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*Original Research Article*

# Molecular Docking Discovered Potential of Cyclooxygenase – 2 Inhibitor Activity of Oily Compounds of Walnuts

Sundari Sundari[1]*, Abdu Mas'ud[1], Dewi R. T. Sari[2]

[1]*Faculty of Teacher Training & Education, University of Khairun, Ternate, Indonesia*
[2]*Department of Pharmacy, Faculty of Medical Science, Universitas Ibrahimy, Situbondo, East Java, Indonesia*

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ABSTRACT

Walnut is a nutritional dietary food containing omega-3 and omega-6 that benefits for the human body. Walnut extract encourages biological properties, including lowering cholesterol, maintaining glucose, and preventing loss of memory and neurodegeneration. This study identified the anti-inflammatory property of walnut fatty acid compounds using molecular docking. Four fatty acid structures of walnut oil, oleic acid, γ – linolenic acid, linolenic acid, and Eicosapentaenoic acid were downloaded from PubChem NCBI database. Those compounds were interacted with cyclooxygenase-2 protein using Molegro Virtual Docker version 5.0, then visualized and analyzed using Discovery studio version 21.1.1. Molecular docking performed several interactions of fatty acids – cyclooxygenase-2 in the active residues. The LYS546, ARG44, THR60, TYR122, GLN543, PRO542, and PHE371 were identified at COX-2 inhibitors (Control) and walnut fatty acids. According to the binding energy, γ-linolenic acid was the lowest binding energy, i.e., -308.0 kJ/mol. Inhibition of fatty acid compounds from walnut extract at inhibitor region reducing cyclooxygenase-2 activities. Low cyclooxygenase-2 expressions might reduce inflammation. This study summarized that the fatty acid compounds of walnut oil promoted anti-inflammatory properties through cyclooxygenase-2 inhibitions.

***Keywords***: Cyclooxygenase -2, Docking, Fatty acid compounds, Walnut.

## Introduction

Walnut is a seed plant belonging to the *Juglandaceae* family and distributed to tropical and subtropical countries. In Indonesia, walnut has a local name *Kenari*. Walnuts are commonly known as nutritional dietary food, producing 40 – 70% oil and some phytochemical compounds[1–10]. Walnuts are rich in omega-3 and omega-6, and omega-3 was higher than pecans. Ninety percent of walnut oil contains unsaturated fatty acids, such as oleic acid, which is required for the human body.[11] All walnut plant contains some secondary metabolites. Walnut leaf contains tannins, fatty acid, ascorbic acid, phenolic acid, quercetin and their derivate, paracomaric acid, and juglone. The fruit husk covers organic materials, malic acid, citric acid, calcium oxalate, and glucose. Walnut seeds are composed of fatty acid, tocopherols, phenolic acid, and phytosterol.[1,3,4,7–9,11,12] Walnuts also contains main polyphenol, such as pedunculagin, ellagitannins, and urolithins B-D. Those polyphenols prevented the initiation and progression of cancer cells, and cardiovascular and neurodegenerative illnesses.[13] Walnut extract promotes some human health benefits as radical scavenger, neurodegenerative prevention, loss of memory prevention, cholesterol balancing, and glucose homeostasis.[13–15] Recent study reported that walnut leaves promoted glucose lowering in type-2 diabetes mellitus patients.[15] The other reports discovered the functional walnut leaf extract has antimicrobial, anthelmintic, antidiarrheal, and keratolytic properties.[9,11] The previous study, walnut oil extract proved to have high radical scavenger and antimicrobial activity. The high antioxidant might have potential anti-inflammatory properties.[1,4,15,5–9, 11,13,14]

