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Interaction of Linolenic Acid from Papaya Plant (Carica Papaya) on Peroxome Proliferator-Actived Receptor Delta as Colorectal Cancer Cell Inhibitor

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ABSTRACT

This study examines the interaction of linolenic acid from the papaya plant (Carica papaya) on peroxisome proliferator-activated receptor delta (PPAR-δ) as an inhibitor of colorectal cancer cells. The research methodology involved computational modeling and simulation using Pymol, Pyrex, and Protein Plus. With Pymol and Pyrex, the binding affinity of linolenic acid to PPAR-δ was obtained with values of -6.9, -6.8, and -6.7, and Root Mean Square Deviation (RMSD) with values of 0, 1.18, and 1.318. Protein Plus results indicate an interaction between linolenic acid and PPAR-δ. This study also took into account the Lepinski Rule of Five to predict the bioavailability of linolenic acid in biological systems. The parameters include molecular mass 249, hydrogen bond donor 1, hydrogen bond receiver 2, log P 0.8005, and molar reactivity 64.0568. The results of this study indicate the potential of linolenic acid from papaya plants as a PPAR-δ inhibitor in the treatment of colorectal cancer.

Keywords: Linolenic Acid, Papaya Plant (Carica papaya), Peroxisome Proliferator, Activated Receptor Delta (PPAR-δ), Colorectal Cancer Cell Inhibition, Lepinski Rule of Five

INTRODUCTION

Colorectal cancer is one of the deadliest diseases whose prevalence continues to increase globally. The disease is often difficult to detect in its early stages and conventional treatment methods often have severe side effects. Therefore, new treatment alternatives that are more effective and safe are needed. One potential approach is the use of phytopharmacology, which

† Footnotes relating to the title and/or authors should appear here.
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involves the use of bioactive compounds from plants for treatment [1]-[3].

The papaya plant (Carica papaya) has been known to contain various bioactive compounds, one of which is linolenic acid. This acid has been shown to have anticancer effects, but its mechanism against colorectal cancer cells is still poorly understood. This study focuses on exploring the interaction of linolenic acid from papaya plants on peroxisome proliferator-activated receptor delta (PPAR-δ), which has been known to play an important role in the process of colorectal carcinogenesis [4]-[6].

A number of recent studies have begun to explore the therapeutic potential of linolenic acid, particularly in the context of cancer treatment. The results of a number of studies show that linolenic acid can inhibit breast cancer cell growth through suppression of the signal transducer and activator of transcription 3 (STAT3) pathway [7]-[8]. Meanwhile, in the context of colorectal cancer, the role of peroxisome proliferator-activated receptor delta (PPAR-δ) is gaining attention. PPAR-δ is known to play an important role in lipid metabolism as well as carcinogenesis. In addition, modulation of PPAR-δ may affect the metastatic process of colorectal cancer. However, knowledge on the interaction between linolenic acid and PPAR-δ is still limited [9]-[10]. Therefore, this study is expected to provide new understanding and contribute to the development of phytopharmaceutical-based colorectal cancer treatment.

The novelty of this study lies in the first exploration of the interaction of linolenic acid from papaya plants with PPAR-δ, which has the potential to inhibit colorectal cancer cells. Previous studies have explored the anticancer effects of linolenic acid and the role of PPAR-δ in colorectal carcinogenesis, but no study has bridged these two domains. Using computational simulation and molecular modeling techniques, this study seeks to understand how linolenic acid from papaya can interact and affect PPAR-δ function [11]-[13].

The contribution of this study is not only to provide a new understanding of the mechanism of action of linolenic acid, but also to open up opportunities for the development of safer and more effective phytopharmaceutical-based colorectal cancer treatments [14]-[15]. The main objective of this study is to assess the potential of linolenic acid from papaya plants as a PPAR-δ inhibitor in the treatment of colorectal cancer.

METHODS

In this study, linolenic acid was initially extracted from papaya (Carica papaya) plants using the soxhlet extraction method. The extracted linolenic acid was then purified and analyzed for its chemical structure using infrared spectroscopy and core magnetic resonance spectroscopy [16]-[17].

Furthermore, this study used computational modeling and simulation methods to understand the interaction of linolenic acid and peroxisome proliferator-activated receptor delta (PPAR-δ). The 3D structure of PPAR-δ was obtained from Protein Data Bank and modified using PyMOL (https://pymol.org/2/) [18]-[21]. Then, molecular docking was performed using PyRx (https://pyrx.sourceforge.io/) to predict the binding affinity of linolenic acid to PPAR-δ. The docking results were analyzed by calculating the Root Mean Square Deviation (RMSD) value to measure the accuracy of the model obtained [22]-[24].

