ORIGINAL PAPER

THE DOCKING STUDY OF THE INTERACTION BETWEEN FOOD SUPPLEMENTS AND BINIMETINIB

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Abstract. *The primary objective of this investigation is to uncover notable interactions between dietary supplements and the pharmaceutical agent Binimetinib with the CYP3A4 receptor, employing the HEX 8.0 docking program. Binding energy is utilized as a critical measure to assess the strength and stability of these interactions. Our analysis reveals a robust binding affinity between Binimetinib and CYP3A4. However, when associated with Naringin and Naringenin, an increase in binding energy is observed, indicating a slightly lower drug metabolism in the presence of these supplements. These findings underscore the critical importance of understanding food-drug interactions and the potential alterations in systemic bioavailability and drug pharmacokinetics that may result. Interactions with CYP3A4 significantly affect treatment efficacy and safety. Dietary habits and supplement intake can influence these interactions. Therefore, a thorough understanding and vigilant monitoring of these dynamics are imperative to ensure the appropriateness and safety of therapeutic regimens.*

Keywords: *Molecular docking; Binimetinib; Naringin; Naringenin; Hyperforin*

1. INTRODUCTION

In the landscape of drug development, one often-underestimated yet pivotal factor influencing the efficacy and safety of new drug candidates is the intricate interplay between drugs and food. The interaction between dietary substances and orally administered drugs poses a significant challenge in the pharmaceutical realm, with multifaceted dynamics. This challenge stems from a variety of factors, including the inherent properties of the drug itself and the dynamic changes occurring in the gastrointestinal tract following food consumption [1, 2].

Understanding the impact of dietary components on drug disposition has emerged as a crucial endeavor in contemporary pharmacology. It entails investigating how various dietary elements can modulate essential processes such as the activity of intestinal enzymes, conjugation reactions, and the functionality of transport proteins [3]. These dietary substances, frequently sourced from botanical origins, have demonstrated their potential to augment or impede drug absorption and distribution in laboratory settings. Nevertheless,

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translating these findings from experimental setups to clinical applications poses significant challenges [4].

Unlocking the mechanisms through which dietary substances modify pharmacokinetic (PK) and pharmacodynamic (PD) outcomes is imperative to accurately assess clinical significance accurately and devise effective management strategies. The prediction of PK properties for novel drug candidates entering clinical trials is inherently complex, and when considering the intricate effects of food, the challenge is magnified [5]. Unfortunately, robust guidelines for evaluating potential interactions between dietary substances and drugs are presently deficient. Clinical studies frequently produce inconclusive results and are challenging to standardize, hindering the establishment of definitive clinical and regulatory recommendations [6]. In this context, the usage of modeling and simulation software presents a promising avenue, offering a quantitative framework for predicting potential interactions between dietary substances and drugs. However, the efficacy of predictive models depends on a comprehensive understanding of the specific bioactive constituents within dietary substances, which serve as marker compounds guiding appropriate clinical trial design [7].

In this article, our objective is to provide a contemporary exploration of the intricate realm of dietary substance–drug interactions. We will address the challenges encountered and potential solutions in conducting and interpreting studies within this domain, shedding light on innovative in silico strategies for forecasting the impact of food on drug candidates. By delving into this often-overlooked aspect of drug development, we aspire to contribute to a deeper comprehension of how food influences the success of promising new drug candidates.

Binimetinib, a small molecule inhibitor targeting MEK1/2, has emerged as a promising therapeutic option in the treatment landscape of various cancers, particularly melanoma and colorectal cancer. MEK1/2, critical components of the MAPK signaling pathway, play pivotal roles in regulating cell proliferation, survival, and differentiation. Dysregulation of this pathway, often driven by mutations such as BRAF V600E, has been implicated in tumorigenesis and disease progression. Binimetinib exerts its antitumor effects by selectively inhibiting MEK1/2, disrupting downstream signaling cascades involved in tumor growth and survival. Preclinical studies have demonstrated its efficacy in inhibiting tumor cell proliferation and inducing apoptosis in various cancer models [9].

