In Silico Anti-Inflammatory Activity of Fucoidan by Inhibiting Inflammatory Marker Proteins Monocyte Chemoattractant Protein 1 (MCP-1) and Prostaglandin G/H Synthase 2

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**Abstract:** Fucoidan, a sulfated polysaccharide derived from brown seaweed, exhibits promising anti-inflammatory properties through interactions with key inflammatory proteins. This study utilized molecular docking simulations to investigate the binding interactions between fucoidan and Monocyte Chemoattractant Protein 1 (MCP-1) and Prostaglandin G/H synthase 2 (COX-2), pivotal in inflammatory pathways. Docking studies revealed a robust interaction between fucoidan and MCP-1, with a lowest binding affinity of -8.7 kcal/mol. Despite encountering unfavourable donor-donor interactions, fucoidan formed significant Van der Waals contacts with crucial residues such as TRP59 and LYS58, suggesting potential inhibition of MCP-1-mediated monocyte recruitment. Similarly, fucoidan demonstrated moderate binding affinity (-7.2 kcal/mol) towards COX-2. Interactions included Van der Waals interactions with residues LYS97, GLN192, and SER353, alongside conventional hydrogen bonds and π interactions. These findings imply fucoidan's capability to potentially inhibit COX-2 activity, thereby attenuating prostaglandin synthesis and inflammation associated with inflammatory disorders. The results underscore fucoidan's potential as a natural anti-inflammatory agent, offering insights into its molecular mechanisms against MCP-1 and COX-2. Future research directions include experimental validations to confirm fucoidan's inhibitory effects on MCP-1 and COX-2 and optimization of fucoidan derivatives for enhanced therapeutic efficacy. Such developments could lead to novel therapies derived from marine sources for treating inflammation-related diseases. In conclusion, this study contributes valuable computational insights into fucoidan's interactions with key inflammatory proteins, paving the way for further exploration and development of fucoidan-based therapeutics targeting MCP-1 and COX-2 in inflammatory disorders.