*Corresponding author. E mail: sundari@unkhair.ac.id
Tel: +62 852-5571-9925

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Inflammatory is a biological and cellular process markedly by high cytokines such as interleukin and cyclooxygenase.[16–18] Cyclooxygenase inhibitor is a promised targeted therapy for reducing inflammation. Several bioactive compounds from natural herbs as anti-inflammatory have been identified.[19–26] Black rice anthocyanins are reported as an anti-inflammatory by pro-inflammatory cytokine blocking.[27] Ginger phenolic compounds also showed anti-inflammatory through inhibiting the cyclooxygenase.[28–34] Coffee bioactivities, including caffeine and quinic acid, also reduced the cyclooxygenase-2 activity.[35–39] Non–polar compounds from Cymbopogon leaves also reduce inflammation by lipoxygenase blocking.[40,41] Oil compounds were also reported as an anti-inflammatory, but the potent anti-inflammatory property of walnut oil compounds was limited to study. A recent meta-analysis study reviewed that the walnut diet significantly down-regulated total cholesterol, triglycerides, and LDL cholesterol. Besides, the walnut diet also repressed anti-inflammatory markers.[42] A positive report also showed that walnut peptide decreased cell apoptosis, had anti-inflammatory effects, and regulated the gut microbiota population.[43] Therefore, this study elucidated the mechanism of cyclooxygenase inhibition of unsaturated fatty acids from walnut oil by molecular docking.

## Materials and Methods

*Ligands structure retrieval*

3D structures of four identified fatty acids in walnut oil including oleic acid, γ-linolenic acid, linolenic acid, and Eicosapentaenoic acid were downloaded from PubChem NCBI database (https://pubchem.ncbi.nlm.nih.gov/). The Accession number of fatty acid structures were oleic acid (CID 445639), γ-linolenic acid (CID 5280933), linolenic acid (CID 5280934), and Eicosapentaenoic acid (CID 446284).

*Protein structure collection and binding cavities detection*

Cyclooxygenase-2 (COX-2) protein structure was retrieved from the protein data bank (PDB) with accession code 3MDL.[44] The structure

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was imported into the Molegro Virtual Docker version 5.0, and their binding cavities were predicted with the parameter van der Waals as molecular surface expansion. The COX-2 binding cavities were X= 23.35; Y= 15.48; Z= 61.54; Radius 16.

*Ligands – protein docking*

Ligands and protein were re-docked with COX-2 protein using Molegro virtual Docker version 5.0 at binding cavities.[45,46] The (2S)-2,3-dihydroxypropyl (5Z,8Z,11Z,14Z)-icosa-5,8,11,14-tetraenoate was used as reference docking.[44] The docking parameter was the scoring function, including the score MolDock score (Grid) with grid resolution 0.3 A. algorithm was set to customize with algorithm MolDock SE, the Number of Run was 10, constrain poses to cavity, and optimize H-bonds after docking. The parameter setting maximum iteration was 1500, maximum population size of 50. Pose generation involved an energy threshold of 100.00 with a minimum threshold of 10 and a maximum threshold of 30. The simplex evolution was set maximum of steps 300 with a neighbour distance factor of 1.00. the binding poses were chosen multiple poses with the number of poses of 5 and RMSD threshold of 1.00.[45, 47].

$$\Delta G\ \left(\frac{kJ}{mol}\right) = MolDock\ Score + Moldock\ [Grid]score + Rerank\ score \ldots\ldots (1)$$[45, 46]

*Data Analysis*

Walnut oil compounds – COX-2 complex structure was visualized and superimposed using PyMol version 2.2. Three-dimensional and two-dimensional structures and ligands interaction were analyzed using Discovery studio version 21.1.1.

## Results and Discussion

The superimposed 3D model of ligands-protein complex presented the same binding site of interaction (Figure 1). Several active sites of control – cyclooxygenase-2 were identified at some ligands. LYS546 was performed as Eicosapentaenoic acid and γ – linolenic acid (Table 1). The ARG44 posed at Eicosapentaenoic acid, γ – linolenic acid, and linolenic acid. Interestingly, ARG 44 posed to control at 2.0Å and 2.6Å by hydrogen bonds. Meanwhile, Eicosapentaenoic acid, γ– linolenic acid, and linolenic acid bound to ARG44 by hydrophobic interaction in two atoms (distance 3.8 and 3.9Å), one atom (distance 4.8Å), and four atoms (5.4; 3.6; 3.8; and 4.2Å), respectively. GLN543 residue is also bound to those compounds with hydrogen bonds. The THR60 posed to eicosapentanoic acid with 1.7Å. TYR122 of COX-2 protein interacted with control by a hydrogen bond with 1.5Å and posed 5.03Å with Eicosapentaenoic acid and 5.2Å with linolenic acid by hydrophobic interaction. The data confirmed that four Walnut compounds blocked cyclooxygenase-2 protein at the same sites as control. Two-dimensional complex structure performed the interaction types involving hydrogen bond, hydrophobic interaction (alkyl, π-alkyl), unfavorable bump, and van der Waals forces. The interaction types and number of interactions affected the binding energy of ligand-protein complexes. Oleic acid showed that 12 van der Waals, 4 hydrogen bonds, and two alkyl bonds promoted the highest binding energy, i.e., -280.6 kJ/mol. The Eicosapentaenoic acid showed lower binding energy than oleic acid with three hydrogen bonds, four hydrophobic interactions, and 11 van der Waals forces (Figure 2). Different from eicosapentaenoic acid, γ-linolenic acid performed a lower binding energy with 308.0 kJ/mol against Eicosapentaenoic acid.

