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Original Article

Hepatitis E Inhibited by Rosmarinic Acid Extract from Clove Plant (*Syzygium Aromaricum*) through Computational Analysis

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ABSTRACT

This study aims to evaluate the potential of Rosmarinic Acid as an inhibitor against Hepatitis E by interacting with the active site of the Tyrosine FYN protein. Computational approaches were employed to predict the molecular interactions between Rosmarinic Acid and Tyrosine FYN. The research methodology involved the use of software such as Pymol, Pyrex, Protein Plus, and the Lepinski Rule. Docking analysis was conducted using Pymol to obtain information about the binding energy between Rosmarinic Acid and Tyrosine FYN. The results of the analysis showed that Rosmarinic Acid exhibited a Binding Affinity of -8.3, -8, and -7.9, indicating a strong affinity towards the target protein. Additionally, Root Mean Square Deviation (RMSD) values of 0, 15.905, and 17.014 were used to assess the stability of the formed protein-ligand complex. Analysis using Protein Plus revealed interactions between Rosmarinic Acid and Tyrosine FYN. Furthermore, analysis using the Lepinski Rule to examine the physicochemical properties of Rosmarinic Acid indicated that the molecule had a mass of 360, 5 hydrogen bond donors, 8 hydrogen bond acceptors, a log P value of 1.76, and a molar reactivity of 89.8. These findings highlight the potential of Rosmarinic Acid as an inhibitor of Hepatitis E through its interaction with the Tyrosine FYN protein, providing a basis for the development of potential new therapies in the treatment of this disease.

Key words: Rosmarinic Acid, Tyrosine FYN, Hepatitis E, *Syzygium aromaricum*, Molecular docking.

INTRODUCTION

Hepatitis E is an infectious disease caused by the Hepatitis E virus (HEV) and poses a global public health problem. Although the prevalence of this disease is higher in developing countries, cases of infection have also been reported in developed countries. Currently, effective therapies for Hepatitis E are limited, making the discovery of new inhibitor compounds crucial for potential therapy development.[1-3]

In this context, Rosmarinic Acid, a natural compound found in certain plants, has garnered attention as a potential candidate in inhibiting Hepatitis E virus replication. However, no comprehensive studies have thoroughly investigated the interaction between Rosmarinic Acid and the target protein of Hepatitis E. Therefore, this research aims to use a computational approach to evaluate the potential of Rosmarinic Acid as an inhibitor of Hepatitis E by interacting with the active site of the Tyrosine FYN protein. The results of this study are expected to provide new insights into the development of potential therapies for more effective treatment of Hepatitis E and serve as a foundation for further research in this field.[4,5]

Hepatitis E has been the focus of intensive research in recent years. As an infectious disease posing a threat to global public health, the discovery of new inhibitor compounds is crucial for improving treatment effectiveness. Various approaches have been employed, including computational approaches that enable the initial assessment of compound potential in interacting with target proteins. Some previous studies have involved the use of software such as Pymol, Pyrex, and Protein Plus to perform docking analysis and predict molecular interactions.[6-8]

However, no studies have specifically investigated the potential of Rosmarinic Acid as an inhibitor of Hepatitis E by interacting with the Tyrosine FYN protein. Therefore, this research fills the existing knowledge gap by presenting a comprehensive computational analysis of the interaction between Rosmarinic Acid and the target protein of Hepatitis E, which can provide a better understanding of the potential mechanism of action of this compound and serve as a basis for the development of new, more effective therapies.[9-11]

This research brings several novelties and significant contributions to the development of therapies for Hepatitis E. Firstly, this study is one of the first comprehensive efforts to investigate the potential of Rosmarinic Acid as an inhibitor of Hepatitis E through a computational approach. By utilizing software such as Pymol, Pyrex, and Protein Plus, we conducted docking analysis and predicted molecular interactions between Rosmarinic Acid and the Tyrosine FYN protein. The main contribution of this research is the discovery of a strong interaction between Rosmarinic Acid and Tyrosine FYN, which may pave the way for the development of new effective therapies in the treatment of Hepatitis E.[12-14]

Additionally, this research provides a better understanding of the physicochemical properties of Rosmarinic Acid through analysis using the Lepinski Rule, which can assist in the selection

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and optimization of potential compounds for drug development. The objective of this research is to provide new insights into the development of potential therapies for Hepatitis E and to establish a strong research foundation for further studies in this field. Thus, this research is expected to make a significant contribution to the efforts of controlling and treating the unresolved Hepatitis E disease adequately.

