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Molecular docking reveals goldband goatfish fatty acid's COX-2 inhibitory potential

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ABSTRACT. Goldband goatfish, known for its high protein and fatty acid content, serves as a valuable food source contributing to human nutrition and well-being. This study delves into the potential anti-inflammatory properties of goldband goatfish fatty acids, specifically palmitic acid, docosahexaenoic acid, and eicosapentaenoic acid, by targeting the inhibition of cyclooxygenase-2 (COX-2) protein. Through molecular docking experiments utilizing Molegro Virtual Docker version 5.0 and Discovery Studio version 21.1.1, the fatty acid structures were redocked with the COX-2 protein, with naproxen employed as a control COX-2 inhibitor. The analysis revealed interactions between the fatty acids and specific residues within the COX-2 inhibitor sites, mirroring the active sites targeted by naproxen, suggesting their potential as effective COX-2 blockers to mitigate inflammation. The findings suggest that the fatty acids present in goldband goatfish possess promising anti-inflammatory effects through their ability to inhibit COX-2 activity. By binding to key residues within the COX-2 inhibitor sites, these fatty acids exhibit similarities to naproxen, a known COX-2 inhibitor. This study lays the groundwork for further investigations, including molecular dynamics simulations and in vitro experiments, to validate the anti-inflammatory efficacy of goldband goatfish fatty acids and their potential as therapeutic agents for combating inflammation. The identification of natural compounds with COX-2 inhibitory properties opens avenues for the development of novel anti-inflammatory treatments derived from marine sources, contributing to the advancement of preventive and therapeutic strategies for inflammatory diseases.

Keywords: Cyclooxygense-2; goldband goatfish; inflammation; ligands-protein complex visualization; molecular docking

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INTRODUCTION

Locally known as ikan biji nangka, or goldband goatfish (*Upeneus moluccensis*, Bleeker 1985), this species is a crucial part of the diet in Maumere Bay, Flores, Indonesia, providing high levels of protein and fatty acids. The mangrove ecosystems in this region play a vital role in the life cycle of the goldband goatfish, serving as breeding, feeding, and nursery grounds. The fish are well adapted to these coastal mangrove waters, which offer a suitable habitat that supports their growth and sustenance. The goldband goatfish are also notable for their accessibility to local fishermen, as they can be effectively captured using gillnets, trammel nets, and other net-based fishing equipment (Vincentius, 2020). This ease of capture has led to a significant annual yield of the fish, with production figures ranging from 68 tons to 83 tons between 2016 and 2021, according to the local fisheries department (Dinas Perikanan Kabupaten Sikka, 2021). This substantial output underscores the importance of Maumere Bay's waters as a productive fishing ground, contributing to the local economy and food security.

Goldband goatfish are highly valued for their exceptional nutritional profile. Proximate analysis reveals that their moisture content ranges from 78% to 80%, while their crude ash content is between 1.5% and 1.9%. They contain 1.4% to 3.7% crude fat and an impressive 20% to 22% crude protein (Doğan & Ertan, 2017). This high protein content is enriched with essential amino acids such as lysine, leucine, aspartic acid, and glutamic acid, making goldband goatfish a highly nutritious food

source that supports human health and dietary needs (Doğan & Ertan, 2017; Küçükgülmez *et al*., 2018).

In addition to their macronutrient content, goldband goatfish are rich in essential minerals. They are particularly abundant in potassium (K) and phosphorus (P), which are crucial for various bodily functions, including muscle contraction and bone health. The fish also contain other vital minerals, including iron (Fe), sodium (Na), magnesium (Mg), cadmium (Cd), chromium (Cr), copper (Cu), manganese (Mn), and zinc (Zn) (Öksüz *et al*., 2011). This diverse mineral composition enhances the nutritional value of the goldband goatfish, making them a significant dietary resource for communities that rely on them as a staple food.

