ORIGINAL PAPER

INTERACTION BETWEEN FOOD SUPPLEMENTS AND DRUGS USING MOLECULAR DOCKING

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Abstract. *This study aims to reveal significant interactions between dietary supplements and pharmaceuticals (Imatinib) with the CYP3A4 receptor using the HEX 8.0 docking program. Binding energy serves as a metric for gauging the strength and stability of these interactions. In the case of Imatinib, a robust connection with CYP3A4 is observed, while associations with Naringin and Naringenin result in decreased binding energy, signifying heightened drug metabolism in the presence of these supplements. These findings underscore the critical importance of comprehending food-drug interactions and the potential adjustments in systemic bioavailability and drug pharmacokinetics. Interactions with CYP3A4 can significantly impact treatment efficacy and safety. Factors such as dietary habits and supplement intake can influence these interactions. Consequently, a comprehensive understanding and vigilant monitoring of these dynamics are imperative to ensure appropriate and safe therapeutic regimens.*

Keywords: *Molecular docking; imatinib; naringin; naringenin; hyperforin.*

1. INTRODUCTION

In the realm of drug development, one often overlooked but critical factor that can significantly impact the success of new drug candidates is the role of food. The interaction between dietary substances and oral drugs presents a formidable challenge in the pharmaceutical world [1]. This challenge arises from a complex interplay of factors, ranging from the intrinsic characteristics of the drug itself to the dynamic changes occurring in the gastrointestinal tract post-meal consumption [2].

Understanding the influence of dietary components on drug disposition has become an essential pursuit in modern pharmacology. It involves examining how various elements in our diet can affect crucial processes, such as the activity of intestinal enzymes, conjugation reactions, and the function of transport proteins.

These dietary substances, often derived from botanical sources, have shown their potential to enhance or hinder drug absorption and distribution in laboratory settings. However, translating these findings from the lab bench to the patient's bedside has proven to be challenging. To determine how dietary substances alter pharmacokinetics (PK) and

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pharmacodynamics (PD) outcomes, it is imperative to delve deeper into the mechanisms at play [3]. Such knowledge is vital not only for assessing clinical significance but also for devising effective management strategies. Predicting the PK properties of new drug candidates entering clinical trials is a daunting task. The challenge becomes even more formidable when is taking into consideration the complexity of food effects [4]. Unfortunately, robust guidelines for evaluating potential interactions between dietary substances and drugs are currently lacking.

Clinical studies often yield inconclusive results and can be challenging to compare, making it difficult to establish definitive clinical and regulatory recommendations. In this landscape, modeling, and simulation software offers a quantitative approach to predicting potential interactions between dietary substances and drugs [5, 6]. However, the key to predictive success lies in a comprehensive understanding of the specific bioactive components within dietary substances, acting as marker compounds to guide appropriate clinical trial design.

On the other hand, this research aims to provide an up-to-date exploration of the intricate world of dietary substance–drug interactions [7]. This study addresses the challenges and potential solutions in conducting and interpreting studies in this domain and sheds light on innovative in-silico strategies for predicting the effects of food on drug candidates. By delving into the complexities of this often-overlooked aspect of drug development [8], this research aims to contribute to a better understanding of how food impacts the success of promising new drug candidates.

Imatinib, a groundbreaking therapeutic agent, has revolutionized the cancer treatment landscape. This remarkable small molecule has played a pivotal role in managing various malignancies, particularly hematologic and solid tumors [9]. Imatinib's journey from laboratory discovery to a clinical blockbuster underscores the power of targeted therapy in the era of precision medicine. Imatinib, known by its trade name Gleevec or Glivec, was initially developed as a specific inhibitor of the BCR-ABL tyrosine kinase, which is the driver oncogene in chronic myeloid leukemia (CML). Imatinib's discovery and its profound impact on CML therapy is a testament to scientific ingenuity and a beacon of hope for countless patients worldwide [10]. The drug's success in CML has paved the way for its application in other malignancies, including gastrointestinal stromal tumors (GISTs), where it targets the KIT protein. The precision and selectivity of Imatinib in inhibiting these oncogenic kinases have translated into remarkable clinical responses and improved patient outcomes [11]. Imatinib has not only reshaped the treatment paradigm for CML and GIST but has also become a symbol of personalized medicine's potential [12]. Its effectiveness and well-tolerated profile have made it a model for developing other targeted therapies, inspiring further research into novel agents for various cancer types. This can be a brief incursion about Imatinib's impact on oncology. As deeper are delved into its mechanisms of action, clinical applications, and ongoing research, will be highlighted the full extent of its contribution to the fight against cancer.