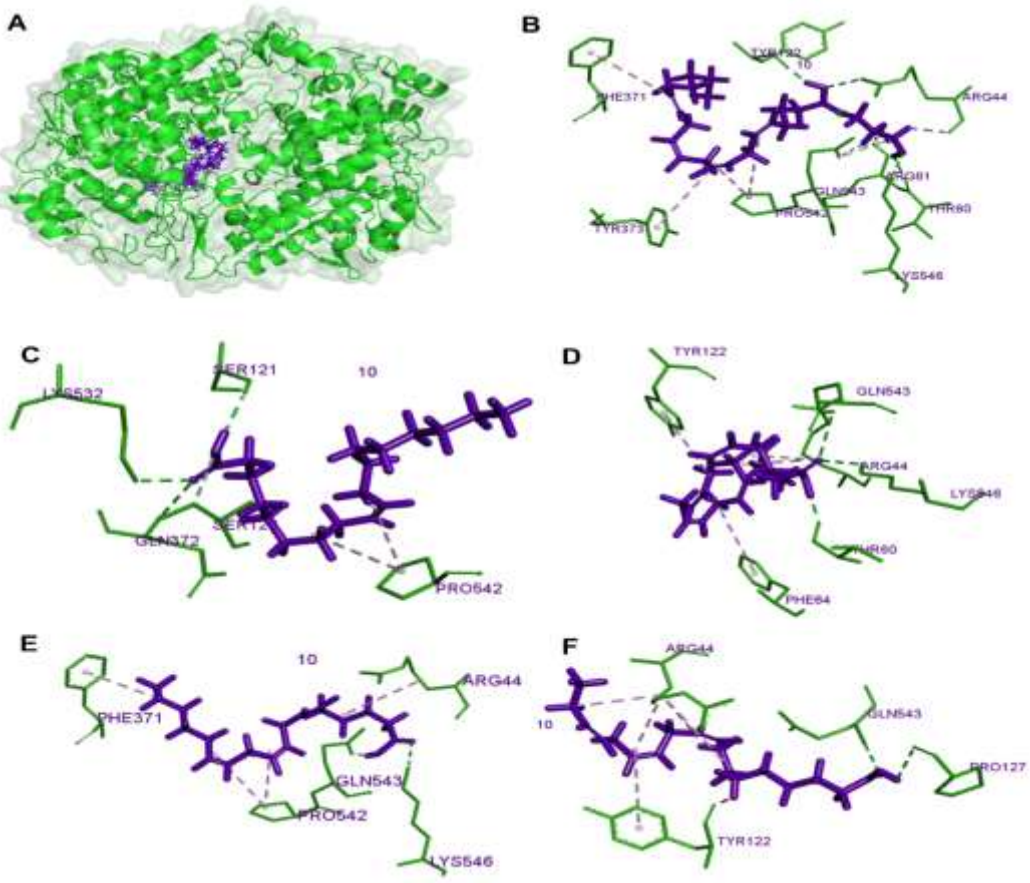


**Figure 1:** The three-dimensional complex structures of walnut oil compounds with cyclooxygenase-2 protein, A. superimposed of ligands-cyclooxygenase-2 protein, B. (2S)-2,3-dihydroxypropyl (5Z,8Z,11Z,14Z)-icosa-5,8,11,14-tetraenoate (Control), C. oleic acid, D. γ-linolenic acid, E. linolenic acid, and F. Eicosapentaenoic acid. The cyclooxygenase-2 protein was illustrated in green color, while the ligands were represented in purple color.