The fatty acid content of goldband goatfish is notably high and diverse, including palmitic acid, stearic acid, palmitoleic acid, oleic acid, eicosatrienoic acid, arachidonic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) (Krisnamurti & Fatchiyah, 2020). These fatty acids, particularly the polyunsaturated fatty acids (PUFAs), are essential for human health. They play a significant role in promoting overall well-being and are crucial for maintaining various bodily functions. The presence of these fatty acids in goldband goatfish makes them a valuable dietary source for those seeking to enhance their nutritional intake with beneficial lipids. The health benefits of fish-derived fatty acids are well-documented, particularly in reducing the risk of chronic diseases. PUFAs, such as omega-3 and omega-6 fatty acids, are known for their ability to lower the incidence of cardiovascular diseases, strokes, type-2 diabetes, and certain types of cancer (Kundam *et al*., 2018). EPA and DHA, in particular, have been shown to improve brain function, exhibit antitumor activities, and regulate lipid and glucose metabolism (Lane *et al*., 2014; Zhang *et al*., 2019). These fatty acids are essential for maintaining cognitive health, preventing tumor growth, and managing metabolic disorders, highlighting the importance of incorporating fish like goldband goatfish into one's diet.

Furthermore, PUFAs play a critical role in regulating inflammation in the body. Omega-3 and omega-6 fatty acids act as lipid precursors that modulate inflammatory responses. Arachidonic acid, a specific type of omega-6 fatty acid, serves as a substrate for cyclooxygenase-1/2 enzymes, leading to the production of pro-inflammatory compounds like prostaglandin H2 (PGH2). However, due to their structural similarity to arachidonic acid, PUFAs can also exhibit anti-inflammatory properties, helping to balance the body's inflammatory processes. This dual role of PUFAs in promoting and regulating inflammation underscores their importance in maintaining health and preventing inflammatory-related conditions (Wall *et al*., 2010; Marion-Letellier *et al*., 2015).

Previous research has demonstrated that various bioactive compounds exhibit anti-inflammatory properties by inhibiting cyclooxygenase (COX) enzymes. For example, compounds found in ginger rhizomes have been shown to inhibit both COX-1 and COX-2, reducing inflammation effectively (Zhang *et al*., 2021). Similarly, compounds present in coffee have been reported to alleviate pain by targeting and inhibiting COX proteins. Additionally, anthocyanins from black rice have been found to prevent inflammation by inhibiting the production of pro-inflammatory cytokines (Sapkota *et al*., 2019). These studies collectively highlight the potential of natural compounds in managing inflammation through COX inhibition (Choi *et al*., 2017; Mahboubi *et al*., 2019; Mao *et al*., 2019; Sapkota *et al*., 2019; Krisnamurti & Fatchiyah, 2020; Nunes *et al*., 2020; Spisni *et al*., 2020; Zhang *et al*., 2021).

Building on this body of research, the study at hand explored the anti-inflammatory properties of fatty acids from goldband goatfish using a molecular docking approach to assess their ability to inhibit COX-2 (Spisni *et al*., 2020). This method allows for the prediction of how these fatty acids interact at the molecular level with COX-2, a key enzyme involved in the inflammatory process (Bare *et al*., 2019a; Bare *et al*., 2019b; Bare *et al*., 2019c). By demonstrating the potential of goldband goatfish fatty acids to inhibit COX-2, the study suggests that these fatty acids could be effective in reducing inflammation, similar to the effects observed with ginger, coffee, and black rice compounds (Sari *et al*., 2019). This adds a new dimension to the nutritional and therapeutic value of goldband goatfish, reinforcing their significance in promoting health and managing inflammation.

MATERIALS AND METHODS

Fatty acid structure retrieval. To study the anti-inflammatory properties of fatty acids found in goldbandfish goatfish, specific fatty acid structures were utilized, including palmitic acid (CID 985), docosahexaenoic acid (CID 445580), eicosapentaenoic acid (CID 446284), and docosapentaenoic acid (CID 5497182). These chemical structures were sourced from the PubChem NCBI database, a comprehensive repository for chemical molecules and their activities against biological assays (Kim *et al*., 2016). By extracting the structural information in sdf file format, researchers ensured they had accurate representations of these fatty acids for further analysis. These sdf files, containing the 3D molecular structures of the fatty acids, were then imported into Molegro Virtual Docker 5.0, a software tool used for molecular docking studies. Molecular docking is a method that predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex (Bitencourt-Ferreira & de Azevedo, 2019). By using Molegro Virtual Docker 5.0, researchers could simulate and analyze how these fatty acids interact with the cyclooxygenase-2 (COX-2) enzyme at the molecular level. This approach provides insights into the potential inhibitory effects of these fatty acids on COX-2, thereby elucidating their anti-inflammatory capabilities.