Molecular docking is a powerful computational technique pivotal in drug discovery, biomolecular interaction analysis, and structural biology. This method has emerged as an indispensable tool for researchers seeking to understand the complex interactions between biomolecules at the atomic level [13]. Molecular docking provides valuable insights into the mechanisms of action and potential therapeutic applications of various compounds simulating the binding of small molecules, such as drugs or ligands, to target proteins or nucleic acids [14].

The fundamental concept behind molecular docking involves predicting a ligand’s most favorable orientation and conformation within the binding site of a target biomolecule. This prediction is based on various factors, including steric effects, electrostatic interactions,

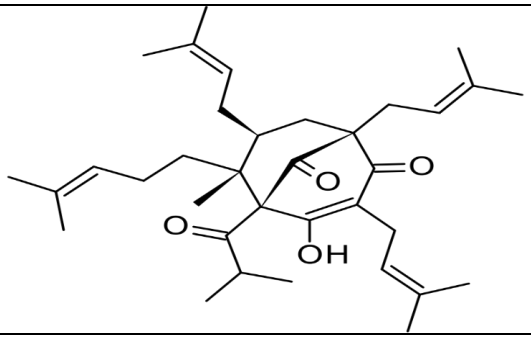
and hydrogen bonding patterns [15]. Through meticulous algorithms and scoring functions, molecular docking simulations enable researchers to identify potential drug candidates, optimize lead compounds, and investigate the binding affinities of ligands to specific biological targets.

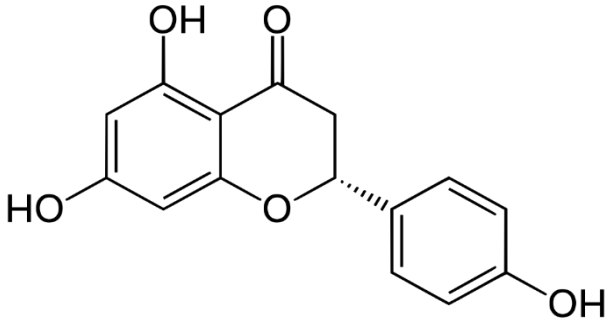
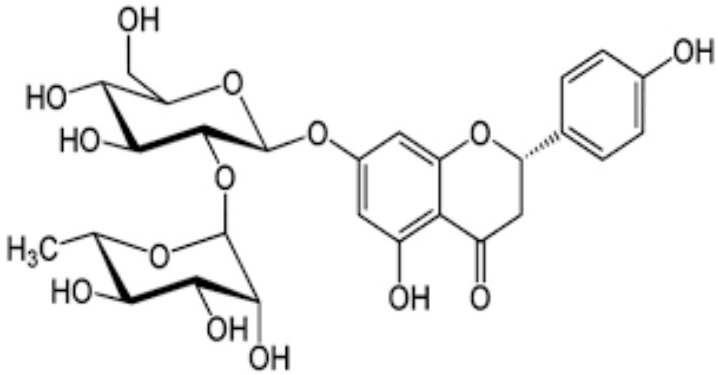
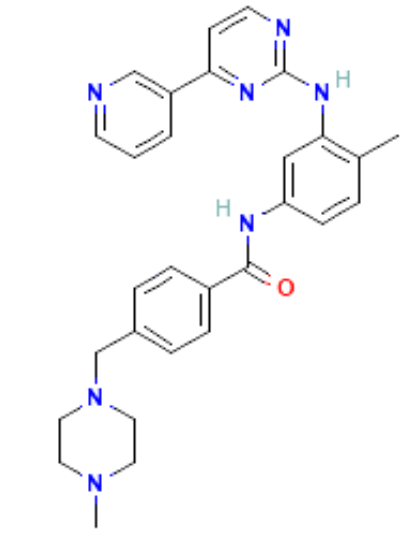
The versatility of molecular docking extends beyond drug discovery, encompassing a wide range of applications in structural biology, bioinformatics, and chemical biology. Researchers employ this technique to elucidate protein-protein interactions, study enzyme-substrate complexes, design new inhibitors, and explore the structural basis of diseases [16]. Moreover, molecular docking has contributed significantly to our understanding of ligand-receptor interactions, enabling the rational design of pharmaceutical agents with enhanced binding and therapeutic efficacy. In this era of computational biology and structural-based drug design, molecular docking has become an integral component of the drug discovery pipeline [17]. As advances in computational methods and hardware continue to accelerate, the scope and accuracy of molecular docking simulations are expanding, offering unprecedented opportunities to expedite the discovery and development of novel therapeutics.