Moreover, clinical trials have shown promising results, with Binimetinib exhibiting significant activity as a single agent or in combination therapy in patients with advanced melanoma and metastatic colorectal cancer [8, 10]. Despite these advancements, challenges remain in optimizing the clinical utility of Binimetinib. Resistance mechanisms, both intrinsic and acquired, can limit its efficacy over time, highlighting the need for rational combination strategies and predictive biomarkers to enhance patient outcomes [11]. Additionally, identifying of patient subpopulations most likely to benefit from Binimetinib treatment, along with strategies to mitigate adverse effects, are areas of active investigation.

In this article, we provide a comprehensive overview of Binimetinib, including its mechanisms of action, preclinical and clinical efficacy data, ongoing research efforts, and future directions in its development as a therapeutic agent for cancer treatment. Molecular docking is a cornerstone in computational biology, wielding immense significance in drug discovery, biomolecular interaction analysis, and structural biology. This computational technique has become as an indispensable tool, facilitating researchers' quest to unravel the intricate interactions between biomolecules at the atomic level. Molecular docking furnishes invaluable insights into the mechanisms of action and potential therapeutic applications of various compounds by simulating the binding of small molecules, such as drugs or ligands, to target proteins or nucleic acids [12].

At its core, molecular docking hinges on predicting the most favorable orientation and conformation of a ligand within the binding site of a target biomolecule. This prediction relies

on a myriad of factors, encompassing steric effects, electrostatic interactions, and hydrogen bonding patterns. By leveraging meticulous algorithms and scoring functions, molecular docking simulations empower researchers to discern potential drug candidates, refine lead compounds, and scrutinize the binding affinities of ligands to specific biological targets [13].

The versatility of molecular docking transcends the realm of drug discovery, permeating a broad spectrum of applications in structural biology, bioinformatics, and chemical biology. Researchers harness this technique to unravel protein-protein interactions, delve into enzyme-substrate complexes, engineer new inhibitors, and delve into the structural underpinnings of diseases. Furthermore, molecular docking has profoundly enriched our comprehension of ligand-receptor interactions, paving the way for the rational design of pharmaceutical agents endowed with heightened binding and therapeutic efficacy [14].

In this epoch of computational biology and structure-based drug design, molecular docking has evolved into an integral cog in the drug discovery machinery. With the continual advancement of computational methods and hardware, the scope and precision of molecular docking simulations burgeon, heralding unprecedented opportunities to expedite the discovery and development of novel therapeutics.

2. MATERIALS AND METHODS

2.1. MATERIALS

We performed a chemical modeling investigation utilizing the HyperChem program [15] on the molecules Hyperforin, Naringin, and Naringenin, along with the drug Binimetinib. Subsequently, the binding interactions of these molecules with the active site of the receptor were analyzed using the Hex software [16]. The receptor structures employed in this study were sourced from the Protein Data Bank [17].

2.2. METHODS

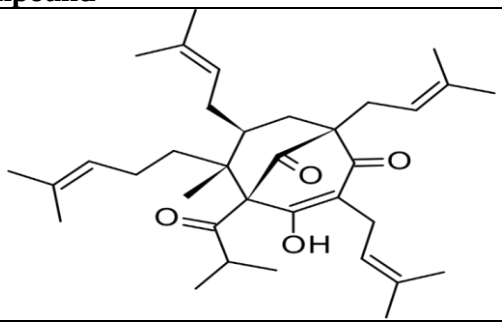
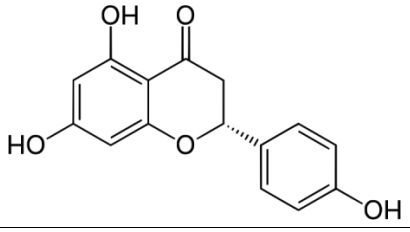
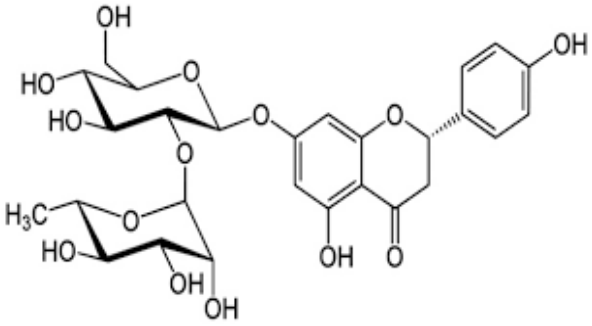
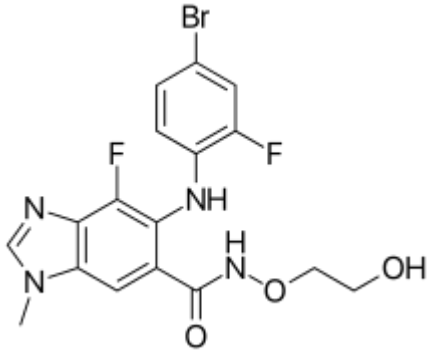
The initial phase involves evaluating the critical aspect of hydrophobicity, also known as lipophilicity, in the development of novel drugs. To achieve this, we computed the partition coefficient values of the molecules Hyperforin, Naringin, and Naringenin, along with the drug binimetinib. Following this, we investigated the significance of docking order and arranged these compounds into complexes using the Hex 8.0.0 program. Within the Hex program, one compound serves as the ligand, while the other acts as the receptor. Finally, we conducted docking simulations of the drug binimetinib and the previously obtained complexes with the biological target [18].