Cyclooxygenase-2 protein retrieval and optimization. The cyclooxygenase-2 (COX-2) protein structure, essential for the molecular docking study, was obtained from the Protein Data Bank using the accession code 3NTB (Duggan *et al*., 2010). To prepare the protein for docking, it was cleaned to remove any undesirable ligands and molecules, ensuring that only the relevant structure was used in the analysis. The cleaned structure, in pdb format, was then imported into Molegro Virtual Docker version 5.0, a software tool designed to facilitate the docking process (Bitencourt-Ferreira & de Azevedo, 2019). Within Molegro Virtual Docker, the binding cavities of the COX-2 protein were identified using van der Waals expansion with a maximum of 5 as the molecular surface parameter. This step is crucial for accurately determining the potential interaction sites for the ligands. The specific binding cavities on the COX-2 protein were located on a grid with coordinates X = -19.67, Y = 52.07, Z = -7.12, and a radius of 12. This defined grid was then used as the docking position, enabling precise simulations of how the fatty acids from goldband goatfish might interact with and potentially inhibit the COX-2 enzyme, thereby providing insights into their anti-inflammatory properties.

Molecular docking simulations. In the study, the fatty acid compounds from goldbandfish goatfish were redocked into the binding cavities of the cyclooxygenase-2 (COX-2) protein to assess their interaction potential. This redocking process was carried out using Molegro Virtual Docker version 5.0, a specialized software for molecular docking studies (Bitencourt-Ferreira & de Azevedo, 2019). The specific settings for the docking simulation included using the Moldock Score function for scoring, with a grid resolution of 0.30 to precisely map the interactions. The algorithm employed was MolDock SE, which is designed for efficient and accurate docking simulations. Key parameters included a maximum of 1500 iterations, a maximum population size of 50, and a pose generation energy threshold set at 100, with 10 to 30 tries per pose generation attempt. Further settings fine-tuned the docking process to ensure accurate and reliable results. The simplex evolution maximum steps were set to 300, with a neighbor distance factor of 1.00, allowing the algorithm to explore various conformations of the fatty acid molecules within the binding site. Multiple poses were generated for each docking attempt, with up to five different poses considered, and an energy threshold of 0.00 was used to filter the poses (Duggan *et al*., 2010). To cluster similar poses, a root-mean-square deviation (RMSD) threshold of 1 was applied. These parameters ensured that the docking simulation could effectively identify the most stable and relevant interactions between the goldband goatfish fatty acids and the COX-2 protein, providing insights into their potential inhibitory effects and anti-inflammatory properties.

Ligands-protein complex visualization and analysis. Several scoring functions supplied by Molegro Virtual Docker were used to quantify the interaction energy between the cyclooxygenase-2

(COX-2) protein and the goldband goatfish fatty acid ligands. The strength and stability of the ligand-protein interactions were specifically assessed using the MolDock Score, Moldock Grid Score, and Rerank Score (Duggan *et al*., 2010; Bare *et al*., 2019a; Bitencourt-Ferreira & de Azevedo, 2019; Bare *et al*., 2020; Sari *et al*., 2022). These values, which indicate the average binding energy of five distinct ligand-protein complex models, are expressed in kilojoules per mole (kJ/mol). With this multi-score technique, the robustness and reproducibility of the docking results are enhanced and the interaction energies are comprehensively understood.

Version 21.1.1 of the Discovery Studio software was used to construct both 2D and 3D visuals in order to further examine and explain the docking data (Bare *et al*., 2019a; Bare *et al*., 2020; Bare *et al*., 2022; Sari *et al*., 2022). The spatial arrangement and interactions between the fatty acid ligands and the COX-2 protein are shown in depth by these graphics. While the 2D views draw attention to certain interactions like hydrogen bonds and hydrophobic contacts (Fig. 2), the 3D views enable researchers to see how the ligands fit and are oriented within the protein's binding cavity (Fig. 1). By using this dual visualization approach, the molecular interactions between the fatty acids in goldband goatfish and COX-2 are better understood, which aids in evaluating the potential of these compounds as anti-inflammatory medicines.

