Deciphering the Anti-Inflammatory Activity of Fucoidan by Molecular Docking

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**Abstract:**Inflammation is a vital biological response to harmful stimuli, but chronic inflammation can lead to severe diseases such as arthritis, cardiovascular diseases, and cancer. Fucoidan, a sulfated polysaccharide from brown seaweed, has shown promising anti-inflammatory properties. This study aims to decipher the anti-inflammatory activity of fucoidan using molecular docking techniques. We focused on two key inflammatory mediators, monocyte chemoattractant protein-1 (MCP-1) and nuclear factor kappa B (NF-κB), to understand the interactions at a molecular level. Our docking studies revealed that fucoidan interacts with MCP-1 and NF-κB with binding affinities of -5.1 kcal/mol and -5.4 kcal/mol, respectively. For MCP-1, fucoidan formed three conventional hydrogen bonds with GLU50 and ASN14, and a carbon-hydrogen bond with CYS12, predominantly involving its sulphate moiety. Similarly, fucoidan's interaction with NF-κB included seven hydrogen bonds with ARG313, GLY224, and ARG49, along with an alkyl bond with ALA225 and a π-alkyl bond with ILE189. The sulphate group of fucoidan was critical in these interactions, particularly with ARG313. These findings underscore the importance of the sulphate moiety in fucoidan's structure for its anti-inflammatory activity. The molecular interactions identified suggest that fucoidan can effectively inhibit MCP-1 and NF-κB, contributing to its potential as a therapeutic agent for inflammatory diseases. This study enhances our understanding of fucoidan's mechanisms and supports further exploration of its clinical applications. Future work should include in vitro and in vivo validations to confirm these findings and explore fucoidan-based derivatives for enhanced efficacy.