2. MATERIALS AND METHODS

A chemical modeling study on the molecules hyperforin, naringin, and naringenin, as well as the drug imatinib, was performed, using the HyperChem software [18-21]. The investigation of the binding of these molecules to the active site of the receptor was performed using HEX software [22]. The receptor molecules utilized in this study were obtained from the Protein Data Bank [23]. To assess the crucial factor of hydrophobicity, also referred to as lipophilicity, in the design of new drugs [24], was calculated the partition coefficient values of the molecules hyperforin, naringin, and naringenin, as well as the drug imatinib. These calculations were carried out with the HyperChem software [18], and the resulting values are presented in Table 1.

Table 1. Structure and partition coefficient of the studied compounds

Structure	Compound	logP (octanol/water)
Hyperforin		9.61

Structure	Compound	logP (octanol/water)
Naringenin		-1.56
Naringin		-3.46
Imatinib		-1.29

3. RESULTS AND DISCUSSION

The first step of this research involved employing the Hyperchem program for molecular modeling, encompassing the compounds hyperforin, naringin, naringenin, and the pharmaceutical drug imatinib. After the modeling process, these compounds were organized into complexes using the Hex 8.0.0 program. In the Hex program, one of the two compounds acts as a ligand, while the other serves as a receptor. Our primary objective in this analysis is

to determine whether the sequence in which these two compounds bind within a complex holds significance (Table 2).

Table 2. Docking order and docking energies for compounds Hyperforin, Naringin, Naringenin, and the drug Imatinib

Receptor	Ligand	Energy
Imatinib	Hyperforin	-161.25
Hyperforin	Imatinib	-161.27
Imatinib	Naringin	-196.68
Naringin	Imatinib	-196.73
Imatinib	Naringerin	-143.35
Naringerin	Imatinib	-143.39

Table 2 shows the binding energies obtained from molecular docking simulations between the receptor Imatinib and three ligands: Hyperforin, Naringin, and Naringenin. These binding energies are essential in understanding the strength and stability of ligands and receptor interactions.

Imatinib and Hyperforin exhibit similar binding energies of approximately -161.25 and -161.27, respectively. This suggests a relatively strong and stable interaction between these two molecules. The close energy values indicate that Imatinib and Hyperforin may share a similar binding mode or binding site on the receptor.

The Imatinib-Naringin interaction displays a notably lower binding energy of -196.68, indicating a potentially stronger interaction than the Imatinib-Hyperforin complex. The more negative energy value suggests a favorable binding affinity between Imatinib and Naringin.

In the case of Imatinib and Naringenin, the binding energy is -143.35, which is intermediate between the Imatinib-Hyperforin and Imatinib-Naringin interactions. This suggests that the Imatinib-Naringenin complex is relatively stable, but the binding affinity may be weaker compared to Imatinib-Naringin.

These binding energy values provide insights into the potential interactions between Imatinib and the three ligands. The results suggest that Naringin exhibits the strongest binding affinity to Imatinib, followed by Hyperforin and Naringenin. These findings can guide further research into developing drug combinations or optimizing Imatinib-based therapies for specific conditions.

Lipophilicity, often quantified as the logarithm of the partition coefficient (logP), is essential in understanding these interactions, which measure a compound's affinity for lipid or octanol phases relative to water. LogP values are pivotal in predicting a molecule's solubility, permeability, and bioavailability. In this context, we examine the logP values for interactions between the tyrosine kinase inhibitor Imatinib and three ligands: Hyperforin, Naringin, and Naringenin.