RESULTS AND DISCUSSION

The interaction between palmitic acid and COX-2 demonstrated a binding energy of approximately -190.4 kJ/mol. This interaction involved seven amino acid residues, categorized into three groups based on their interaction types. The hydrophobic alkyl interactions included residues VAL116, VAL349, VAL523, ALA527, and LEU531. Additionally, TYR355 was involved in a hydrophobic pi-alkyl interaction, and LEU531 also participated in an unfavourable bump interaction. These interactions highlight the non-polar nature of palmitic acid's binding with COX-2, primarily driven by hydrophobic forces (Fig. 1).

In contrast, docosahexaenoic acid (DHA) showed a stronger binding affinity with COX-2, with a binding energy of -299.6 kJ/mol. The interaction involved several amino acid residues, such as TYR385 forming a conventional hydrogen bond, and multiple residues (VAL116, VAL349, VAL523, ALA527, LEU352, LEU359, LEU351, ILE345, LEU531) engaging in hydrophobic alkyl interactions. Additionally, TYR355, TRP387, and PHE518 were involved in hydrophobic pi-alkyl interactions. This complex interaction profile indicates that DHA forms more extensive and stronger bonds with COX-2 compared to palmitic acid, likely contributing to its higher binding energy and potentially greater anti-inflammatory efficacy.

Eicosapentaenoic acid (EPA) exhibited the highest binding energy among the fatty acids studied, with an energy of -347 kJ/mol when interacting with COX-2. The interaction involved TYR385 forming a conventional hydrogen bond and SER530 engaging in a carbon hydrogen bond. Hydrophobic alkyl interactions were observed with residues VAL116, VAL349, VAL523, ALA527, LEU352, MET522, LEU531, and ARG120. Additionally, hydrophobic pi-alkyl interactions were noted with TYR355 and PHE518. The extensive and diverse nature of EPA's interactions with COX-2, including hydrogen bonding and multiple hydrophobic contacts, underscores its strong binding affinity and potential as an effective anti-inflammatory agent.

Naproxen's interaction with cyclooxygenase-2 (COX-2) is characterized by a series of amino acid residues that form stable bonds with the ligand. In this interaction, twelve amino acid residues are involved, contributing to the overall binding energy of approximately -208.4 kJ/mol. These residues engage in various types of interactions, including hydrogen bonds, hydrophobic interactions, and pi-alkyl interactions. Notably, residues such as VAL523 and ALA527 participate in a hydrogen bond type called carbon hydrogen bond, while VAL523 also engages in a pi-sigma hydrophobic interaction. Additionally, VAL116, LEU359, and LEU352 form hydrophobic alkyl interactions, while TYR355, PHE518, VAL349, LEU531, and ALA527 are involved in hydrophobic pi-alkyl

interactions. These interactions collectively contribute to the stable binding of naproxen within the COX-2 enzyme, potentially inhibiting its activity and exerting anti-inflammatory effects.