In the data interpretation stage, Protein Plus (https://proteins.plus/) was used to analyze and visualize the interaction between linolenic acid and PPAR-δ [25]-[28]. In addition, this study also used Lipinski's Rule of Five with SwissADME software (http://www.swissadme.ch/) to predict the bioavailability of linolenic acid in biological systems. The results of all these analyses were then used to understand how linolenic acid from papaya could function as a PPAR-δ inhibitor in the treatment of colorectal cancer [29]-[32].

Figure 1 presents a concise flowchart of the research process, which unfolds through five distinct stages. Initially, in Stage 1, the 3D structure of the target protein is acquired from the Protein Data Bank, providing a foundational blueprint for subsequent analyses. Moving to Stage 2, this structure is then modified and visualized using PyMOL, a versatile molecular visualization system. Stage 3 involves the application of PyRx, a software tool for computational docking, to predict how different molecules, such as pharmaceutical compounds, interact with the protein. The fourth stage utilizes Protein Plus for an in-depth analysis and visualization of these

molecular interactions. Finally, the process culminates in Stage 5 with the use of SwissADME software, applying Lipinski's Rule of Five, to assess the bioavailability and pharmacokinetic properties of the compounds, ensuring their potential effectiveness as therapeutic agents. This structured approach is crucial for understanding molecular interactions and predicting the efficacy of compounds in biological systems.

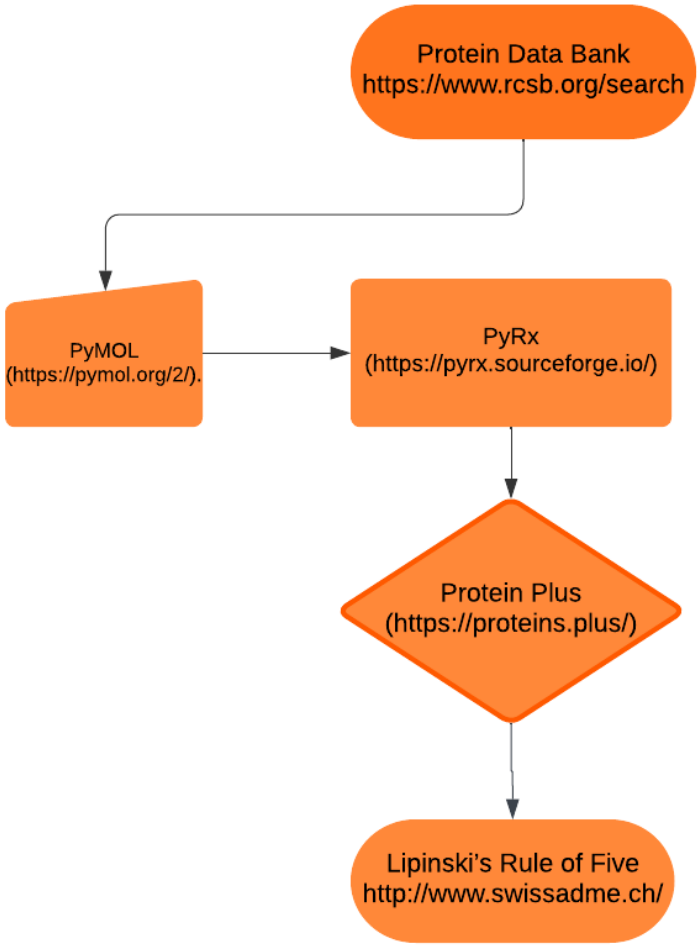

Figure 1. Flowchart Research

RESULT AND DISCUSSION

Molecular docking results showed the interaction between linolenic acid and peroxisome proliferator-activated receptor delta (PPAR-δ). The binding affinity values obtained were -6.9, -6.8, and -6.7, indicating a strong affinity between linolenic acid and PPAR-δ. The low RMSD values (0, 1.18, and 1.318) also indicate that the obtained model has good accuracy. This indicates that linolenic acid is able to bind to PPAR-δ and has the potential to inhibit its activity [33]-[34]. Table 1 shows the results of binding affinity and RMSD

Table 1. Binding affinity and RMSD results

Ligand	Binding Affinity (Kcal/mol)	rmsd/ub (Å)	rmsd/lb (Å)
2znp_5280934_uff_E=2066.03	-6.9	0.0	0.0
2znp_5280934_uff_E=2066.03	-6.8	2.423	1.18
2znp_5280934_uff_E=2066.03	-6.7	10.021	6.356
2znp_5280934_uff_E=2066.03	-6.7	7.479	3.246
2znp_5280934_uff_E=2066.03	-6.4	3.443	1.318
2znp_5280934_uff_E=2066.03	-6.4	10.274	6.667
2znp_5280934_uff_E=2066.03	-6.4	8.497	5.403
2znp_5280934_uff_E=2066.03	-6.3	8.243	4.133
2znp_5280934_uff_E=2066.03	-6.3	9.0	5.976

Further interaction analysis using Protein Plus validated the molecular docking results and provided a deeper understanding of the interaction. Linolenic acid was seen to interact with several important amino acid residues within the PPAR-δ binding site. This suggests that linolenic acid has the potential to influence PPAR-δ activity, which may impact the process of colorectal carcinogenesis [35]-[37]. Figure 2 illustrates a 3D visualization of these interactions, highlighting the specific points where linolenic acid binds to the receptor, thereby offering a visual representation of its potential mechanistic action.