**Keywords:** Fucoidan; Molecular Docking; Anti-inflammatory; Sulphate Moiety

# Introduction

Inflammation is a complex and multifaceted biological response that plays a crucial role in the body's defense against harmful stimuli, including pathogens, damaged cells, and irritants [(Medzhitov, 2008)](https://paperpile.com/c/z6tJNF/Tzyu). This protective mechanism involves a coordinated interplay of immune cells, blood vessels, and molecular mediators, orchestrating a response aimed at eliminating the initial cause of cell injury and initiating tissue repair [(Nathan & Ding, 2010)](https://paperpile.com/c/z6tJNF/AQwJ). While acute inflammation is essential for wound healing and fighting infections, chronic inflammation has been implicated in the pathogenesis of numerous diseases, including rheumatoid arthritis, atherosclerosis, and various types of cancer [(Libby, 2007)](https://paperpile.com/c/z6tJNF/pl9G).The inflammatory process is tightly regulated by a network of pro-inflammatory and anti-inflammatory mediators, including cytokines, chemokines, and lipid mediators [(Serhan & Savill, 2005)](https://paperpile.com/c/z6tJNF/KULe). Dysregulation of this delicate balance can lead to persistent inflammation, tissue damage, and the development of chronic diseases[(Rajeshkumar & Lakshmi, 2021; Sivakumar et al., 2021)](https://paperpile.com/c/z6tJNF/Q8NBl+3myQr). Therefore, understanding the molecular mechanisms underlying inflammation and identifying novel anti-inflammatory agents are critical for developing effective therapeutic strategies to manage inflammatory disorders [(Tabas & Glass, 2013)](https://paperpile.com/c/z6tJNF/3wBo).In recent years, natural products have emerged as a rich source of bioactive compounds with potential anti-inflammatory properties [(Newman & Cragg, 2020)](https://paperpile.com/c/z6tJNF/hfbH). A study assessed the anti-inflammatory and antioxidant effects of a formulation containing lycopene, raspberry, green tea, and silver nanoparticles. Using BSA and DPPH assays, the highest inhibition was observed at 50 μL concentration. The results suggest that this combination enhances anti-inflammatory and antioxidant activities effectively [(Chaithanya et al., 2021)](https://paperpile.com/c/z6tJNF/KQRw). Grape seed oil gel infused with silver nanoparticles showed significant anti-inflammatory activity compared to the standard (p = 0.045), while antioxidant activity was slightly lower but not statistically significant (p = 0.400). Activity increased with higher concentrations [(“Evaluation of Antioxidant and Anti Inflammatory Activity of Grape Seed Oil Infused with Silver Nanoparticles an in Vitro Study,” 2021)](https://paperpile.com/c/z6tJNF/BlIL). Microbial interactions with dental stem cells exacerbate inflammation and impair tissue regeneration in periodontitis [(Ezhilarasan & Varghese, 2022)](https://paperpile.com/c/z6tJNF/pTzC). Among these, fucoidan, a sulfated polysaccharide found predominantly in various species of brown seaweed, has garnered significant attention from researchers and clinicians alike [(Fitton, 2011)](https://paperpile.com/c/z6tJNF/SDTD). Fucoidan's complex structure, characterized by a backbone of α-(1→3)-linked fucose residues with varying degrees of branching, sulfation, and acetylation, contributes to its diverse biological activities, including anticoagulant, antiviral, antitumor, and notably, anti-inflammatory properties [(Ale et al., 2011)](https://paperpile.com/c/z6tJNF/4OMc).The anti-inflammatory effects of fucoidan have been attributed to its ability to modulate multiple aspects of the immune response. Studies have demonstrated that fucoidan can inhibit the production of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), while promoting the expression of anti-inflammatory mediators [(Cumashi et al., 2007)](https://paperpile.com/c/z6tJNF/FW6n). Additionally, fucoidan has been shown to interfere with leukocyte recruitment to sites of inflammation and to modulate the activation of key transcription factors involved in inflammatory gene expression, such as nuclear factor-κB (NF-κB) [(Li et al., 2008)](https://paperpile.com/c/z6tJNF/Ygtk).To fully harness the therapeutic potential of fucoidan, it is essential to elucidate the molecular mechanisms underlying its anti-inflammatory activity. Molecular docking, a powerful computational technique, offers a valuable approach to predict and analyze the interactions between fucoidan and key proteins involved in the inflammatory cascade at the atomic level [(Meng et al., 2011)](https://paperpile.com/c/z6tJNF/JjiK). This in silico method allows researchers to simulate the binding of fucoidan to potential molecular targets, providing insights into the structural basis of its bioactivity and guiding the identification of critical binding sites and interactions.By employing molecular docking techniques, researchers can explore the affinity and specificity of fucoidan for various inflammatory mediators, including cytokine receptors, enzymes involved in inflammatory signaling pathways, and transcription factors[(Chokkattu et al., 2023; Dharman et al., 2023; Govindaraj & Shanmugam, 2023)](https://paperpile.com/c/z6tJNF/hHoMG+cvnto+RGGtt). This approach not only enhances our understanding of fucoidan's mode of action but also facilitates the rational design of more potent and selective anti-inflammatory agents based on the fucoidan scaffold [(Kitchen et al., 2004)](https://paperpile.com/c/z6tJNF/ygNv).In this study, we aim to leverage the power of molecular docking to decipher the anti-inflammatory activity of fucoidan at the molecular level. By systematically investigating its interactions with key proteins implicated in inflammatory processes, we seek to elucidate the structural determinants of fucoidan's beneficial effects. This research not only contributes to our fundamental understanding of the mechanisms underlying natural anti-inflammatory compounds but also paves the way for the development of novel therapeutic strategies to combat inflammatory disorders.Furthermore, this investigation aligns with the growing interest in marine-derived natural products as a source of innovative pharmaceuticals [(Molinski et al., 2009)](https://paperpile.com/c/z6tJNF/gleF). By focusing on fucoidan, a compound with a long history of use in traditional medicine and a promising profile in preclinical studies, we aim to bridge the gap between traditional knowledge and modern drug discovery approaches. The insights gained from this molecular docking study may inform future research directions, including the design of fucoidan derivatives with enhanced anti-inflammatory properties and improved pharmacokinetic profiles.

