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Exploring molecular docking strategies to target Cox-1 pain receptors with Caffeic Acid, Caftaric Acid, Alkyl Amide, and Indomethacin Ligands in the context of Fibromyalgia: A Pyrex software approach

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ABSTRACT

This research investigates the potential therapeutic effects of four ligands on fibromyalgia-related pain: caffeic acid, Caftaric acid, alkyl amide, and indomethacin. It will achieve this by studying their interaction with Cox-1 pain receptors. Computational simulations will gain insights into the binding affinities and molecular interactions between these ligands and Cox-1. Pyrex software will be used to employ molecular docking techniques for this study. The analysis will focus on four ligands with diverse origins and mechanisms of action: caffeic acid, Caftaric acid, alkyl amide, and indomethacin. The analysis showed that alkyl amide exhibited promising binding energy (-9), better than the reference ligand indomethacin. The values for Caftaric acid (-8.2) and Caffeic acid (-6.5) were comparable to the redocking score. The ADME prediction of Alkylamide showed good gastrointestinal absorption and comparably higher log p values. The main objective of this research is to bridge the gap between computational modeling and clinical applications of fibromyalgia treatment. The findings will provide valuable insights for future experimental studies and potential advancements in managing fibromyalgia.

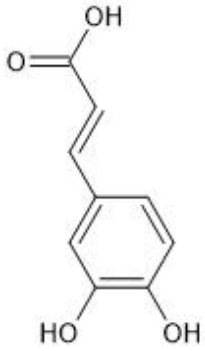
INTRODUCTION

Fibromyalgia is a chronic pain disorder characterized by widespread musculoskeletal pain, fatigue, and tender points.[1]. While the exact cause of fibromyalgia remains elusive, it is believed to involve abnormalities in pain processing within the central nervous system[2]. Cyclooxygenase-1 (Cox-1), an enzyme responsible for prostaglandin synthesis, has been implicated in the modulation of pain and inflammation. Using the Pyrex software, molecular Docking is used to investigate the potential interactions between fibromyalgia-related Cox-1 and four different ligands caffeic acid, Caftaric acid, alkyl amide, and indomethacin. Molecular Docking Molecular Docking is a computational technique employed in drug discovery and medicinal chemistry to predict the binding affinity and interaction between a ligand (small molecule) and a target protein [3]. Cyclooxygenases convert arachidonic acid into prostaglandins, which are vital in the body's inflammatory and pain responses. Cox-1 is primarily responsible for maintaining normal physiological functions, including protecting the gastric lining. In contrast, Cox-2 is inducible and associated with inflammation and pain. However, Cox-1 also plays a role in mediating pain responses. In the context of fibromyalgia, understanding the interaction between Cox-1 and potential ligands can offer insights into pain modulation and therapeutic interventions.[4. Caffeic acid is a naturally occurring polyphenol in various plants, particularly coffee and fruits. It is known for its antioxidant properties and potential anti-inflammatory effects, which could be relevant in managing fibromyalgia-related pain.[5]

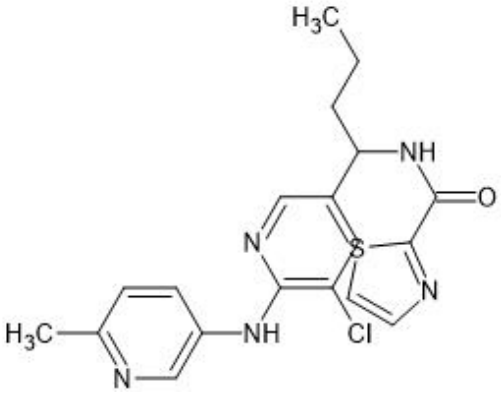
Caftaric acid [6]is another phenolic compound commonly found in coffee. Like caffeic acid, it possesses antioxidant and anti-inflammatory properties that may be beneficial in alleviating fibromyalgia symptoms.

Alkyl amides [7]are synthetic compounds designed to target specific pain receptors. They have shown promise in modulating pain signaling pathways and may be relevant to fibromyalgia.