3. RESULTS AND DISCUSSION

3.1. RESULTS

The determination of log P values was conducted using the HyperChem program [15], and the outcomes are displayed in Table 1.

Table 1. Structure and partition coefficient of the studied compounds

Structure	Compound	logP (octanol/water)
Hyperforin		9.61
Naringenin		-1.56
Naringin		-3.46
Binimetinib		3.80

Following the modeling procedure, the compounds were assembled into complexes using the Hex 8.0.0 program. Our main aim in this investigation is to assess the importance of the binding sequence of these two compounds within a complex (Table 2, Fig. 1).

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

Receptor	Ligand	Energy [kcal/mol]
Hyperforin	Binimetinib	-149.85
Binimetinib	Hyperforin	-149.98
Naringin	Binimetinib	-178.03
Binimetinib	Naringin	-178.05
Naringerin	Binimetinib	-130.44
Binimetinib	Naringerin	-130.52

A crucial aspect in comprehending these interactions lies in lipophilicity, often expressed as the logarithm of the partition coefficient (logP). This metric gauges a compound's attraction to lipid or octanol phases compared to water. LogP values serve as vital indicators for predicting a molecule's solubility, permeability, and bioavailability [19]. In this study, we scrutinize the logP values concerning the interactions between the tyrosine kinase inhibitor Binimetinib and three ligands: Hyperforin, Naringin, and Naringenin (Table 3).

Table 3. Structure and partition coefficient of the studied compounds

Compound	logP (octanol/water)
Binimetinib-Hyperforin	14.38
Hyperforin-Binimetinib	14.38
Binimetinib-Naringin	1.15
Naringin-Binimetinib	1.15
Binimetinib-Naringerin	2.67
Naringerin-Binimetinib	2.67

In the subsequent stage of our investigation, we reveal the results obtained from our molecular docking simulations involving the complexes and the Protein Data Bank (PDB) receptor 1W0E (representing CYP3A4). CYP3A4 enzymes are pivotal in drug metabolism. By incorporating structural insights, the objective is to unveil the interactions between our complexes and this enzyme, elucidating the three-dimensional aspects of these interactions and their potential pharmacological significance [20].