Table 3. Structure and partition coefficient of the studied compounds

Compound	logP (octanol/water)
Imatinib-Hyperforin	18.25
Hyperforin-Imatinib	18.25
Imatinib-Naringin	5.02
Naringin-Imatinib	5.02
Imatinib-Naringerin	6.24
Naringerin-Imatinib	6.24

Table 3 presents logP values for the interactions between Imatinib and the mentioned ligands, which provide insights into the lipophilicity of these complexes. Both Imatinib-

Hyperforin and Hyperforin-Imatinib interactions share a high logP value of 18.25. This result suggests that a strong lipophilic affinity characterizes the interaction between Imatinib and Hyperforin. Such a high logP value indicates that these two compounds may exhibit significant hydrophobic interactions, impacting their solubility and distribution in biological systems. The logP value for the Imatinib-Naringin interaction is notably lower at 5.02. This lower value indicates that the complex formed by Imatinib and Naringin is less lipophilic compared to the Imatinib-Hyperforin interaction. The relatively lower lipophilicity could influence the bioavailability and distribution of this complex in the body. Similar to the Imatinib-Naringin interaction, the logP value for the Imatinib-Naringenin interaction is 6.24, indicating moderate lipophilicity. This moderate lipophilicity suggests that the Imatinib-Naringenin complex falls between the highly lipophilic Imatinib-Hyperforin and the less lipophilic Imatinib-Naringin complexes in terms of their hydrophobic character.

These logP values provide valuable information about the hydrophobic nature of these drug-ligand interactions [25]. Higher logP values indicate stronger hydrophobic interactions between the molecules, potentially influencing drug solubility, absorption, and distribution. Understanding the lipophilic properties of these complexes is crucial in optimizing drug formulations, predicting pharmacokinetics, and ultimately guiding drug design efforts for enhanced therapeutic outcomes.

In the next phase of this study, has presented the outcomes of the molecular docking simulations between our complexes and the Protein Data Bank (PDB) receptor 1W0E (for CYP3A4). CYP3A4 enzymes play a crucial role in drug metabolism. By integrating structural information, this research aims to uncover how our complexes interact with this enzyme, shedding light on the three-dimensional aspects of these interactions and their potential pharmacological implications [26].

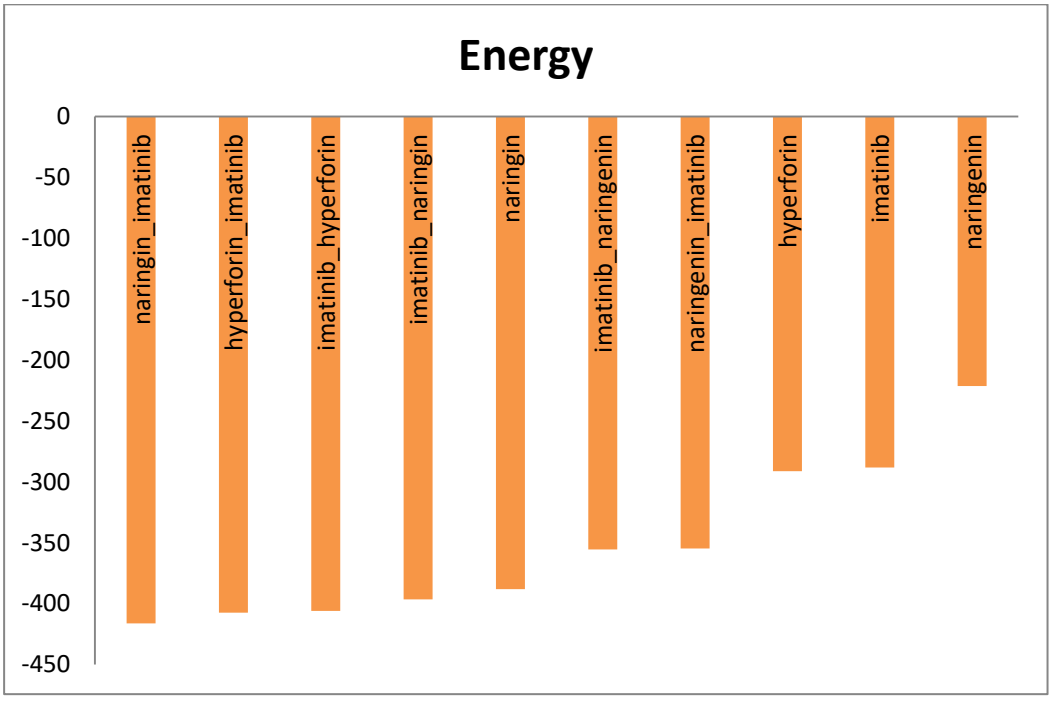


Figure 1. The docking results of the binding energies with the CYP3A4 receptor

Fig. 1 shows the binding energies for various drug-ligand complexes; these binding energies, expressed in negative values (lower values indicating stronger binding), reflect the strength and stability of the interactions between the drugs and their respective ligands.