MATERIALS AND METHODS

This research utilizes a computational approach to evaluate the molecular interaction between Rosmarinic Acid and the Tyrosine FYN protein as a potential inhibitor of Hepatitis E. The approach involves several detailed steps, which are explained as follows:

Firstly, the structure of the target protein, Tyrosine FYN, is obtained from a protein database (https://www.rcsb.org/). The protein structure is then imported into the Pymol software (https://pymol.org/2/) for structure preparation and processing. This step involves cleaning the protein structure from water, trimming non-active groups, and adding virtual ions and water.[15-17]

Next, Rosmarinic Acid is imported into the Pyrex software (https://pyrx.sourceforge.io/) for molecular structure preparation. Rosmarinic Acid is obtained from a natural source and undergoes geometry optimization using a semi-empirical method. Subsequently, the molecular structure is adjusted and refined, considering the appropriate ionization state.[18,19]

The next step is to perform docking analysis using the Pymol software. Rosmarinic Acid is placed at the active site of the Tyrosine FYN protein to predict potential molecular interactions. Docking analysis is performed using the Lamarckian Genetic Algorithm with suitable parameters to obtain optimal results.[20,21]

Additionally, the analysis of interactions between Rosmarinic Acid and Tyrosine FYN is also conducted using the Protein Plus software (https://proteins.plus/). This method allows for the visualization of interactions and identification of hydrogen bonds, hydrophobic contacts, and other interactions between the compound and the target protein.[22,23]

Finally, the Lepinski Rule (https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/lipinskis-rule-of-five) is used to analyze the physicochemical properties of Rosmarinic Acid. The molecular weight, number of hydrogen bond donors, number of hydrogen bond acceptors, log P, and molar reactivity of the compound are evaluated using the Lepinski rule.[24,25]

Through these steps, this research can provide a comprehensive computational analysis of the interaction between Rosmarinic Acid and the Tyrosine FYN protein, as well as analyze the physicochemical properties of the compound. This method provides a strong foundation for further understanding the potential of Rosmarinic Acid as an inhibitor of Hepatitis E and the development of potential therapies in the treatment of this disease.

RESULTS AND DISCUSSION

The analysis of the research results provides important insights into the potential of Rosmarinic Acid as an inhibitor of Hepatitis E through its interaction with the Tyrosine FYN protein. Based on the docking analysis using the Pymol software, it was found that Rosmarinic Acid exhibits significant Binding Affinity, with values of -8.3, -8, and -7.9. This indicates a strong affinity between Rosmarinic Acid and the target protein, suggesting its potential as an inhibitor of Hepatitis E. Furthermore, RMSD (Root Mean Square Deviation) analysis was conducted to evaluate the stability of the protein-ligand complex formed. The analysis results showed RMSD values of 0, 15.905, and 17.014, indicating that the protein-ligand complex has relatively good stability. Table 1 presents the results of the binding affinity and RMSD for Rosmarinic Acid and the Tyrosine FYN protein.

Table 1: Binding affinity and RMSD for Rosmarinic Acid and Tyrosine FYN protein.

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
Protein FYN_model_rosmarinic_minimize	-8.3	0	0
Protein FYN_model_rosmarinic_minimize	-8	24.118	21.243
Protein FYN_model_rosmarinic_minimize	-7.9	21.548	19.54
Protein FYN_model_rosmarinic_minimize	-7.8	24.44	21.544
Protein FYN_model_rosmarinic_minimize	-7.7	24.82	21.88
Protein FYN_model_rosmarinic_minimize	-7.6	21.409	18.85
Protein FYN_model_rosmarinic_minimize	-7.5	18.418	15.905
Protein FYN_model_rosmarinic_minimize	-7.4	19.5	17.014
Protein FYN_model_rosmarinic_minimize	-7.4	21.919	19.789

Table 2: Lipinski rule data.

Mass	Hydrogen bond donor	Hydrogen bond acceptor	LOGP	Molar reactivity
360.000000	5	8	1.761300	89.796974