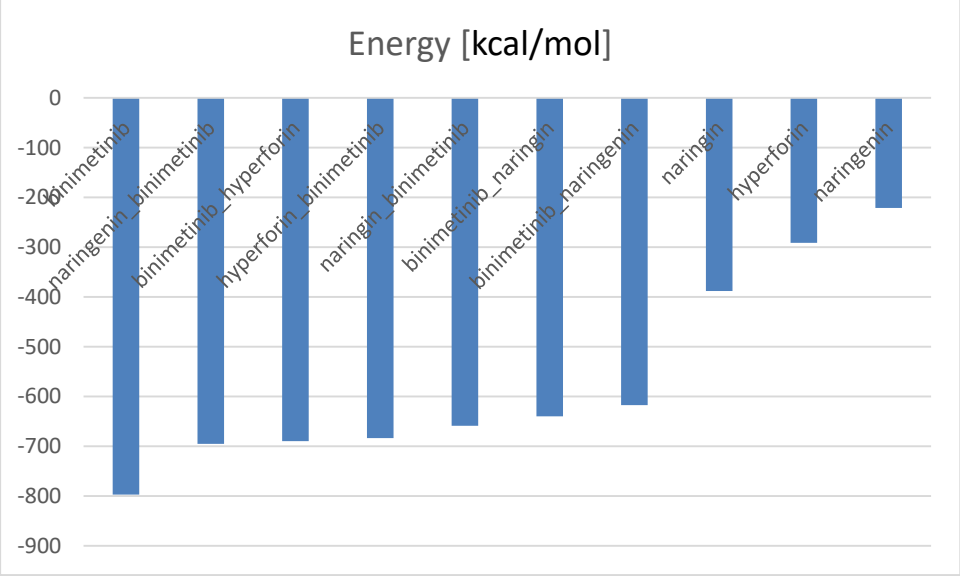


Figure 1. Docking results of the binding energies with CYP3A4 receptor

3.2. DISCUSSION

Table 1 presents the structures and corresponding partition coefficients (logP values) of the investigated compounds: Hyperforin, Naringenin, Naringin, and Binimetinib. LogP values are crucial indicators of a compound's lipophilicity, representing its affinity for lipid or octanol phases relative to water. Hyperforin exhibits a notably high logP value of 9.61, indicating a strong preference for the octanol phase over water. This suggests that Hyperforin is highly lipophilic, which may impact its solubility and bioavailability. The high lipophilicity

of Hyperforin could influence its pharmacokinetic properties and distribution within the body. Conversely, Naringenin and Naringin display negative logP values (-1.56 and -3.46, respectively), indicating a stronger affinity for the aqueous phase than for octanol. This suggests that Naringenin and Naringin are more hydrophilic. Their hydrophilicity may affect their solubility characteristics and distribution within biological systems.

Binimetinib possesses a logP value of 3.81, indicating a moderate preference for the octanol phase. This suggests that Binimetinib exhibits moderate lipophilicity, which could influence its absorption, distribution, metabolism, and excretion (ADME) properties. The differences in logP values among the studied compounds highlight their varying degrees of lipophilicity, which can significantly impact their pharmacokinetic and pharmacodynamic properties. Understanding these differences is crucial in drug design and optimization, as it allows for predicting and modulating of a compound's behavior within biological systems [21].

The table presents the docking order and corresponding docking energies for the interactions between the drug Binimetinib and the compounds Hyperforin, Naringin, and Naringenin. Docking energies provide insights into the stability and strength of binding interactions between ligands and receptors during molecular docking simulations.

Firstly, comparing the docking energies for Hyperforin and Binimetinib, we observe a slight decrease in energy when Binimetinib is docked as the ligand (-149.85) compared to when it is docked as the receptor (-149.98 kcal/mol) (Table 2). Although the difference is minimal, it suggests a potential preference for a specific orientation of the ligand-receptor complex, influencing the overall stability of the interaction.

Similarly, it observed a consistent trend in the interactions involving Naringin and Naringenin with Binimetinib. The docking energy is slightly lower when Binimetinib is docked as the ligand compared to when it is docked as the receptor (-178.03 *vs*. -178.05 **kcal/mol** for Naringin and -130.44 vs. -130.52 kcal/mol for Naringenin) (Table 2). Again, while the difference may seem subtle, it indicates a potential preference for a particular docking orientation that optimizes the binding interaction.

These findings suggest that the docking order can influence the stability and strength of the binding interactions between Binimetinib and the studied compounds. While the differences in docking energies may be minor, they imply that certain orientations of the ligand-receptor complex may be slightly more favorable than others. Therefore, considering the docking order is crucial for accurately assessing the binding affinity and optimizing drug design strategies [18].

In conclusion, the observed variations in docking energies indicate that the docking order matters and can impact the stability and efficacy of the ligand-receptor interactions. Further investigations into the structural and molecular determinants underlying these preferences could provide valuable insights for drug discovery and optimization processes [22].

LogP is a measure of the lipophilicity of a compound, representing its tendency to partition between a non-polar solvent (octanol) and water. A higher logP value indicates greater hydrophobicity, meaning the compound prefers to dissolve in octanol rather than water. Looking at Table 3, we see different pairs of compounds with their corresponding logP values: Binimetinib-Hyperforin complex has a logP of 14.38, indicating it strongly favors octanol over water and Binimetinib-Naringin and Binimetinib-Naringerin complexes both have logP values of 1.15 and 2.67, respectively, indicating they have lower lipophilicity compared to binimetinib and hyperforin [21].