Indomethacin: Indomethacin is a non-steroidal anti-



Caffeic acid



Alkylamide

inflammatory drug (NSAID) that inhibits Cox-1 and Cox-2. It relieves pain and reduces inflammation in various conditions, including rheumatoid arthritis and osteoarthritis. Molecular Docking with Pyrex Software Pyrex is a widely used molecular docking software tool that enables researchers to simulate the interactions between ligands and target proteins. Using Pyrex, researchers can predict the binding affinity, identify potential binding sites, and analyze the interactions at the molecular level.[8]

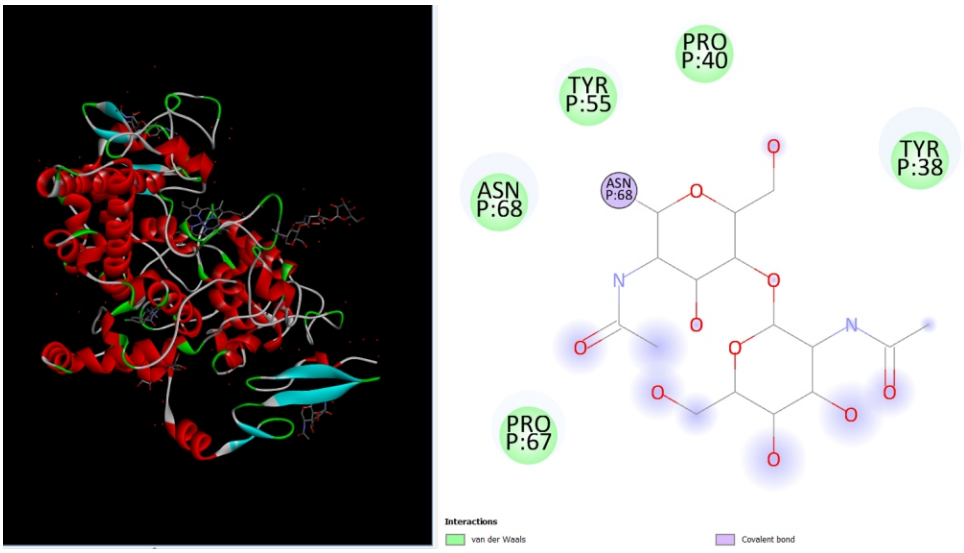
MATERIALS AND METHODS

The 3D receptor structure with 2OYU Indomethacin-(s) alpha ethyl thioethanolamine bound cyclooxygenase was obtained from the RCSB Database (www.rcsb.org/pdb). PyRX software was utilized for this study. It is developed in Python and can be downloaded and executed on any computer that meets the required configuration and specifications. A Dell Intel Core i5 8th Generation system with 8 GB RAM, running Windows 10 software and featuring HD Graphics, was used for this study. The Sdf format of ligands was downloaded from Pub Chem to obtain input files. Auto dock Vina was used for Docking using PyRX, which provides the Vina algorithm. The receptor and ligand were loaded and prepared for Docking. The PDBQT files were then prepared, and the grid box was established by selecting the protein and ligand and proceeding by clicking forward. After the grid box was generated, it was adjusted according to the docking requirements, and the level of docking exhaustiveness was specified by entering the relevant numerical value. Finally, the docking process was initiated by clicking the forward button, and the poses, affinities, and RMSD values were obtained. The PDB/PDBQT protein and vina output files were then opened in PYMOL for analysis.