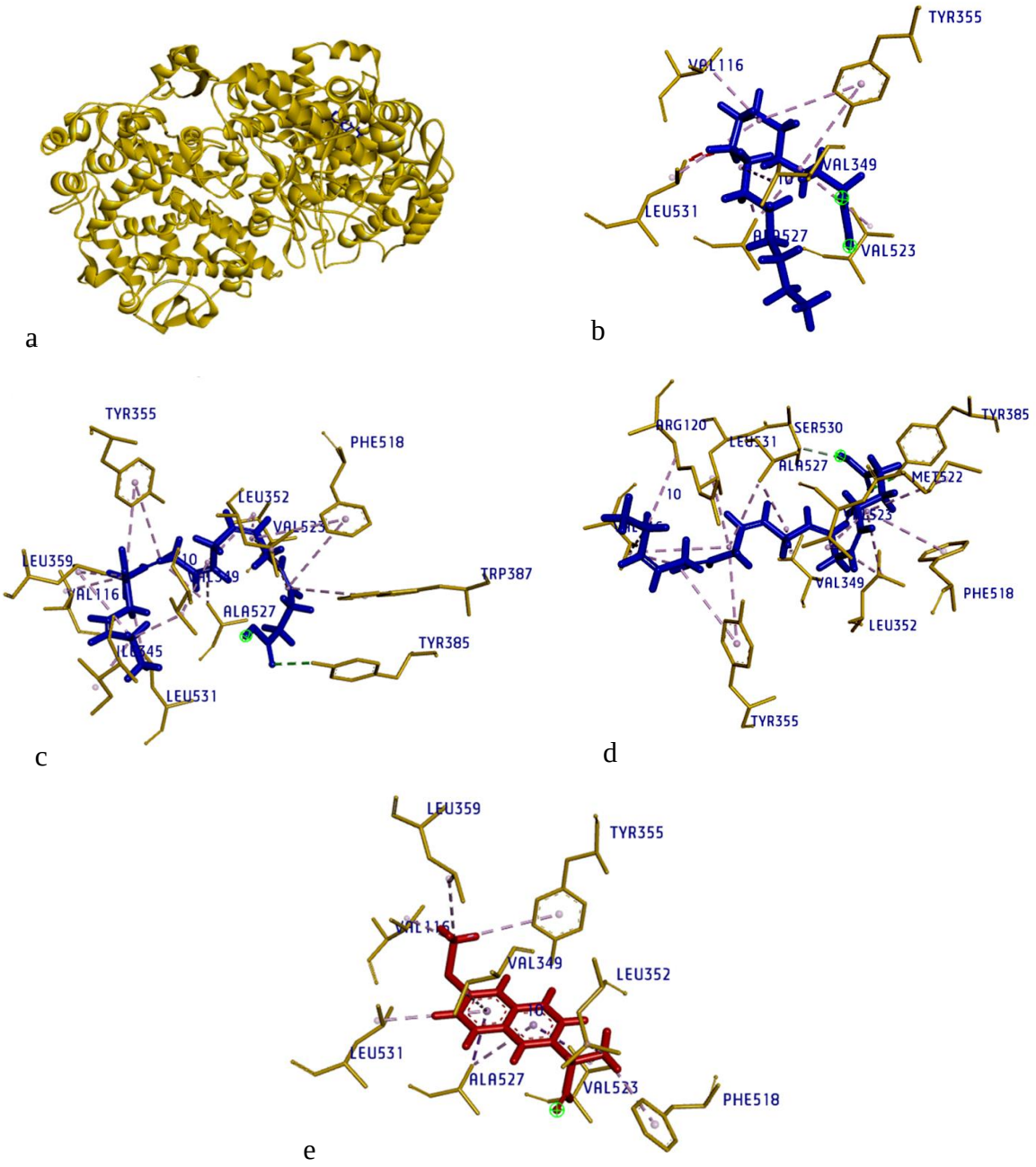

Fig. 1. 3D structure of interaction fatty acid-cyclooxygenase-2: a. Overview structure complex ligand-protein; b. Palmitic acid; c. Docosahexaenoic acid; d. Eicosapentaenoic acid; e. Naproxen

The diverse array of interactions observed between naproxen and COX-2 highlights the complex nature of ligand-protein binding. By engaging multiple amino acid residues through various interaction types, naproxen achieves a strong and stable binding within the enzyme's active site. This robust interaction profile likely contributes to naproxen's efficacy as a COX-2 inhibitor and its ability to alleviate inflammation. Understanding the specific amino acid residues involved in the interaction with naproxen provides valuable insights into the molecular mechanisms underlying its anti-inflammatory effects, facilitating the development of novel therapeutic agents targeting COX-2 for the treatment of inflammatory conditions.

The 3D structure of the interaction between fatty acids and cyclooxygenase-2 (COX-2) provides a comprehensive overview of how these ligands bind to the enzyme. The complex structure, visualized in 3D, allows researchers to observe the spatial orientation and specific binding sites of each fatty acid within the COX-2 enzyme. This holistic view is crucial for understanding the molecular basis of the binding interactions, revealing how the fatty acids fit into the binding cavities of COX-2 and how they might inhibit its activity. The detailed visualization aids in identifying the key amino acid residues involved in the interactions, offering insights into the potential efficacy of these compounds as anti-inflammatory agents (Fig. 1).