The combination of Binimetinib-Hyperforin might result in complex pharmacokinetic interactions due to their vastly different lipophilicities. This could influence their distribution, metabolism, and ultimately, their efficacy and safety profiles. Binimetinib's complexes with

naringin and naringen in might be less problematic due to their similar logP values. However, these interactions should still be considered, especially regarding potential effects on drug absorption and distribution.

Understanding the lipophilicity of compounds is crucial for drug delivery systems. Highly lipophilic drugs may face challenges in reaching their target sites or may exhibit prolonged half-lives due to sequestration in fatty tissues. Differences in lipophilicity between co-administered drugs can alter pharmacokinetics and potential drug interactions. These interactions can affect therapeutic outcomes and may require dosage adjustments or careful monitoring.

LogP values are often used in computational models to predict a compound's absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties. Further research in this area could refine drug development processes. In conclusion, the table provides valuable insights into the lipophilic nature of the listed compounds, offering implications for drug design, pharmacokinetics, and clinical practice. Understanding these factors is essential for optimizing drug therapies and minimizing potential risks associated with drug interactions and adverse effects [22].

Upon analyzing the docking energies provided in Fig. 1, it becomes evident that the docking order significantly influences the binding energy of the medicament/complex, indicating that the docking order does matter in this context. For instance, consider the interaction between Binimetinib and Hyperforin. When Binimetinib is the ligand, the energy of the complex is -689.85, whereas, when Hyperforin is the ligand, the energy decreases to -683.69 kcal/mol. This difference in energy suggests that the ligand-receptor complex's orientation affects the stability and strength of the interaction, with one orientation being slightly more favorable than the other.

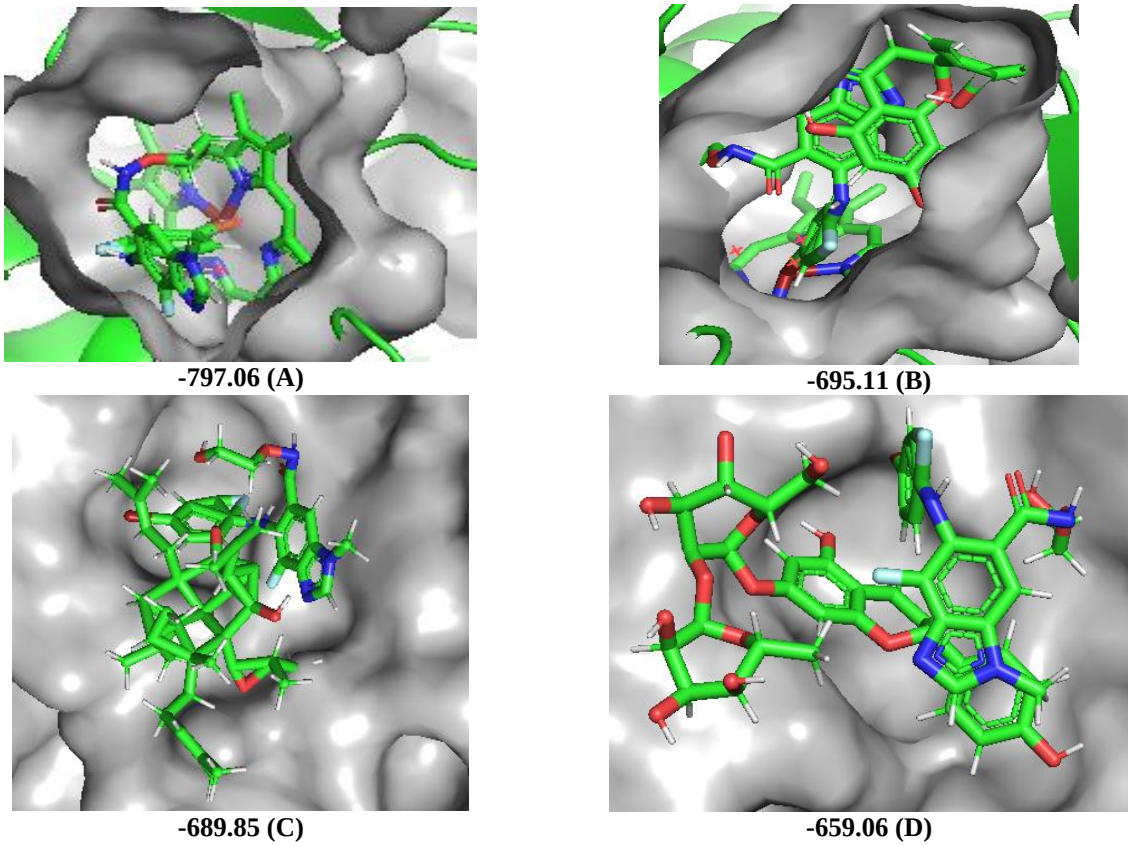
Similarly, for the interaction involving Naringenin and Binimetinib, was observed a significant difference in energy between the two docking scenarios (-617.26 kcal/mol for Binimetinib as the ligand vs. -695.11 kcal/mol for Naringenin as the ligand). This substantial variation underscores the importance of the docking order, indicating that specific orientations of the ligand-receptor complex are more energetically favorable than others. The docking energies for the individual compounds (Naringenin, Hyperforin, and Naringin) also vary depending on whether they are alone or involved in a complex with Binimetinib [23]. This suggests that the presence of Binimetinib influences the energy of the compounds, further highlighting the significance of considering the docking order in assessing the stability and efficacy of the ligand-receptor interactions.