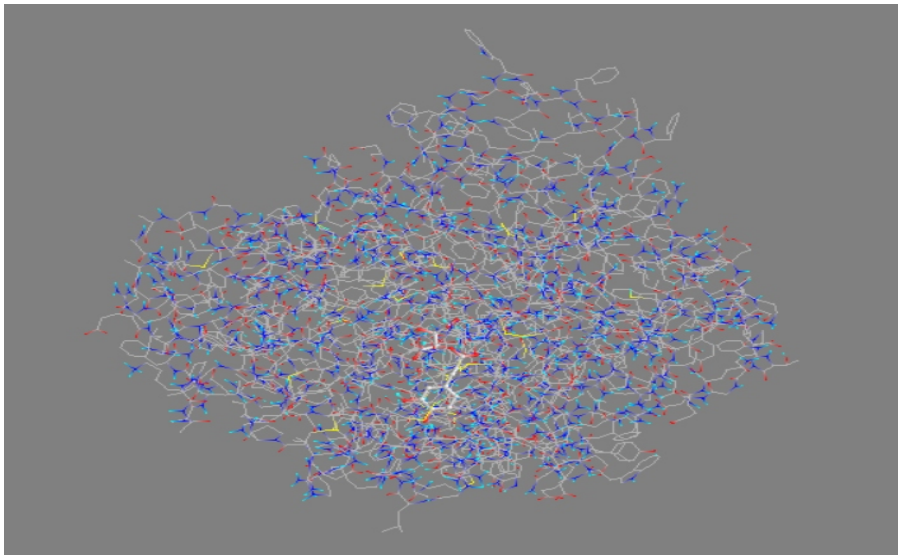
Swiss ADME

Drug-likeliness RADAR of compounds with good activity and ADME prediction were obtained using Swiss ADME Bioavailability. Redocking was performed using the same procedure, and the binding affinity was obtained[9].

RESULTS



RECEPTOR PDBID 2OYU Indomethacin-(s) alpha ethyl thioethanolamine bound cyclooxygenase
(Source : https://www1.rcsb.org/3d-view/jsmol/2OYU/undefined)



Docked ligand Cafftaric acid image using Pyrex software and Biova discovery Visualizer. The ligand is seated in a pocket of the protein.

Table 1: Docking Results

Ligand	*Binding Affinity	rmsd/ub	rmsd/lb
Indomethacin	**-7.2**	**0**	**0**
Caftaric acid	-8.2	0	0
Alkyl amide	-9	0	0
Caffeic acid	-6.5	0	0

***n=9** (Binding Affinity Of 2OYU Protein and Ligands in the Context of Fibromyalgia using Pyrex Software)

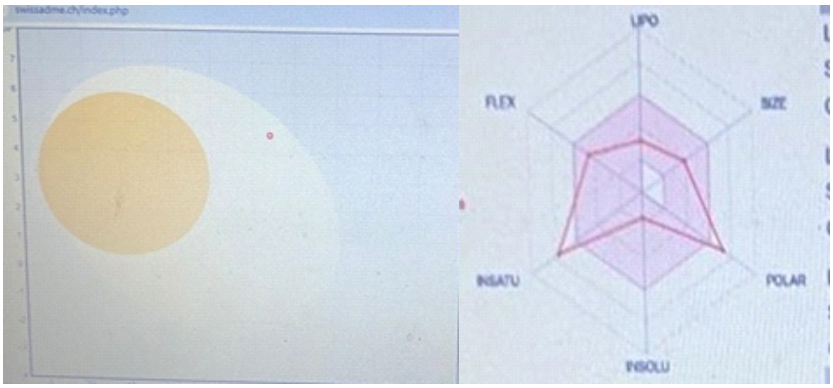


Figure 3 : Boiled egg and Bioavailability Radar Cafftaric acid using Swiss ADME software predicting the blood-brain barrier and lipophilicity and hydrophilicity

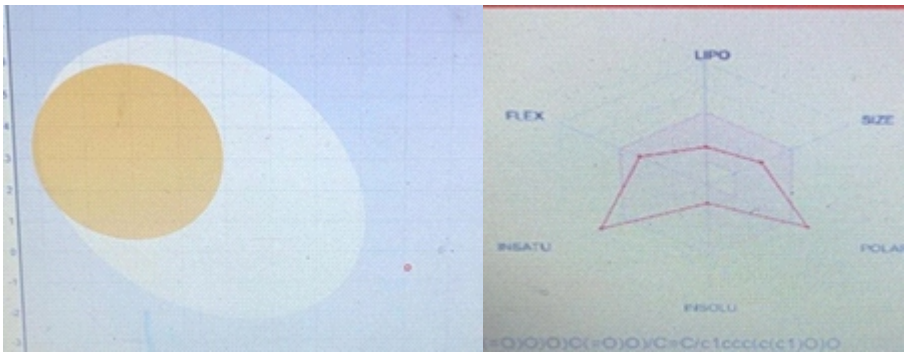


Figure 4 : Figure Boiled egg and Bioavailability Radar Alkyl amide using Swiss ADME software predicting the blood-brain barrier and lipophilicity and hydrophilicity