For palmitic acid, the 3D structure shows its interaction with the COX-2 enzyme, highlighting key hydrophobic interactions. Specifically, palmitic acid binds within the enzyme's binding cavity, interacting primarily with hydrophobic residues such as VAL116, VAL349, VAL523, ALA527, and LEU531. Additionally, it forms a pi-alkyl interaction with TYR355 and an unfavourable bump interaction with LEU531. These interactions indicate that palmitic acid primarily relies on hydrophobic contacts to stabilize its binding within the COX-2 enzyme, which may contribute to its moderate binding energy.

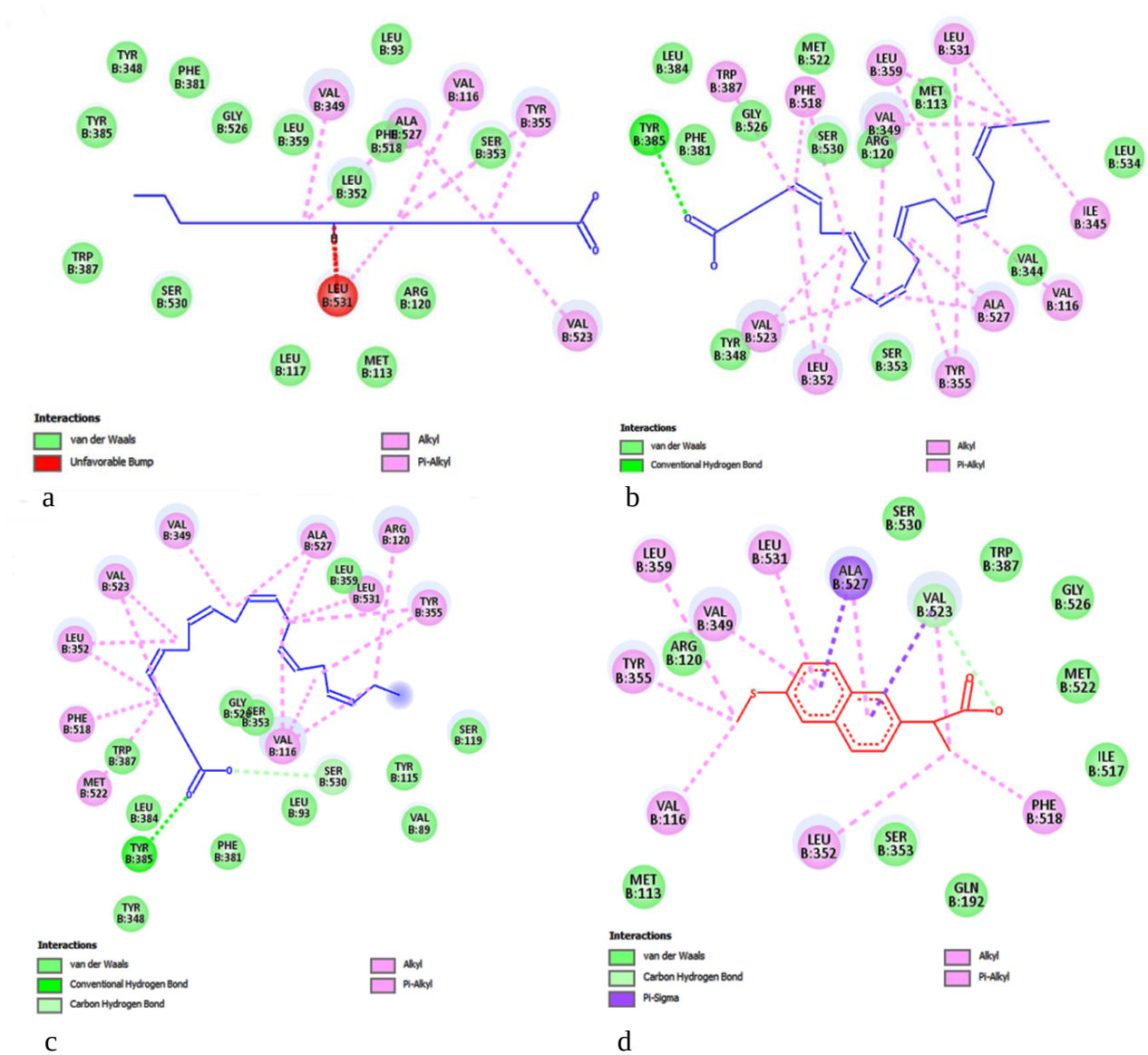

Fig. 2. 2D structure of interaction fatty acid-cyclooxygenase-2: a. Palmitic acid; b. Docosahexaenoic acid; c. Eicosapentaenoic acid; d. Naproxen

The interaction of docosahexaenoic acid (DHA) with COX-2 is more complex and extensive. The 3D structure reveals that DHA forms numerous interactions with the enzyme, including conventional hydrogen bonds with TYR385 and various hydrophobic interactions with residues such as VAL116, VAL349, VAL523, ALA527, LEU352, LEU359, LEU351, ILE345, and LEU531 (Fig. 1). Pi-alkyl interactions are also noted with TYR355, TRP387, and PHE518. These diverse interactions suggest a strong and stable binding of DHA within the COX-2 enzyme, reflecting its higher binding energy compared to palmitic acid. Similarly, eicosapentaenoic acid (EPA) exhibits even stronger binding, forming hydrogen bonds with TYR385 and SER530, along with multiple hydrophobic interactions with residues including VAL116, VAL349, VAL523, ALA527, LEU352, MET522, LEU531, and ARG120, and pi-alkyl interactions with TYR355 and PHE518. The robust binding profile of EPA underscores its potential as a highly effective COX-2 inhibitor.

Table 1. Interaction of fatty acid-cyclooxygenase-2