In conclusion, the observed differences in docking energies for the medicament/complex demonstrate that the docking order is crucial in determining the binding energy and stability of the ligand-receptor interactions. Understanding and optimizing the docking order is essential for accurately predicting drug candidates' efficacy and therapeutic potential in complex biological systems.

The findings suggest that Binimetinib demonstrates stronger binding energies and superior binding stability compared to the complexes formed between Binimetinib and its co-administered compounds, Naringin, Naringenin, and Hyperforin [18]. Further investigation and structural analysis, particularly within the three-dimensional context involving the CYP3A4 receptor, can offer deeper insights into these interactions' mechanisms and potential clinical significance.

These variances in binding energies highlight the site-specific nature of these interactions. The distinct binding configurations formed by the complexes lead to unique binding energies, potentially influencing the pharmacological effects and therapeutic outcomes associated with these compounds. Comprehending the site-specific binding of these complexes is crucial for refining drug design and forecasting the pharmacokinetics and

pharmacodynamics of these interactions [18]. Further structural analyses within the framework of the CYP3A4 receptor can offer deeper insights into the precise binding sites and the resulting clinical significance of these interactions (Fig. 2).



-797.06 (A) **-695.11 (B)**

-689.85 (C) **-659.06 (D)**

Figure 2. Docking images and binding energies values of the CYP3A4 receptor with A Binimetinib, B the Naringenin-Binimetinib complex, C the Binimetinib - Hyperforin complex, D the Naringin - Binimetinib complex.

4. CONCLUSIONS

The conclusions drawn from our study emphasize the remarkable binding capabilities of the complexes involving Binimetinib and dietary supplements such as Naringin, Hyperforin, and Naringenin. We observed consistently enhanced stability in the binding energies of these complexes compared to their constituents. This heightened 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, with different binding sites within the CYP3A4 receptor yielding distinct interactions and subsequently differing binding energies.

Moreover, these differences in binding energies carry significant implications for the pharmacological effects of these compounds. Depending on the specific binding sites and the stability of the complexes, these interactions may influence over 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, which can, in turn, inform drug design and optimization efforts.

Our findings, generated through the HEX 8.0 docking program, notably highlight Binimetinib's robust binding affinity with the CYP3A4 receptor. Furthermore, the observed increase in binding energy when associated with the analyzed supplements suggests a potential decrease in the drug's metabolism in their presence. This emphasizes the critical role of understanding food-drug interactions and their impact on systemic bioavailability and drug pharmacokinetics. Given the pivotal role of CYP3A4 in drug metabolism, interactions with this enzyme can significantly affect treatment effectiveness and safety. Therefore, comprehensive comprehension and monitoring of these interactions are imperative to ensure appropriate and safe treatment regimens.

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