**Keywords:** Fucoidan, MCP-1, COX-2, molecular docking, anti-inflammatory, brown seaweed

# Introduction

Inflammation, a fundamental biological response to tissue injury or infection, plays a pivotal role in various chronic diseases, including arthritis, cardiovascular disorders, and cancer [(Medzhitov, 2008; Nathan, 2002)](https://paperpile.com/c/ZldolB/OoCE+3C67). Central to the inflammatory process are several key mediators, including monocyte chemoattractant protein 1 (MCP-1) and Prostaglandin G/H synthase 2 (COX-2), which orchestrate immune cell recruitment and inflammatory signaling pathways [(Charo & Taubman, 2004; Herschman, 1996)](https://paperpile.com/c/ZldolB/rR4o+6JOW). MCP-1, a potent chemokine, facilitates the migration of monocytes to sites of inflammation, contributing to the amplification of immune responses and tissue damage in inflammatory diseases [(Hitchon & El-Gabalawy, 2011; Vane & Botting, 2003)](https://paperpile.com/c/ZldolB/3NV3+ki4I). Meanwhile, COX-2 is an inducible enzyme that catalyzes the conversion of arachidonic acid into prostaglandins, which are crucial mediators of inflammation and pain [(Herschman, 1996; Vane & Botting, 2003)](https://paperpile.com/c/ZldolB/6JOW+ki4I).A study assessed the anti-inflammatory and antioxidant effects of a formulation containing lycopene, raspberry, green tea (95% polyphenols), and silver nanoparticles using BSA and DPPH assays. Results showed that the formulation had the highest inhibition at 50 μL concentration, indicating strong anti-inflammatory and antioxidant properties [(Chaithanya et al., 2021)](https://paperpile.com/c/ZldolB/v9kf). The antioxidant and anti-inflammatory activity of grape seed oil (GSO) gel infused with silver nanoparticles. Results showed that the gel exhibited both activities. While antioxidant activity was slightly lower than the standard (p = 0.400), its anti-inflammatory activity was significantly higher at most concentrations (p = 0.045), with both increasing as concentration increased [(“Evaluation of Antioxidant and Anti Inflammatory Activity of Grape Seed Oil Infused with Silver Nanoparticles an in Vitro Study,” 2021)](https://paperpile.com/c/ZldolB/p5Vv). In periodontitis, pathogens interact with dental stem cells, inducing pro-inflammatory cytokine production and reducing osteogenic differentiation by downregulating key markers like alkaline phosphatase and osteopontin. These microbial interactions exacerbate inflammation and diminish the regenerative capacity of stem cells. Understanding this interaction is essential for developing stem cell-based regenerative therapies for periodontitis management [(Ezhilarasan & Varghese, 2022)](https://paperpile.com/c/ZldolB/JG6T).Efforts to mitigate inflammation often involve targeting these key inflammatory markers[(Doshi et al., 2023; Lampl et al., 2023; Pandiyan et al., 2023)](https://paperpile.com/c/ZldolB/TvToK+UoCmV+yy42S). Fucoidan, a complex sulfated polysaccharide derived from various species of brown seaweed, has emerged as a promising candidate due to its multifaceted biological activities, including anti-inflammatory properties [(Fitton, 2011; V. Pomin, 2012)](https://paperpile.com/c/ZldolB/WWnO+Tlgw). Studies have indicated that fucoidan exerts inhibitory effects on MCP-1 and COX-2, suggesting its potential as a therapeutic agent for inflammatory disorders [(Atashrazm et al., 2015; Cumashi et al., 2007)](https://paperpile.com/c/ZldolB/GqNo+7bDH). However, the precise mechanisms underlying fucoidan's anti-inflammatory effects remain a subject of ongoing investigation.[(Ramsundar et al., 2023; Rieshy et al., 2023; Singh et al., 2023)](https://paperpile.com/c/ZldolB/ODs9g+UHxar+c0xyc)In silico methodologies, such as molecular docking and molecular dynamics simulations, offer valuable tools for exploring the interactions between bioactive compounds like fucoidan and target proteins involved in inflammatory pathways [(Kitchen et al., 2004; Shoichet & Kobilka, 2012)](https://paperpile.com/c/ZldolB/OXgl+jSRK). These computational approaches provide insights into the binding modes and affinity of fucoidan towards MCP-1 and COX-2, aiding in the rational design and optimization of novel anti-inflammatory agents [(Gandhi et al., 2021; Katyal et al., 2023; Priyadharshini et al., 2023)](https://paperpile.com/c/ZldolB/FPqcj+3ZQm6+B69s9). Fucoidan's structural diversity and sulfation patterns contribute to its bioactivity by enabling interactions with specific molecular targets implicated in inflammation [(V. Pomin, 2012; V. H. Pomin, 2009, 2012)](https://paperpile.com/c/ZldolB/Tlgw+DmYb+bUv6). For instance, studies have demonstrated that fucoidan inhibits MCP-1-mediated monocyte migration by interfering with chemokine-receptor interactions or downstream signaling pathways [(Atashrazm et al., 2015)](https://paperpile.com/c/ZldolB/GqNo). Additionally, fucoidan has been shown to suppress COX-2 expression and prostaglandin production, thereby attenuating inflammatory responses and associated tissue damage [(Cumashi et al., 2007)](https://paperpile.com/c/ZldolB/7bDH).The therapeutic potential of fucoidan extends beyond its direct anti-inflammatory effects [(Pavithra et al., 2023; Shenoy et al., 2023; Thomas & Jain, 2023)](https://paperpile.com/c/ZldolB/aMKnz+GNOtD+zQqSC). It exhibits immunomodulatory properties, influencing the balance between pro-inflammatory and anti-inflammatory cytokines, which are critical in regulating immune responses [(Fitton, 2011)](https://paperpile.com/c/ZldolB/WWnO). Moreover, fucoidan's antioxidant activity contributes to its protective effects against oxidative stress, a common feature of inflammatory conditions [(V. H. Pomin, 2012)](https://paperpile.com/c/ZldolB/DmYb). Molecular docking studies have provided mechanistic insights into fucoidan's interactions with MCP-1 and COX-2 [(Rajeshkumar & Lakshmi, 2021; Sivakumar et al., 2021)](https://paperpile.com/c/ZldolB/q5W1t+mlnc3). Docking simulations predict the binding sites and affinity of fucoidan molecules within the active sites of these proteins, highlighting potential molecular mechanisms underlying its anti-inflammatory effects [(Kitchen et al., 2004; Shoichet & Kobilka, 2012)](https://paperpile.com/c/ZldolB/OXgl+jSRK). Computational analyses reveal specific residues and structural motifs crucial for the binding of fucoidan to MCP-1 and COX-2, guiding experimental validation and optimization of fucoidan-based therapies [(Rajeshkumar & Lakshmi, 2021; Sivakumar et al., 2021)](https://paperpile.com/c/ZldolB/q5W1t+mlnc3).Furthermore, molecular dynamics simulations elucidate the dynamic behavior of fucoidan-protein complexes over time, providing insights into the stability and flexibility of these interactions under physiological conditions [(Shoichet & Kobilka, 2012)](https://paperpile.com/c/ZldolB/jSRK). Such simulations enable researchers to assess the robustness of fucoidan binding and predict its efficacy in modulating MCP-1 and COX-2 activities in complex biological environments [(Chokkattu et al., 2023; Dharman et al., 2023; Govindaraj & Shanmugam, 2023)](https://paperpile.com/c/ZldolB/zzpIb+2nusZ+XMtHU).Through in silico approaches, we gain valuable insights into the molecular mechanisms underlying fucoidan's therapeutic effects, paving the way for its development as a novel therapeutic agent for inflammatory disorders. By integrating computational modeling with experimental validation, future research can further elucidate the therapeutic potential of fucoidan and optimize its efficacy in clinical settings.