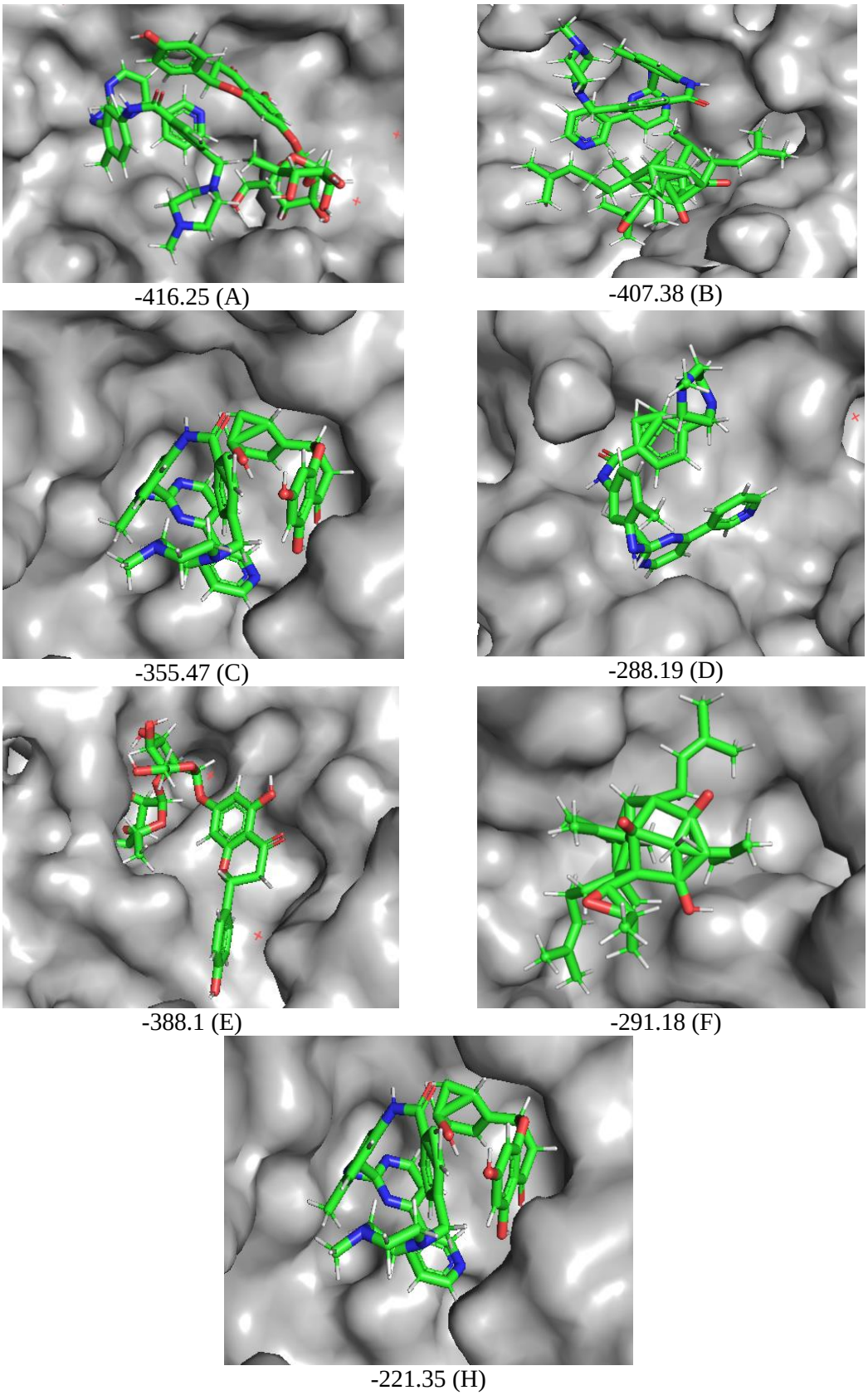


Figure 2. Images of the docking and binding energy values of the CYP3A4 receptor with A the naringin-imatinib complex, B the hyperforin-imatinib complex, C the imatinib-naringenin complex, D Imatinib, E Naringin, F Hyperforin, and H Naringenin