According to Lepinski's Rule of Five, compounds with a molecular mass of less than 500, no more than 5 hydrogen bond donors, no more than 10 hydrogen bond acceptors, and a logP value of no more than 5 have good oral bioavailability potential. Linolenic acid which has a molecular mass of 249, 1 hydrogen bond donor, 2 hydrogen bond acceptors, and a logP value of 0.8005 indicates that this compound has good bioavailability potential. The molar reactivity of 64.0568 also indicates that linolenic acid has sufficient reactivity potential in biological systems. This suggests that linolenic acid not only has potential as a PPAR-δ inhibitor, but also has the potential to be absorbed and react effectively in the body [38]-[39]. Table 2 shows the data from Lipinski.

Table 2. Lipinski data

Mass	Hydrogen bond donor	Hydrogen bond acceptor	LOGP	Molar reactivity
249.000000	1	2	0.800550	64.056801

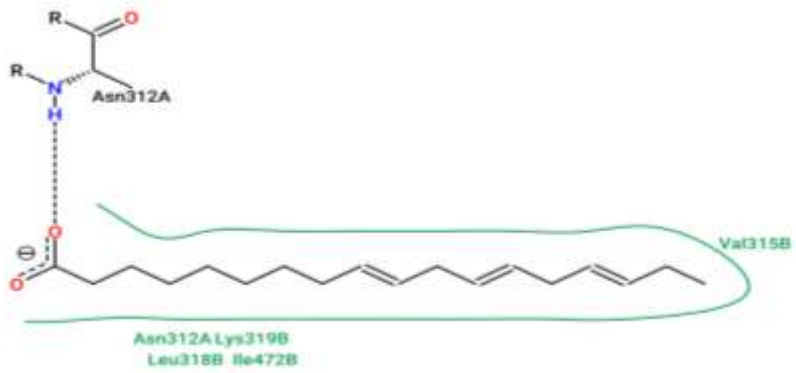

Figure 2. 3D visualization

Based on the analysis, it can be interpreted that linolenic acid from the papaya plant (Carica papaya) has potential as an inhibitor of peroxisome proliferator-activated receptor delta (PPAR-δ). The fact that linolenic acid shows a strong affinity towards PPAR-δ, coupled with its low RMSD value, indicates its ability to interact and potentially modulate PPAR-δ activity. Given the role of PPAR-δ in the process of colorectal carcinogenesis, these results suggest the potential of linolenic acid as an anticancer agent in the context of colorectal cancer [40]-[41].

Protein Plus analysis provides a deeper understanding of how linolenic acid interacts with PPAR-δ at the molecular level. The interaction of linolenic acid with key amino acid residues in the PPAR-δ binding site showed potential inhibition of PPAR-δ activity. Thus, linolenic acid could play a role in preventing or stopping the process of colorectal carcinogenesis by inhibiting PPAR-δ activity [42]-[43]. Figure 3 presents linolenic acid as a ligand before optimization, providing insight into its initial molecular structure, and Figure 4 depicts the linolenic acid ligand after optimization, illustrating the changes and improvements in its molecular configuration for effective interaction. Figure 5, showcasing the "PPRAD net protein," further illustrates the complex network of protein interactions involving PPAR-δ, highlighting its significance in the broader biological context.

In addition, evaluation of the bioavailability of linolenic acid using Lipinski's Rule of Five showed that this compound has characteristics that correspond to compounds that have good oral bioavailability. In other words, linolenic acid has the potential to be effectively absorbed and utilized by the body. The high molar reactivity indicates that linolenic acid can react under biological conditions and has the potential to respond to biological environmental conditions. Overall, the interpretation of this study is that linolenic acid from papaya plant has potential as an inhibitory agent for colorectal cancer cells [44]-[45].

From the perspective of previous research, this study provides a significant step forward in linking linolenic acid, which has been known to have anticancer effects, to its specific role in colorectal carcinogenesis through the inhibition of peroxisome proliferator-activated receptor delta (PPAR-δ). Although previous studies have shown the anticancer effects of linolenic acid and the role of PPAR-δ in colorectal cancer, this study is the first to directly demonstrate the link between the two. This paves the way for further research that could lead to more effective and safe phytopharmaceutical-based therapies for colorectal cancer [46]-[48].