# Materials and Methods

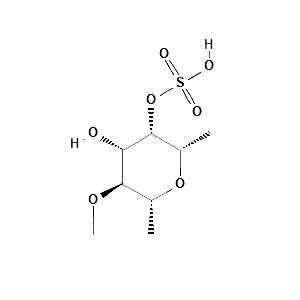
Fucoidan (C8H16O7S) is a sulphated polysaccharide with a molecular weight of 256.28 g/mol per unit. It is found in the cell walls of brown seaweeds, providing structural rigidity and mechanical support to these marine plants. In this study, fucoidan serves as the ligand, and its structure (PubChem CID: 129532628) was retrieved from PubChem (National Library of Medicine, NCBI, NIH).Two important human inflammatory biomarker proteins, Monocyte Chemoattractant Protein 1 (MCP-1) (PDB: 1DOK) [(Lubkowski et al., 1997)](https://paperpile.com/c/ZldolB/wvVk) and Prostaglandin G/H synthase 2 (PDB: 6V3R) [(Uddin et al., 2020)](https://paperpile.com/c/ZldolB/DkU9), were selected for the study. Their molecular structures were obtained from the RCSB Protein Data Bank(Saadh et al., 2024). Using BIOVIA Discovery Studio Visualizer 2024 (v24.1.0.23298) developed by Dassault Systems Biovia Corp., both protein structures were visualized, and unwanted ligands, chains, and water molecules were removed. Polar charges were added to the structures(Almatrafi et al., 2024).Molecular docking was conducted between the ligand (fucoidan) and the inflammation-inducing proteins MCP-1 and Prostaglandin G/H synthase 2 using the Virtual screening software PyRx-Python Prescription 0.8 with Autodock Vina (Molecular docking engine) [(Akshatha et al., 2021; Dallakyan & Olson, 2015; Meng et al., 2011)](https://paperpile.com/c/ZldolB/owV4+dLHy+Hhfw). The adjusted grid center and dimension coordinates are recorded and tabulated in Table 1. The best-fit model was identified based on the lowest binding affinity. The bond interactions between the ligand and the proteins were visualized, interpreted, and recorded using BIOVIA Discovery Studio Visualizer 2024.

