commercial drug sorafenib and natural compounds sourced from PubChem. Among the tested compounds, rutin emerged as a standout candidate, exhibiting the most favorable binding energy within the active site of the hHDGF receptor complex. This superior binding energy suggests a robust interaction, emphasizing rutin's potential as an effective inhibitor against hHDGF.

ACKNOWLEDGEMENT

We would like to acknowledge the invaluable support of the Institute for Research and Community Development Unika Atma Jaya, the Directorate of Research and Development UI, and the Institute for Research and Community Service UNAS.

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