These results indicate that the complexes formed between Imatinib and its co-administered compounds, Naringin, Naringenin, and Hyperforin, generally result in stronger binding energies and exhibit superior binding stability than when these molecules are considered individually. This enhanced binding affinity may affect drug pharmacokinetics and pharmacodynamics [27]. Further research and structural analysis, particularly considering the three-dimensional context with the CYP3A4 receptor, can provide deeper insights into these interactions' mechanisms and potential clinical significance.

The significant variations in binding energies observed in Fig. 2 can be attributed to the fundamental concept that the complexes are binding at different sites compared to the substances taken alone. The specific binding sites and orientations within the receptor, in this case, CYP3A4, play a pivotal role in dictating the stability of these interactions.

The binding energy of the Naringin-Imatinib complex is notably different from the individual energies of Naringin and Imatinib (E and D, respectively). This difference reflects the unique and potentially more stable binding site created by the interaction of these two compounds within the receptor's structure.

Similarly, the Hyperforin-Imatinib complex exhibits a distinct binding energy compared to Hyperforin (F) alone. The complex's stability indicates that it binds at a site that optimizes the interaction between these molecules.

The Imatinib-Naringenin complex also demonstrates a unique binding energy when contrasted with the individual states of Imatinib (D) and Naringenin (H). The complex formation introduces a specific binding site that enhances their stability. These differences in binding energies underscore the site-dependent nature of these interactions. The unique binding configurations created by the complexes result in distinctive binding energies, which may have implications for the pharmacological effects and therapeutic outcomes associated with these compounds.

Understanding the site-specific binding of these complexes is essential for optimizing drug design and predicting the pharmacokinetics and pharmacodynamics of these interactions [28]. Further structural analyses within the context of the CYP3A4 receptor can provide deeper insights into the specific binding sites and the resulting clinical relevance of these interactions.

4. CONCLUSIONS

The binding energies of the complexes, such as Imatinib-Naringin, Imatinib-Hyperforin, and Imatinib-Naringenin, consistently exhibit enhanced stability compared to their constituents. This enhanced stability suggests that the interactions within these complexes are not merely additive but create unique and more stable binding configurations. The variations in binding energies among the complexes and individual substances underscore the importance of site-specific binding. Different binding sites within the CYP3A4 receptor result in distinct interactions, leading to differences in binding energies.

The differences in binding energies have implications for the pharmacological effects of these compounds. Depending on the specific binding sites and the stability of the complexes, these interactions may influence drug metabolism, bioavailability, and therapeutic efficacy. Further structural analysis within the context of the CYP3A4 receptor is essential for a comprehensive understanding of the specific binding sites and the clinical relevance of these interactions. Such analyses can guide drug design and optimization efforts.

The results obtained through the HEX 8.0 docking program indicate significant interactions between the analyzed supplements, Imatinib and the CYP3A4 receptor. It is

observed that it forms a strong bond with CYP3A4, and associations with the analyzed supplements lead to a decrease in binding energy, suggesting a more intense metabolism of the drug in the presence of these supplements. These results highlight the importance of understanding food-drug interactions and potential alterations in systemic bioavailability and drug pharmacokinetics. Interactions with CYP3A4 can affect the effectiveness and safety of treatment, and factors such as food and supplement consumption can influence these interactions. Therefore, understanding and monitoring these interactions are essential to ensure appropriate and safe treatment.

The study highlights the complex nature of drug-ligand interactions, where the same drug may exhibit varying binding energies when interacting with different ligands. This complexity necessitates a detailed understanding of these interactions to make informed decisions in the clinical practice.

These conclusions emphasize the significance of considering both the stability of complexes and the site-specific nature of binding when assessing the pharmacological relevance of drug-ligand interactions. The findings have implications for optimizing drug formulations, predicting pharmacokinetics, and ultimately guiding drug design efforts for enhanced therapeutic outcomes.

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