# Materials and Methods

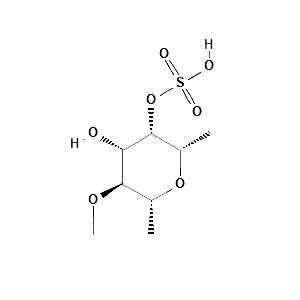
Fucoidan (C₈H₁₆O₇S) is a sulfated polysaccharide characterized by a molecular weight of 256.28 g/mol. It is found in the cell walls of brown seaweeds, where it provides structural rigidity and mechanical support to the marine plants. In this study, fucoidan was used as the ligand, and its molecular structure (PubChem CID: 129532628) was sourced from PubChem, a database maintained by the National Library of Medicine, NCBI, and NIH.The study focused on two significant inflammatory biomarker proteins: Monocyte Chemoattractant Protein-1 (MCP-1) (PDB: 1DON) [(Handel & Domaille, 1996)](https://paperpile.com/c/z6tJNF/wO20) and Nuclear Factor NF-kappa-B (NFκB) (PDB: 7CLI) [(Pan et al., 2023)](https://paperpile.com/c/z6tJNF/oRfA). The molecular structures of these proteins were retrieved from the Protein Data Bank (RCSB PDB). The protein structures were visualized, and any non-essential ligands, chains, and water molecules were removed. Polar charges were added using the BIOVIA Discovery Studio Visualizer 2024 (v24.1.0.23298), developed by Dassault Systèmes Biovia Corp(Saadh et al., 2024).Molecular docking simulations were carried out to explore interactions between fucoidan and the inflammatory marker proteins MCP-1 and NFκB. These simulations were performed using the PyRx-Python Prescription 0.8 software, with AutoDock Vina serving as the docking engine [(Akshatha et al., 2021; Dallakyan & Olson, 2015; Trott & Olson, 2010)](https://paperpile.com/c/z6tJNF/7wyX+G1dd+a72S). The grid center and dimensions were adjusted and recorded, as shown in Table 1. The optimal docking model was selected based on the lowest binding affinity. Bond interactions between fucoidan and the proteins were visualized, analyzed, and documented using the BIOVIA Discovery Studio Visualizer 2024.

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

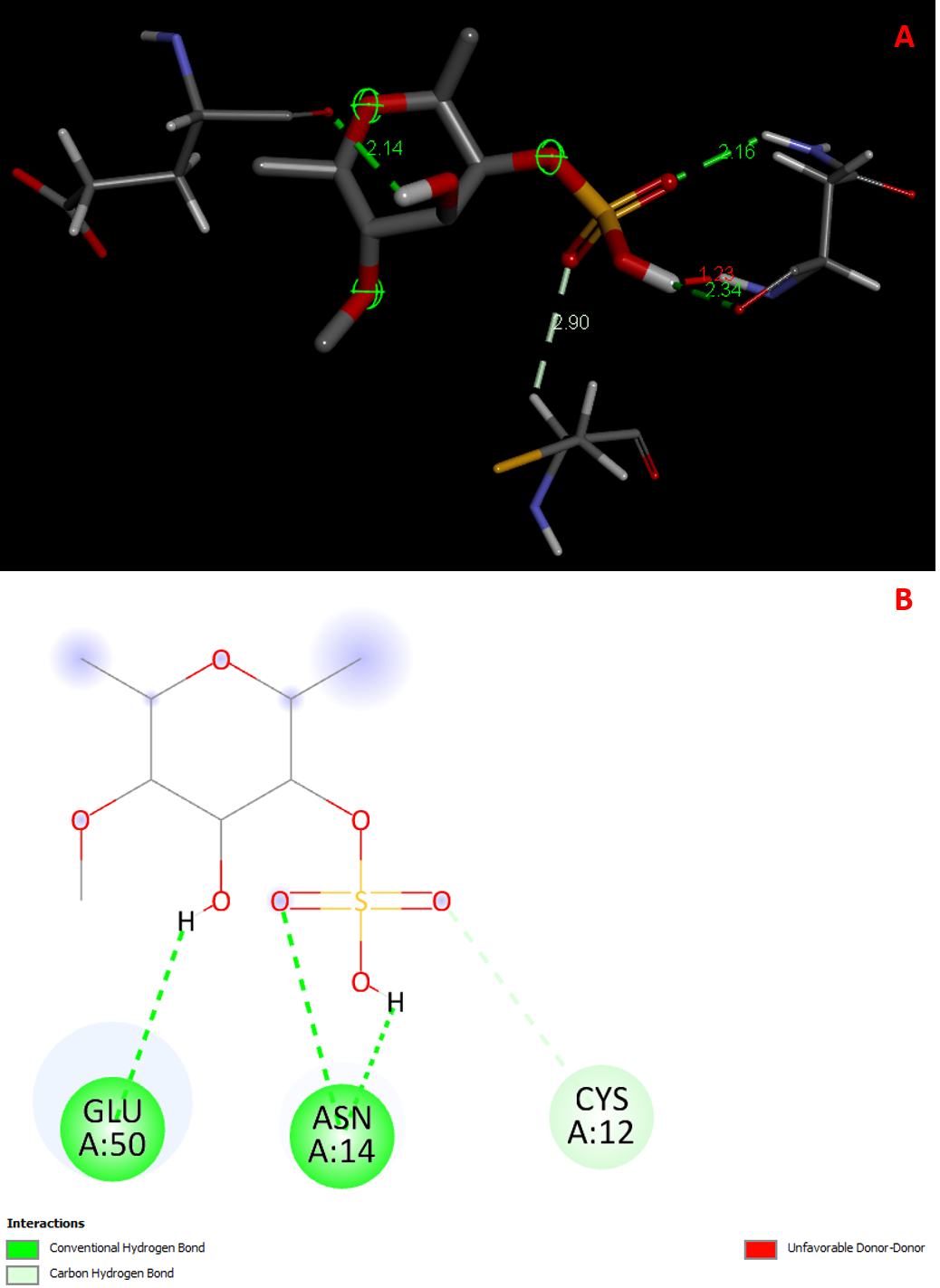
|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Grid Centre** | |  | **Dimensions (Å)** | | |
| **Protein** | **PDB** | **X** | **Y** | **Z** | **X** | **Y** | **Z** |
| Monocyte chemoattractant protein-1 (MCP-1) | 1DON | 52.42 | -4.09 | 9.69 | 52.74 | 57.76 | 52.39 |
| Nuclear factor NF-kappa-B (NFκB) | 7CLI | -15.74 | 4.99 | -9.69 | 51.49 | 95.2 | 88.05 |