**Table 1.** The grid centre and dimension parameters set for MCP-1 and NFκB

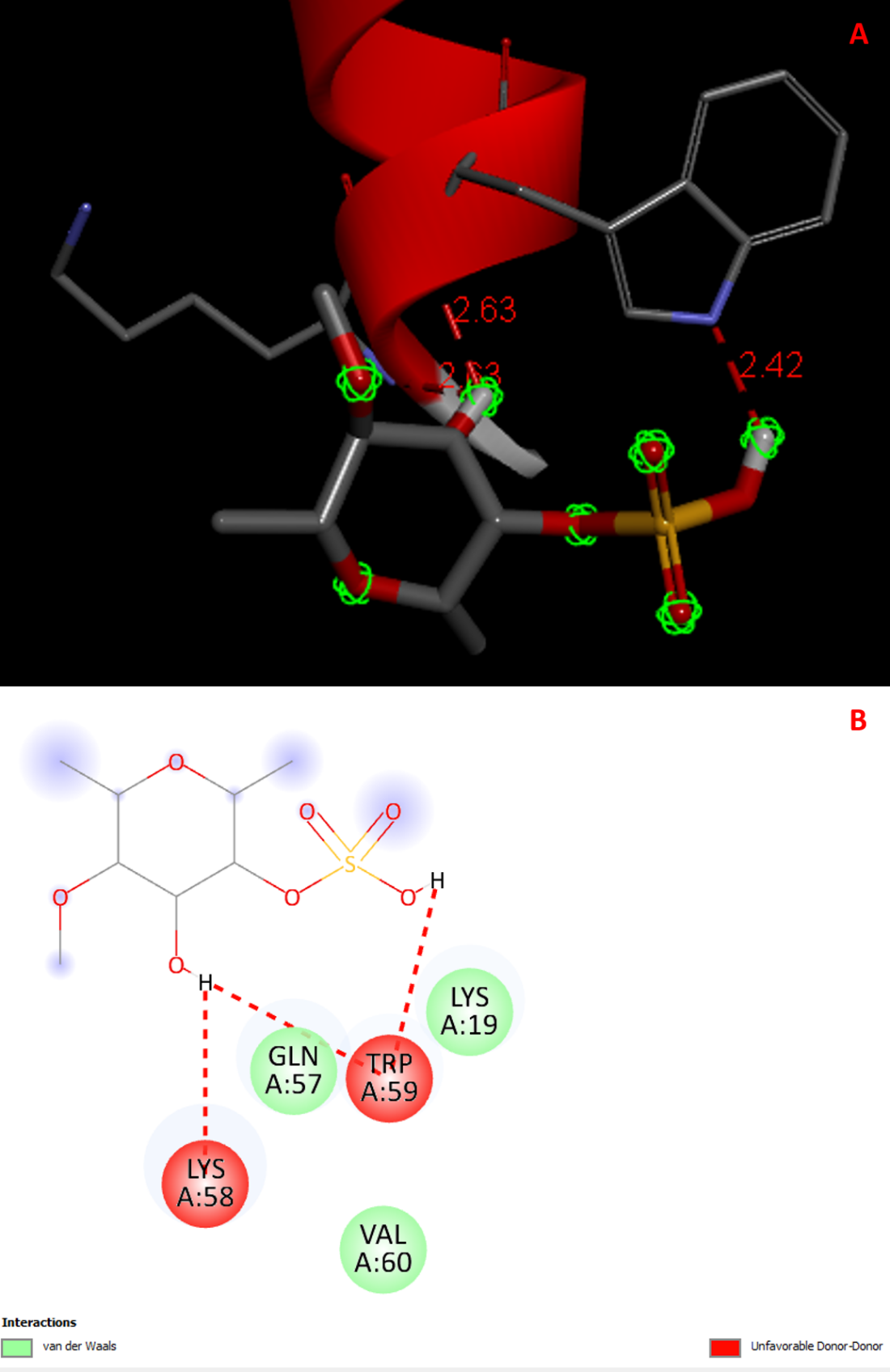
|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Grid Centre** | |  | **Dimensions (Å)** | | |
| Protein | PDB | X | Y | Z | X | Y | Z |
| Monocyte Chemoattractant Protein 1 (MCP-1) | 1DOK | 8.55 | 40.5 | 33.29 | 65.26 | 42.41 | 56.97 |
| Prostaglandin G/H synthase 2 | 6V3R | -41.95 | -33.21 | 20.82 | 84.31 | 98.03 | 87.04 |