From a methodological perspective, this study uses computational simulation and molecular modeling approaches to understand the interaction of linolenic acid and PPAR-δ. This allows researchers to explore and predict such interactions without the need to conduct direct experiments, which can be time-consuming and costly [49]-[50]. This method has been shown to be effective in other studies in understanding molecular interactions and their role in various diseases, and these results suggest that it is also applicable in the context of linolenic acid and PPAR-δ.

From the perspective of clinical potential, this study suggests that linolenic acid from the papaya plant may function as an inhibitor of PPAR-δ, which could potentially be used as a therapeutic agent in the treatment of colorectal cancer. Although more studies are needed to validate these effects in clinical models, these results suggest that phytopharmaceuticals based on linolenic acid could potentially be a safer and effective alternative in treating colorectal cancer [51]-[53].

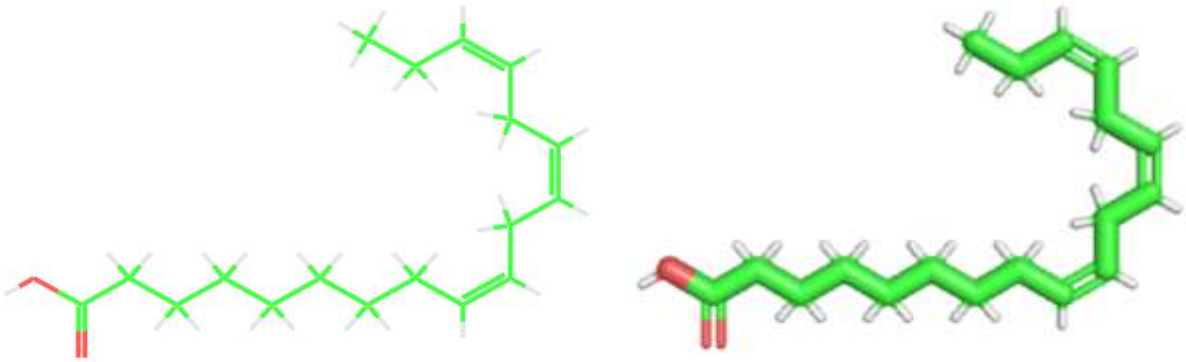

Figure 3. Linolenic Acid ligand before optimization

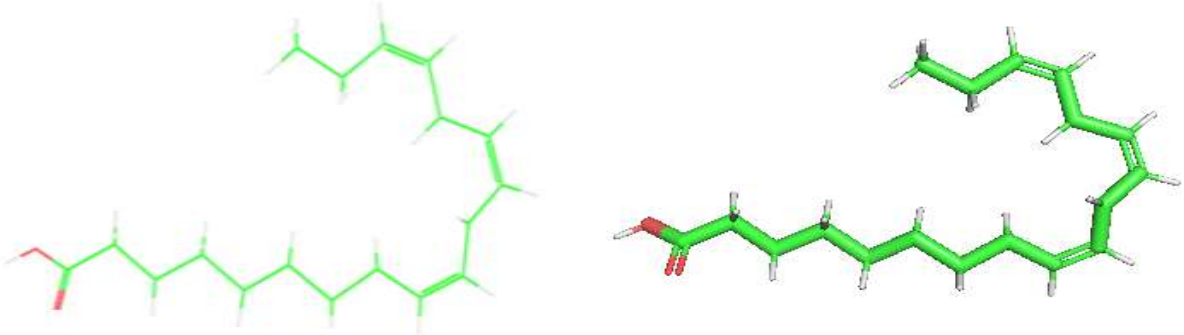

Figure 4. Linolenic Acid ligand after optimization

Figure 5. PPRAD net protein

CONCLUSION

This study explores the potential of linolenic acid from the papaya plant (Carica papaya) as an inhibitor of peroxisome proliferator-activated receptor delta (PPAR-δ) in the context of colorectal cancer. Through computational modeling and simulation approaches, the results showed that linolenic acid has a strong affinity to PPAR-δ and has the potential to influence its activity. Further interpretation suggests that linolenic acid may function as an inhibitor of PPAR-δ, which may contribute to the prevention or termination of the colorectal carcinogenesis process. In addition, linolenic acid also shows good characteristics in terms of bioavailability and reactivity in biological systems. Thus, this study demonstrates the potential of linolenic acid from papaya plants as an anticancer agent for the treatment of colorectal cancer. However, further studies are needed to validate these findings in clinical models and develop more effective and safe phytopharmaceutical-based therapies.

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