Table 2 : Swiss ADME Prediction

Property	Cafftaric acid	Alkyl amide
lipophilicity	Log p 0.25	Log p 3.15
Water solubility	Log s-1.55	Log s-7.3
Absorption	GI -low BBB-no	GI -high BBB-No
Drug Likeliness	Lipinski-0 Violation	Lipinski-0 Violation

(This table shows the blood-brain barrier penetration and the drug-likeliness characteristics that are essential for developing a pharmaceutical formulation)

DISCUSSION

The analysis showed that alkyl amide exhibited promising binding energy (-9), better than the reference ligand indomethacin. The values for Caftaric acid (-8.2) and Caffeic acid (-6.5) were comparable to the redocking score. (Table 1). The ADME prediction of Alkylamide showed good gastrointestinal absorption and comparably higher log p values. (Table 2). Although computational modeling identified alkyl amide as a promising candidate with superior binding energy and favorable drug absorption characteristics compared to established treatments like indomethacin, further in vitro and in vivo studies are essential. These biological experiments will validate the effectiveness and safety of alkyl amide for fibromyalgia, bridging the gap between computational modeling and real-world applications. Ultimately, these findings pave the way for future advancements in fibromyalgia management. These ligands have been proven for use in neuropathic pain [10]. Fibromyalgia is a complex condition to manage, causing chronic pain and other symptoms that severely affect a patient's quality of life. Though traditional treatments, such as indomethacin, have offered some relief, researchers are always searching for safer and more effective therapeutic options. One potential tool for identifying promising candidates is computational modeling. Recent research has employed computational analyses and ADME predictions to explore the potential of alkyl amide as a novel fibromyalgia treatment. The computational analysis found that alkyl amide had a higher binding energy than other ligands, including Caftaric acid, Caffeic acid, and even indomethacin. This suggests that alkyl amide may interact more effectively with the target site implicated in fibromyalgia pathophysiology, making it a promising candidate for further investigation.

Additionally, ADME predictions showed that alkyl amide had favorable gastrointestinal absorption and higher log P values, indicating that it could be effectively administered orally and have enhanced bioavailability. While computational modeling provides valuable insights into ligand-target interactions and pharmacokinetic properties, validating these findings through rigorous in vitro and in vivo studies is essential. This is crucial to determine alkyl amide's efficacy and safety profile in the context of fibromyalgia. Clinical trials are also necessary to assess the real-world effectiveness of alkyl amide compared to existing therapies, given the complex nature of fibromyalgia and the variability in individual treatment responses. Computational modeling is essential in identifying potential drug candidates with enhanced therapeutic profiles. However, it's vital to acknowledge the limitations of computational modeling and take a multidisciplinary approach to drug discovery, including computational biology, medicinal chemistry, and pharmacology, as well as collaborative efforts between computational scientists, pharmacologists, and clinicians. Through these efforts, we can advance our understanding of fibromyalgia pathophysiology and identify innovative therapeutic strategies to improve patient quality of life.

CONCLUSION

Molecular docking studies using Pyrex software can provide valuable insights into the potential interactions between Cox-1 and various ligands such as caffeic acid, Caftaric acid, alkyl amide, and indomethacin. Understanding these interactions at the molecular level may shed light on the modulation of pain pathways and the development of novel treatments for fibromyalgia. While computational simulations are a crucial first step, further research and experimental validation are necessary to confirm the therapeutic potential of these ligands in the context of fibromyalgia management. Since both compounds have no blood-brain penetration, derivatives may be prepared for better BBB and bioavailability.

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