Ligand (binding energy (kJ/mol))	Residues (distance (A) Hydrogen bond	Hydrophobic	Unfavorable
Palmitic acid (-190.4)		Alkyl: VAL116 (4.1); VAL349 (4.7); VAL523 (5.02); ALA527 (3.9); ALA527 (3.5); LEU531 (5.4) Pi-Alkyl: TYR355 (5.3); TYR355 (5.1)	Unfavorable Bump: LEU531 (1.3), LEU531 (1.4)
Docosahexaenoic acid (-299.6)	Conventional Hydrogen Bond: TYR385 (3.84)	Alkyl: VAL116 (2.8), VAL349 (5.1), VAL523 (3.8), VAL523 (4.9), ALA527 (4.2), ALA527 (3.9), LEU352 (4.9), LEU352 (4.2), LEU359 (4.6), LEU531 (5.2), ILE345 (3.4), VAL349 (3.0), LEU359 (4.5), LEU531 (4.8) Pi-Alkyl: TYR355 (5.0), TYR355 (5.2), TRP387 (5.2), PHE518 (5.1), PHE518 (5.3)	
Eicosapentaenoic acid (-347)	Carbon Hydrogen Bond: TYR385 (3.0), SER530 (3.2)	Alkyl: VAL116 (5.4), VAL116 (3.6), VAL349 (4.2), VAL523 (4.8), VAL523 (4.7), ALA527 (3.7), ALA527 (4.2), LEU352 (4.9), MET522 (5.1), LEU352 (3.8), LEU531 (5.0), VAL116 (4.6), ARG120 (4.7) Pi-Alkyl: TYR355 (5.4), TYR355 (5.1), PHE518 (4.6)	
Naproxen (-208,4)	Carbon Hydrogen Bond: VAL523 (2.8)	Pi-Sigma: VAL523 (3.8), ALA527 (3.4) Alkyl: VAL116 (3.6), LEU359 (4.5), LEU352 (3.8), VAL523 (4.3). Pi-Alkyl: TYR355 (5.3), PHE518 (4.1), VAL349 (5.0), LEU531 (5.2), ALA527 (4.4)	

Additionally, the interaction of Naproxen, a known COX-2 inhibitor, provides a reference point for comparing the efficacy of fatty acids. Naproxen's 3D structure within COX-2 shows its well-established binding interactions, which serve as a benchmark for assessing the potential of palmitic acid, DHA, and EPA as COX-2 inhibitors. By comparing the binding modes and interaction energies of these fatty acids with those of Naproxen, researchers can better understand the relative strengths and weaknesses of each fatty acid as an anti-inflammatory agent, potentially guiding the development of new therapeutic strategies based on these natural compounds.