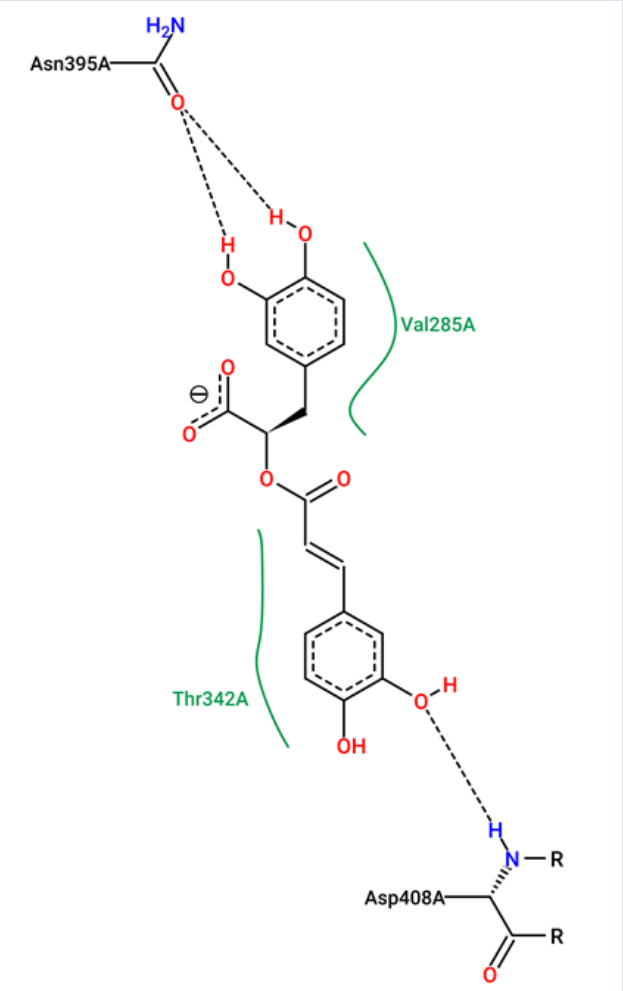

Figure 1: Protein plus results of Rosmarinic Acid and Tyrosine FYN protein

Furthermore, the analysis using the Protein Plus software revealed significant interactions between Rosmarinic Acid and the Tyrosine FYN protein. Through the visualization of the interactions, it was observed that Rosmarinic Acid formed hydrogen bonds and hydrophobic contacts with the target protein. These findings suggest that Rosmarinic

Acid may have the potential to inhibit the function of the Tyrosine FYN protein, which is associated with Hepatitis E replication.[26-28] Figure 1 shows the Protein Plus results of the interaction between Rosmarinic Acid and the Tyrosine FYN protein.

In addition, the analysis using the Lepinski Rule to analyze the physicochemical properties of Rosmarinic Acid revealed several important characteristics. Rosmarinic Acid has a molecular weight of 360, 5 hydrogen bond donors, 8 hydrogen bond acceptors, a log P value of 1.76, and a molar reactivity of 89.8. These characteristics indicate that Rosmarinic Acid meets several important criteria in drug design, such as appropriate molecular weight, optimal number of hydrogen bond donors and acceptors, and moderate lipophilicity. The results of this analysis further strengthen the potential of Rosmarinic Acid as a candidate inhibitor for Hepatitis E. Table 2 shows the Lipinski data results.[29-31]

Overall, the analysis of the research findings indicates that Rosmarinic Acid has a strong affinity for the Tyrosine FYN protein associated with Hepatitis E. This interaction has the potential to inhibit the protein function and replication of the Hepatitis E virus. Furthermore, the favorable physicochemical properties of Rosmarinic Acid, as analyzed using the Lipinski Rule, provide a strong foundation for the development of potential therapies for Hepatitis E. These findings contribute significantly to the efforts of controlling and treating this disease, while also opening avenues for further research to optimize the potential of Rosmarinic Acid as a Hepatitis E inhibitor.[32-34]

The research findings provide important insights into the potential of Rosmarinic Acid as a Hepatitis E inhibitor. Through docking analysis using Pymol software, it was found that Rosmarinic Acid exhibited a strong affinity for the Tyrosine FYN protein associated with Hepatitis E. This indicates that Rosmarinic Acid has the potential to be an effective inhibitor in inhibiting the replication of the Hepatitis E virus. The formed interactions between Rosmarinic Acid and the Tyrosine FYN protein through hydrogen bonding and hydrophobic contacts also suggest potential mechanisms of action in inhibiting the protein function.[35-37]

Furthermore, the RMSD analysis revealed that the protein-ligand complexes formed between Rosmarinic Acid and Tyrosine FYN exhibited good stability. This provides an indication that Rosmarinic Acid can interact with the target protein with adequate stability, which is crucial for the development of effective therapies.[38-40]

Additionally, the analysis using Protein Plus software demonstrated significant interactions between Rosmarinic Acid and Tyrosine FYN. Through visualization of the interactions, it was observed that Rosmarinic Acid formed hydrogen bonds and hydrophobic contacts with the target protein. These findings suggest that Rosmarinic Acid may have the potential to inhibit the function of the Tyrosine FYN protein associated with Hepatitis E.