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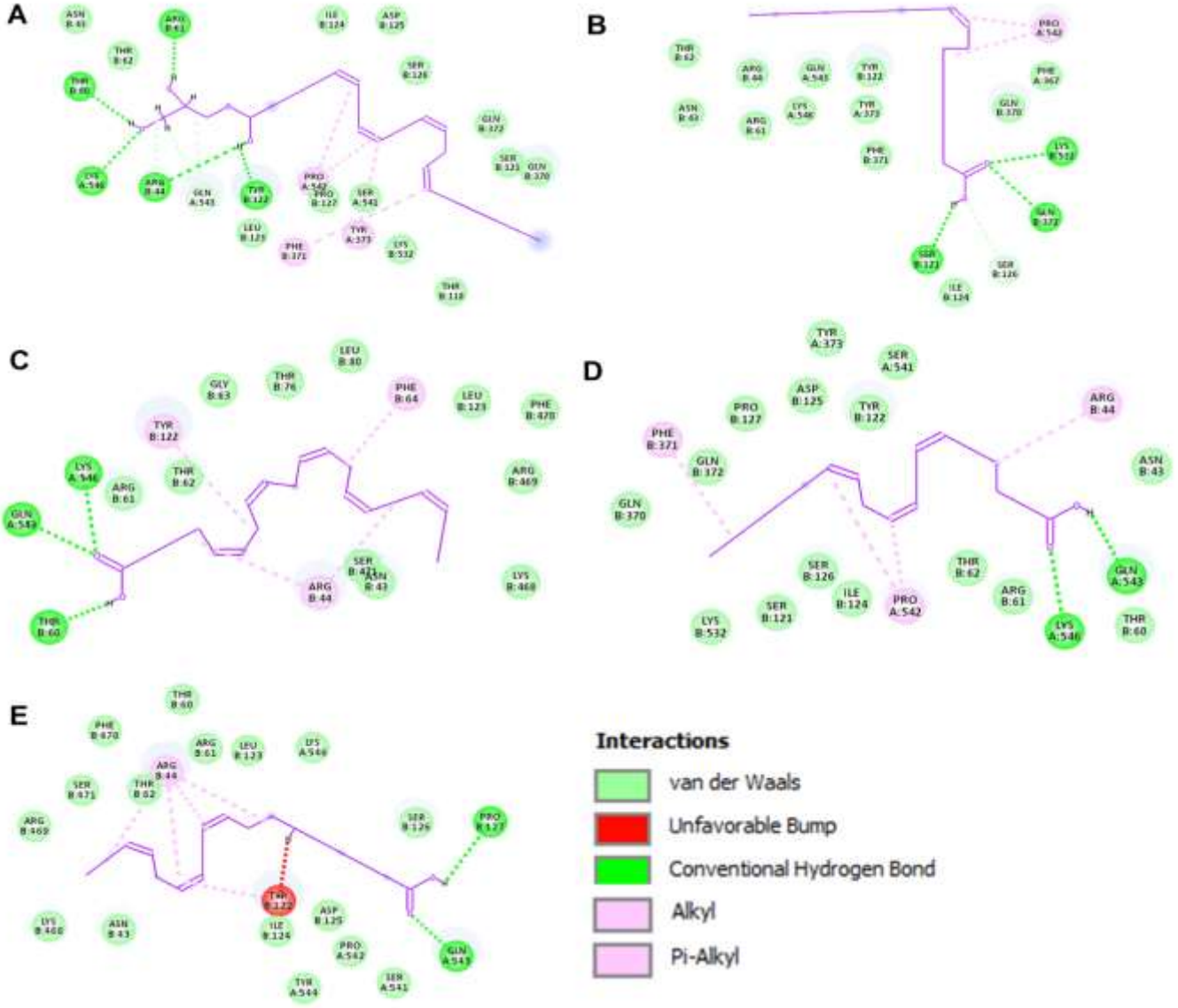


**Figure 2:** Two-dimensional complex structures of ligands-COX-2 protein, A. (2S)-2,3-dihydroxypropyl (5Z,8Z,11Z,14Z)-icosa-5,8,11,14-tetraenoate (Control), B. oleic acid, C. γ-linolenic acid, D. linolenic acid, and E. Eicosapentaenoic acid.

γ-linolenic acid interacted with COX-2 protein by two hydrogen bonds, four hydrophobic interactions, and 15 van der Waals forces. Linolenic acid showed two hydrogen bonds, 5 hydrophobic interactions, and 13 van der Waals forces. Interestingly, γ-linolenic acid showed a lower binding energy than linolenic acid, but the interaction between them was 2 van der Waals forces. This data suggests that, even though the van der Waals forces did not show interaction, they contributed to the binding energy. Furthermore, according to the two-dimensional structure of ligands-COX-2 complex protein, the simple structure of ligands revealed fewer active residues of COX-2 than the complex structure, as shown in the structure of γ-linolenic acid.