# Results

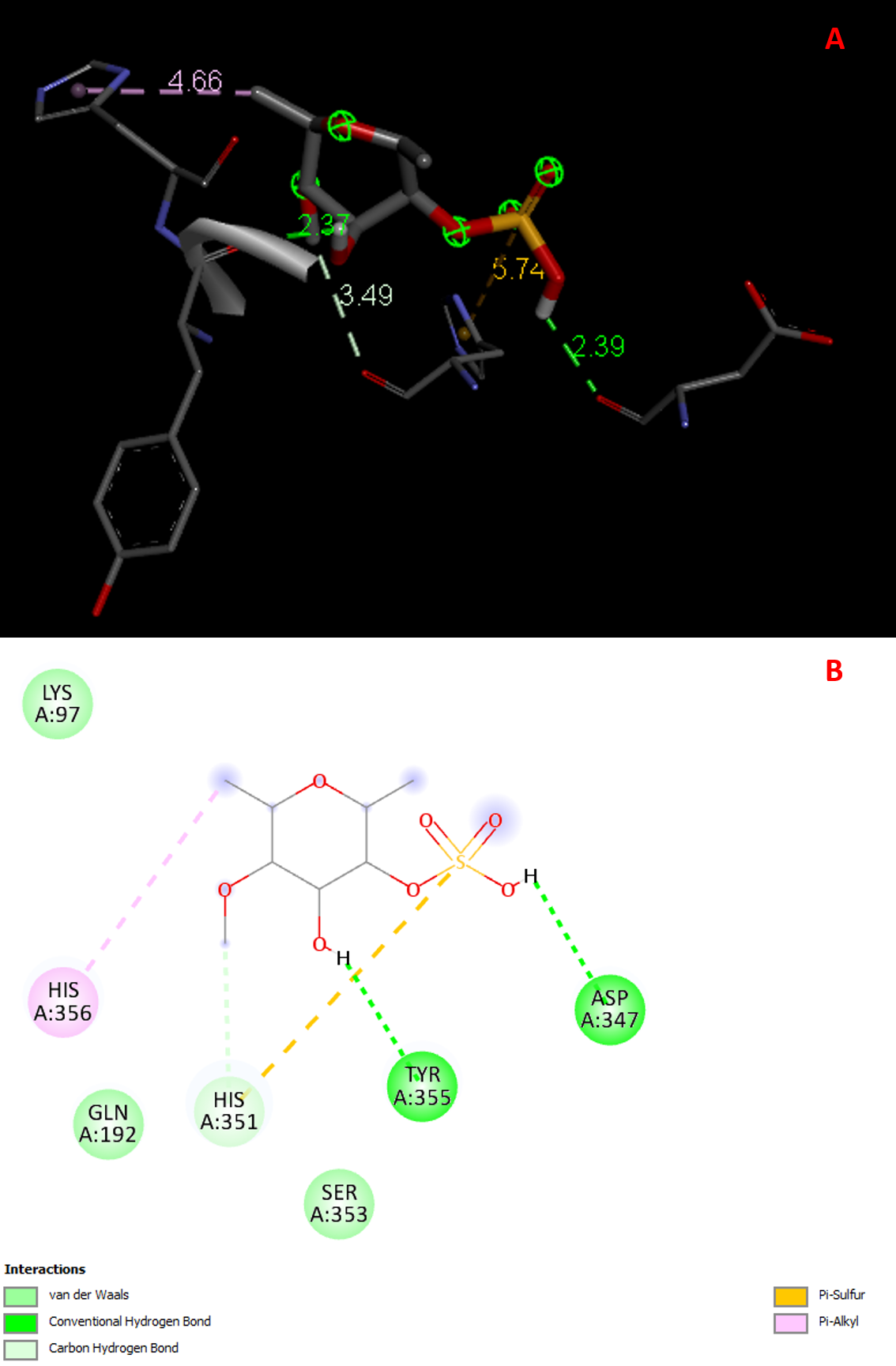
The molecular structure of fucoidan, including a single sulphate group, is depicted in Figure 1. The lowest binding affinity obtained between fucoidan and Monocyte Chemoattractant Protein 1 (MCP-1) was -8.7 kcal/mol (Table 2). Molecular docking revealed that fucoidan interacts with MCP-1 through three unfavorable donor-donor reactions (two bonds with TRP59 and one with LYS58) and three Van der Waals interactions (GLN57, LYS19, VAL60) (Figure 2 and Table 4).The binding affinity between fucoidan and Prostaglandin G/H synthase 2 was -7.2 kcal/mol (Table 3). The bond interactions include three Van der Waals interactions (LYS97, GLN192, SER353), two conventional hydrogen bonds (ASP347, TYR355), one carbon-hydrogen bond (HIS351), one π-sulfur interaction, and one π-alkyl interaction (Figure 3 and Table 5).