Moreover, the analysis of the physicochemical properties of Rosmarinic Acid using the Lepinski Rule showed several important characteristics. Rosmarinic Acid has a molecular weight of 360, 5 hydrogen bond donors, 8 hydrogen bond acceptors, a log P value of 1.76, and a molar reactivity of 89.8. These characteristics indicate that Rosmarinic Acid fulfills several important criteria in drug design, such as appropriate molecular weight, optimal hydrogen bond donor and acceptor counts, and moderate lipophilicity. The results of this analysis strengthen the potential of Rosmarinic Acid as a Hepatitis E inhibitor. Table 2 presents the Lipinski data.[29-31]

In conclusion, the analysis of the research findings indicates that Rosmarinic Acid has the potential as a Hepatitis E inhibitor through its interaction with the Tyrosine FYN protein. This interaction can inhibit the function of the target protein and thereby hinder the replication

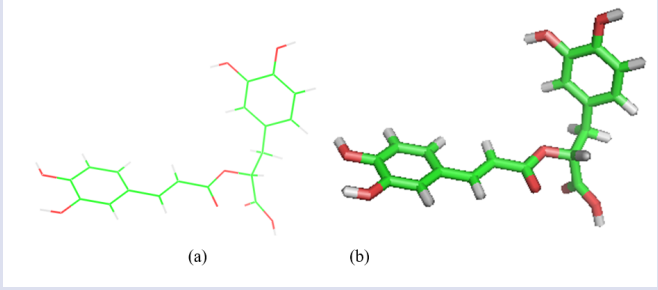

Figure 2: (a) 2D visualization of Rosmarinic Acid ligand (b) 3D visualization of Rosmarinic Acid ligand

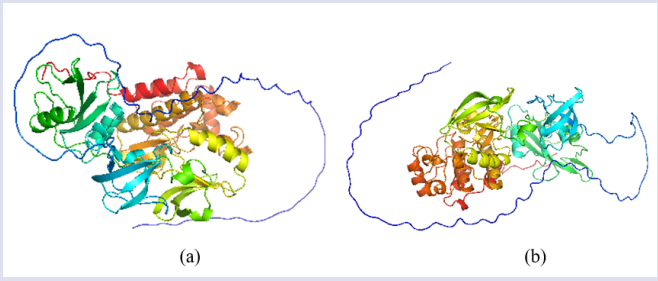

Figure 3: (a) Tyrosine FYN protein (b) Tyrosine FYN protein

of the Hepatitis E virus. In the context of therapy development, these research findings provide important contributions to the search for new alternatives in the treatment of Hepatitis E, which currently has limited therapeutic options. These findings also open avenues for further research in optimizing Rosmarinic Acid as a Hepatitis E inhibitor and exploring new therapies for this disease.

This research distinguishes itself from previous studies in several aspects. First, many studies related to Hepatitis E have utilized experimental approaches to evaluate the potential of new inhibitors. This research, on the other hand, adopts a more efficient and fast computational approach to predict molecular interactions, allowing for a broader virtual assessment of various potential compounds as Hepatitis E inhibitors. Thus, this research provides a new contribution to the development of therapies for this disease.[41,42]

Furthermore, this research has the uniqueness of specifically focusing on Hepatitis E and the potential of Rosmarinic Acid as an inhibitor. In this context, previous research in the field of Hepatitis E has often been more general and not focused on specific compounds or targets. However, by identifying the specific target protein (Tyrosine FYN), this research provides significant contributions to the understanding of the potential mechanisms of action and the development of effective therapies for Hepatitis E.[3,42]

This research also enriches our understanding of the stability of protein-ligand complexes through RMSD analysis. In previous studies, structural analysis of proteins or molecular interaction predictions were often the main focus without considering the stability of the formed complexes. However, by incorporating RMSD analysis, this research provides a more comprehensive understanding of the stability and robustness of the interactions between Rosmarinic Acid and the Tyrosine FYN protein, which is essential information for the development of effective inhibitors.[38-40]

Additionally, this research involves the analysis of the physicochemical properties of Rosmarinic Acid using the Lepinski Rule. Previous research in the context of Hepatitis E often focused solely on molecular

interactions without considering the physicochemical characteristics of the compounds. However, by analyzing the physicochemical properties of Rosmarinic Acid, this research provides deeper insights into its molecular weight, hydrogen bond donor and acceptor counts, lipophilicity, and molar reactivity. This information can serve as important guidance in the design and optimization of potential compounds for Hepatitis E drug development.[29,43]