# Results and Discussion

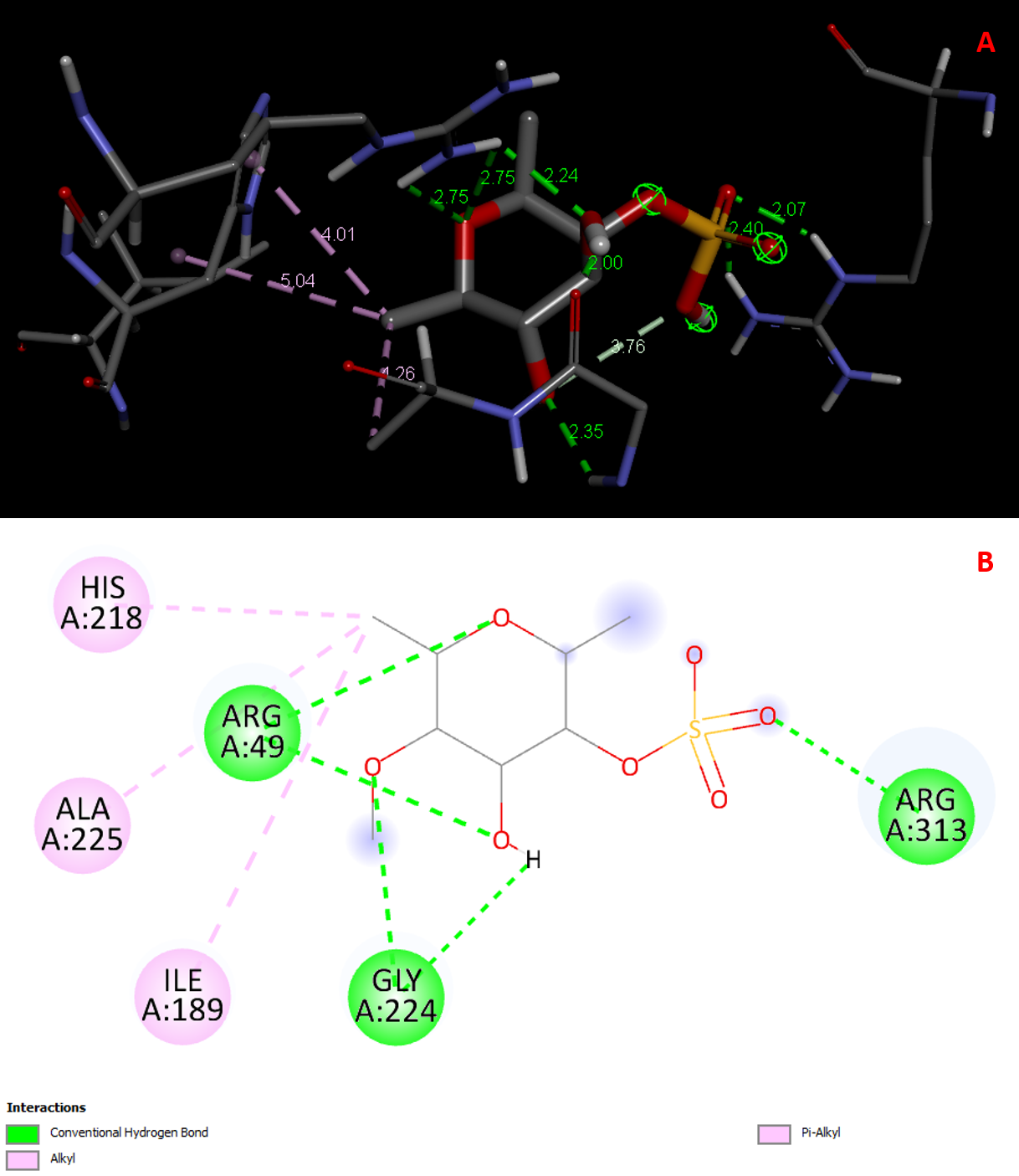
The molecular structure of a single fucoidan unit, including its sulfate moiety, is illustrated in Figure 1. The docking studies revealed that the lowest binding affinity between fucoidan and Monocyte Chemoattractant Protein-1 (MCP-1) was -5.1 kcal/mol (Table 2). The interaction analysis showed that fucoidan formed three conventional hydrogen bonds with MCP-1: two involving the sulfate group and one carbon-hydrogen bond (Fig. 2 and Table 4). The amino acid residues participating in these hydrogen bonds are GLU50 and ASN14, while the carbon-hydrogen bond involves CYS12 (Table 4).For the interaction between fucoidan and Nuclear Factor NF-kappa-B (NFκB), the binding affinity was -5.4 kcal/mol (Table 3). The binding interactions included seven hydrogen bonds: two each with ARG313 and GLY224, and three with ARG49. Additionally, fucoidan formed one alkyl bond with ALA225 and one π-alkyl bond with ILE189 (Fig. 3 and Table 5). Notably, ARG313 interacts with the sulfate moiety of fucoidan (Almatrafi et al., 2024). This interaction indicates that the sulfate group of fucoidan plays a crucial role in its interaction with both MCP-1 and NFκB, highlighting fucoidan's potential as an anti-inflammatory agent[(Gandhi et al., 2021; Katyal et al., 2023; Priyadharshini et al., 2023)](https://paperpile.com/c/z6tJNF/QQWpX+mlocR+a9cyC)