Several amino acid residues were found to be consistently involved in the interaction sites between fatty acids (palmitic acid, docosahexaenoic acid, eicosapentaenoic acid) and cyclooxygenase-2 (COX-2), as well as with Naproxen (Table 1). Among these residues, VAL523, VAL116, ALA527, TYR355, VAL349, and LEU531 were identified in the active sites of all fatty acids and Naproxen within the COX-2 enzyme. This consistency suggests a common binding pattern

shared by these compounds, indicating their potential to interact with COX-2 in a similar manner. Additionally, the residue LEU359 was specifically involved in the interaction with docosahexaenoic acid, further highlighting the distinct yet overlapping interaction profiles of different fatty acids with COX-2.

Furthermore, two residues of COX-2, LEU352 and PHE518, were identified in the interaction sites of docosahexaenoic acid and eicosapentaenoic acid. This indicates that these fatty acids share some common binding features with Naproxen, specifically interacting with these particular residues within the COX-2 enzyme. The consistent involvement of certain amino acid residues across different fatty acids and Naproxen suggests a shared mechanism of action in inhibiting COX-2 activity, which could contribute to their anti-inflammatory effects. These findings provide valuable insights into the molecular basis of fatty acids' interaction with COX-2 and their potential as natural anti-inflammatory agents.

COX-2 is an enzyme pivotal in the inflammatory response as it catalyses the synthesis of prostaglandin H2 (PGH2), a precursor to various pro-inflammatory prostaglandins (Rumzhum & Ammit, 2016; Ferrer *et al*., 2019). This study sheds light on the inhibitory effects of fatty acids derived from goldband goatfish on COX-2 protein activity, specifically targeting inhibitor sites. Prior research conducted by Duggan *et al*. (2010) identified specific amino acid residues, including VAL523, VAL116, ALA527, TYR355, VAL349, and LEU531, as the inhibitor sites of COX-2 protein (Sundari *et al*., 2022). These findings provide crucial insights into the molecular mechanisms underlying the inhibition of COX-2 activity, offering potential avenues for the development of novel anti-inflammatory therapies.

Moreover, several compounds with anti-inflammatory properties have been reported to act as inhibitors of COX-2. For instance, malic acid, xylose, benzoic acid, succinic acid, fumaric acid, rhamnose, and ethyl butyrate derived from *Elaeocarpus sphaericus* Schum fruit extract have demonstrated effectiveness in preventing inflammation as COX-2 inhibitors (Primiani *et al*., 2022). Additionally, compounds found in walnut oil have exhibited inhibitory effects on COX-2 protein activity. Notably, chlorogenic acid and quinic acid have been shown to inhibit COX-2 activity by blocking substrate sites, further highlighting the diverse range of natural compounds that can modulate inflammatory pathways through COX-2 inhibition (Bare *et al*., 2019a; Bare *et al*., 2019b).

These findings collectively underscore the potential of targeting COX-2 as a therapeutic strategy for managing inflammatory conditions. By elucidating the mechanisms by which various compounds, including fatty acids from goldband goatfish, exert their anti-inflammatory effects through COX-2 inhibition, researchers can explore novel avenues for drug development. Understanding the specific molecular interactions between these compounds and COX-2 provides valuable insights into their efficacy and potential for clinical use in treating inflammatory diseases.

CONCLUSION

The fatty acid compounds found in goldband goatfish, including palmitic acid, docosahexaenoic acid, and eicosapentaenoic acid, have been shown to exhibit anti-inflammatory effects by inhibiting the activity of cyclooxygenase-2 (COX-2). These compounds act as inhibitors of COX-2, a key enzyme involved in the synthesis of pro-inflammatory prostaglandins, thereby mitigating the inflammatory response.

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