Cyclooxygenase (COX) is an enzyme that catalyzes prostaglandin synthesis from arachidonic acid, plays prostaglandin synthesis from arachidonic acid, and plays a pivotal role in inflammatory biological processes. Briefly, arachidonic acid (AA) was released from the phospholipid bilayer and bound to activated COX to produce prostaglandin G2 (PGG2). The PGG2 convert into prostaglandin H2 (PGH2) by reduction process using peroxidase enzyme. Overexpression of cyclooxygenase rapidly increases prostaglandin leading to inflammation.[48–54] Thus, the inhibition of cyclooxygenase is an alternative target for preventing inflammation. A silico study promoted that several natural compounds performed COX2 inhibition. Palmitoyl derivates showed active residues in Arg120, Tyr355, Asn375, Phe529, Ser530, and Tyr385 with hydrogen bonds.[55] A previous study reported that ibuprofen was potentially anti-analgesic by cyclooxygenase-1 and cyclooxygenase-2 inhibitions[54]. Fluorocurcumin, a curcumin analog, was reported to downregulate cyclooxygenase-2 and Nfκβ expression in mice.[56] Furthermore, synthesized inhibitor compounds, doronine derivates inhibited COX-2 protein and were potentially used as prophylaxis inflammation drugs.[57] Some Lichen compounds, Atranorin, Lecanoric acid, Usnic acid, Salazinic Acid, and Diffractic acid, inhibited against cyclooxygenase-2 protein.[58] Ayurvedic herbal compounds also performed cyclooxygenase-2 inhibitor with gallic acid was the highest inhibitory effect.[59] Novel flavones also revealed anti-inflammatory activity by interacting with cyclooxygenase-2 protein, the interaction residues of novel isoflavones were Tyr385, Tyr355, Trp387, Arg120, Val349, Leu352, Leu117, and Tyr358.[60] The QSAR and docking studies reported cyclic amide and herbal medicine compounds as cyclooxygenase-2 inhibitors for 'Alzheimer's therapy.[61] In addition, other herbal compounds, such as ginger, coffee, tamarind, lemon grass, and sappan heartwood, proved to have analgesic effects by cyclooxygenase-2 blockers.[34,36, 41, 62–65]

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**Table 1:** Ligands, binding energy, and active sites of ligands – COX-2 complexes

| Ligand | Binding Energy (kJ/mol) | Hydrogen Bond | Hydrophobic |
|---|---|---|---|
| (2S)-2,3-dihydroxypropyl (5Z,8Z,11Z,14Z)-icosa-5,8,11,14-tetraenoate | -321.2 | LYS546 (2.6), ARG44 (3.1), THR60 (2.7), ARG61 (2.0), TYR122 (1.5), GLN543 (3.08), GLN543 (2.9), ARG44 (2.6) | PRO542 (5.0), PRO542 (3.5), TYR373 (5.2), PHE371 (5.4) |
| Oleic acid | -280.6 | GLN372 (3.3), LYS532 (2.7), SER121(2.2), SER126 (3.5) | PRO542 (4.9), PRO542 (4.08) |
| Eicosapentanoic acid | -303.2 | GLN543 (3.2), LYS546 (3.05), THR60 (1.7) | ARG44 (3.8), ARG44 (3.9), PHE64 (4.8), TYR122(5.03) |
| γ – linolenic acid | -308.0 | LYS546 (2.6), GLN543 (2.02) | PRO542 (4.5), PRO542 (3.9), ARG44 (4.8), PHE371 (4.3) |
| linolenic acid | -286.2 | GLN543 (2.7), PRO127 (2.7) | ARG44 (5.4), ARG44 (3.6), ARG44 (3.8), ARG44 (4.2), TYR122 (5.2) |

## Conclusion

In conclusion, Oleic acid, Eicosapentaenoic acid, γ-linolenic acid, and linolenic acid inhibited the cyclooxygenase-2 at the inhibitor sites and revealed anti-inflammatory properties. Further *in-vitro* and *in-vivo* investigations are required.

## Conflict of Interest

The authors declare no conflict of interest.

## Authors' Declaration

The authors hereby declare that the work presented in this article is original and that they will bear any liability for claims relating to the content of this article.

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