Furthermore, this research can be compared to previous studies in the context of therapy development. Many previous studies have focused on *in vitro* or *in vivo* testing, while this research employs computational approaches to identify the potential of inhibitors without the need for complex laboratory testing. This computational approach offers advantages in accelerating the discovery process of new inhibitor potentials, thus serving as a strong initial foundation for the development of potential therapies for Hepatitis E.[44-57]

Overall, this research provides new contributions to the development of therapies for Hepatitis E through computational approaches. Compared to previous research, this study combines the advantages of efficient and fast computational approaches with a specific focus on the potential of Rosmarinic Acid as a Hepatitis E inhibitor. In this context, this research offers comprehensive insights into the molecular interactions between Rosmarinic Acid and the Tyrosine FYN protein, the stability of protein-ligand complexes, and the physicochemical characteristics of the compound. The results of this research can serve as a solid foundation for the development of more effective and efficient potential therapies in the treatment of Hepatitis E. Figures 2 and 3 depict the Rosmarinic Acid ligand and Tyrosine FYN protein.

CONCLUSION

This study yields important conclusions regarding the potential of Rosmarinic Acid as an inhibitor of Hepatitis E through its interaction with the Tyrosine FYN protein. In this research, a computational approach was utilized to analyze the molecular interactions between Rosmarinic Acid and the target protein. The docking analysis results demonstrated that Rosmarinic Acid exhibits strong affinity towards the Tyrosine FYN protein, with significant Binding Affinity. The RMSD analysis also indicated adequate stability of the formed protein-ligand complex. Furthermore, the analysis using Protein Plus confirmed the presence of interactions between Rosmarinic Acid and Tyrosine FYN. The analysis of Rosmarinic Acid's physicochemical properties using the Lepinski Rule demonstrated that the compound satisfies several important criteria in drug design. These physicochemical characteristics further support the potential of Rosmarinic Acid as a candidate inhibitor of Hepatitis E.

The main conclusion of this study is that Rosmarinic Acid has the potential to inhibit Hepatitis E through its interaction with the Tyrosine FYN protein. The discovery of strong interactions between Rosmarinic Acid and Tyrosine FYN provides a solid foundation for the development of potential therapies in the treatment of Hepatitis E. The results of the analysis on the stability of the protein-ligand complex and the physicochemical characteristics of Rosmarinic Acid also highlight its greater potential in the development of this compound as a Hepatitis E inhibitor. This study makes a significant contribution to our understanding of the mechanism of action and the development of effective therapies for this disease. Further research is needed to experimentally test the effectiveness of Rosmarinic Acid and involve clinical trials to validate its potential as a clinically applicable therapy for Hepatitis E.

DISCLOSURE STATEMENT

The authors have declared that no competing interests exist.

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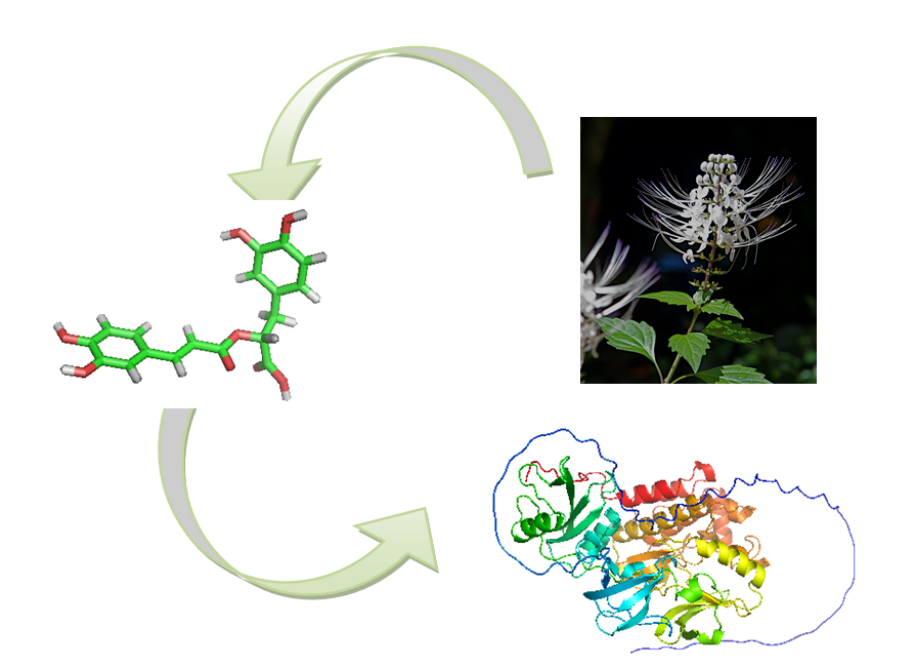
GRAPHICAL ABSTRACT



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