**Figure 1.** Molecular structure of a fucoidan showing a single sulphate group



**Figure 2.** Molecular interactions between the ligand fucoidan and Monocyte Chemoattractant Protein 1 (MCP-1) showing three unfavourable donor-donor reactions (two bonds with TRP59 and one with LYS58) and three Van der Waals interactions (GLN57; LYS19; VAL60); A) Three-dimensional view, B) Two-dimensional view.



**Figure 3.** Molecular interactions between the ligand fucoidan and Prostaglandin G/H synthase 2 showing three Van der Waals interactions (LYS97; GLN192; SER353), two conventional hydrogen bonds (ASP347; TYR355), one carbon-hydrogen bond (HIS351), one π-sulfur, and one π-alkyl interactions; A) Three-dimensional view, B) Two-dimensional view.

**Table 2.** The table retrieved after molecular docking between fucoidan and Monocyte Chemoattractant Protein 1 (MCP-1)

|  |  |  |  |
| --- | --- | --- | --- |
| **Ligand** | **Binding Affinity** | **rmsd/ub** | **rmsd/lb** |
| 1dok\_A\_129532628 | -4.6 | 0 | 0 |
| 1dok\_A\_129532628 | -4.4 | 3.294 | 1.771 |
| 1dok\_A\_129532628 | -4.3 | 22.494 | 20.879 |
| 1dok\_A\_129532628 | -4.2 | 21.779 | 20.254 |
| 1dok\_A\_129532628 | -4.2 | 18.914 | 16.785 |
| 1dok\_A\_129532628 | -4.1 | 5.634 | 2.882 |
| 1dok\_A\_129532628 | -4 | 20.61 | 18.651 |
| 1dok\_A\_129532628 | -4 | 3.625 | 1.784 |
| 1dok\_A\_129532628 | -3.9 | 21.799 | 19.966 |

**Table 3.** The table retrieved after molecular docking between fucoidan and Prostaglandin G/H synthase 2 showing binding affinity.

|  |  |  |  |
| --- | --- | --- | --- |
| **Ligand** | **Binding Affinity** | **rmsd/ub** | **rmsd/lb** |
| 6v3r\_A\_129532628 | -5.1 | 0 | 0 |
| 6v3r\_A\_129532628 | -5.1 | 8.983 | 6.944 |
| 6v3r\_A\_129532628 | -5 | 32.583 | 30.91 |
| 6v3r\_A\_129532628 | -5 | 6.755 | 4.45 |
| 6v3r\_A\_129532628 | -4.9 | 5.455 | 2.703 |
| 6v3r\_A\_129532628 | -4.8 | 29.388 | 27.894 |
| 6v3r\_A\_129532628 | -4.7 | 8.949 | 7.309 |
| 6v3r\_A\_129532628 | -4.7 | 31.304 | 29.967 |
| 6v3r\_A\_129532628 | -4.6 | 30.974 | 29.753 |

**Table 4.** The table showing bond interactions and its length between fucoidan and Monocyte Chemoattractant Protein 1 (MCP-1) showing amino acid residues involves in it

|  |  |  |  |
| --- | --- | --- | --- |
| **Bond Interactions** | **No. of bonds** | **Bond length (Å)** | **Amino acid residue** |
| Van der Waals | 3 |  | GLN57  LYS19  VAL60 |
| Unfavourable Donor-Donor | 3 | 2.42 | TRP59 |
| 2.63 | TRP59 |
| 2.63 | LYS58 |
| Total number of interactions | 6 |  |  |

**Table 5.** The table showing bond interactions and its length between fucoidan and Prostaglandin G/H synthase 2 showing amino acid residues involves in it

|  |  |  |  |
| --- | --- | --- | --- |
| **Bond Interactions** | **No. of bonds** | **Bond length (Å)** | **Amino acid residue** |
| Van der Waals | 3 |  | LYS97  GLN192  SER353 |
| Conventional hydrogen bond | 2 | 2.39 | ASP347 |
| 2.37 | TYR355 |
| Carbon-hydrogen bond | 1 | 3.49 | HIS351 |
| Pi-sulfur | 1 | 5.74 | HIS351 |
| Pi-alkyl | 1 | 4.66 | HIS356 |
| Total number of interactions | 8 |  |  |

# Discussion

The molecular docking simulations presented in this study provide valuable insights into the interactions between fucoidan and two key inflammatory proteins, MCP-1 and COX-2. These proteins play crucial roles in inflammatory processes, making them promising targets for therapeutic intervention [(Charo & Taubman, 2004; Vane & Botting, 2003)](https://paperpile.com/c/ZldolB/rR4o+ki4I).For MCP-1, the lowest binding affinity observed was -8.7 kcal/mol, indicating a strong interaction between fucoidan and the protein (Table 2). Analysis of the docking poses revealed several interactions, including three unfavourable donor-donor interactions and three Van der Waals interactions (Fig. 2 and Table 4). Specifically, fucoidan showed interactions with key residues such as TRP59 and LYS58 through donor-donor interactions, highlighting potential areas for further optimization of fucoidan derivatives to improve binding affinity and specificity towards MCP-1 [(Atashrazm et al., 2015; Cumashi et al., 2007)](https://paperpile.com/c/ZldolB/GqNo+7bDH).In the case of COX-2, the docking study revealed a binding affinity of -7.2 kcal/mol, indicating a moderately strong interaction between fucoidan and the enzyme (Table 3). The binding interactions included three Van der Waals interactions (LYS97, GLN192, SER353), two conventional hydrogen bonds (ASP347, TYR355), one carbon-hydrogen bond (HIS351), and π-π interactions (Fig. 3 and Table 5). These interactions suggest that fucoidan can potentially inhibit COX-2 activity by occupying the active site and forming stabilizing interactions with critical residues involved in substrate binding and catalysis [(Kitchen et al., 2004; Shoichet & Kobilka, 2012)](https://paperpile.com/c/ZldolB/OXgl+jSRK).The observed interactions between fucoidan and MCP-1 or COX-2 are consistent with previous studies indicating the broad-spectrum anti-inflammatory properties of fucoidan [(Fitton, 2011; V. H. Pomin, 2012)](https://paperpile.com/c/ZldolB/WWnO+DmYb). By inhibiting MCP-1, fucoidan may mitigate the recruitment of monocytes to sites of inflammation, thereby suppressing the amplification of inflammatory responses and tissue damage [(Vane & Botting, 2003)](https://paperpile.com/c/ZldolB/ki4I). Similarly, the inhibition of COX-2 by fucoidan could lead to reduced prostaglandin synthesis, alleviating inflammation and associated pain [(Herschman, 1996; Vane & Botting, 2003)](https://paperpile.com/c/ZldolB/6JOW+ki4I).The findings from this docking study suggest that fucoidan's anti-inflammatory effects may be attributed to its ability to interact with specific residues within the active sites of MCP-1 and COX-2. However, further experimental validation, such as in vitro enzyme assays and in vivo studies, is necessary to confirm the inhibitory activity of fucoidan against MCP-1 and COX-2 and evaluate its therapeutic potential in treating inflammatory diseases [(Medzhitov, 2008; Nathan, 2002)](https://paperpile.com/c/ZldolB/OoCE+3C67).Moreover, future research could explore structural modifications of fucoidan to enhance its affinity and selectivity towards MCP-1 and COX-2, potentially leading to the development of more potent anti-inflammatory agents derived from marine sources [(Atashrazm et al., 2015; Cumashi et al., 2007)](https://paperpile.com/c/ZldolB/GqNo+7bDH). Computational approaches, including molecular dynamics simulations, could further elucidate the dynamic behavior of fucoidan-protein complexes and provide insights into the stability and longevity of these interactions under physiological conditions [(Shoichet & Kobilka, 2012)](https://paperpile.com/c/ZldolB/jSRK).

# Conclusion

In conclusion, molecular docking studies suggest fucoidan interacts effectively with MCP-1 and COX-2, highlighting its potential as an anti-inflammatory agent. Strong binding affinities and specific interactions observed indicate fucoidan's ability to inhibit MCP-1-mediated monocyte recruitment and COX-2 activity. Future research should focus on validating these findings through experimental assays and optimizing fucoidan derivatives for enhanced therapeutic efficacy against inflammatory disorders.

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