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**Figure 1**. Molecular structure of fucoidan showing one sulphate group



**Figure 2.** Molecular interactions between the ligand fucoidan and Monocyte chemoattractant protein-1 (MCP-1) showing three hydrogen bonds and the sulphate group interaction is clearly seen, and one carbon-hydrogen bond A) Three-dimensional view, B) Two-dimensional view.



**Figure 3.** Molecular interactions between the ligand fucoidan and nuclear factor NF-kappa-B (NFκB) showing seven hydrogen bond, two alkyl and one π-alkyl bonds A) Three-dimensional view, B) Two-dimensional view.

**Table 2.** The table retrieved after molecular docking between fucoidan and MCP-1 showing binding affinity.

|  |  |  |  |
| --- | --- | --- | --- |
| **Ligand** | **Binding Affinity** | **rmsd/ub** | **rmsd/lb** |
| 1don-1\_model1\_129532628 | -5.1 | 0 | 0 |
| 1don-1\_model1\_129532628 | -4.7 | 4.877 | 2.934 |
| 1don-1\_model1\_129532628 | -4.6 | 2.031 | 1.723 |
| 1don-1\_model1\_129532628 | -4.5 | 5.518 | 3.047 |
| 1don-1\_model1\_129532628 | -4.5 | 13.623 | 11.751 |
| 1don-1\_model1\_129532628 | -4.4 | 3.455 | 2.512 |
| 1don-1\_model1\_129532628 | -4.4 | 3.682 | 2.618 |
| 1don-1\_model1\_129532628 | -4.4 | 12.846 | 11.131 |
| 1don-1\_model1\_129532628 | -4.4 | 4.477 | 3.212 |

**Table 3.** The table retrieved after molecular docking between fucoidan and NFκB showing binding affinity.

|  |  |  |  |
| --- | --- | --- | --- |
| Ligand | Binding Affinity | rmsd/ub | rmsd/lb |
| 7cli-1\_129532628 | -5.4 | 0 | 0 |
| 7cli-1\_129532628 | -5.2 | 5.071 | 2.461 |
| 7cli-1\_129532628 | -4.9 | 5.012 | 2.417 |
| 7cli-1\_129532628 | -4.8 | 3.051 | 2.068 |
| 7cli-1\_129532628 | -4.8 | 3.605 | 1.93 |
| 7cli-1\_129532628 | -4.7 | 4.809 | 2.826 |
| 7cli-1\_129532628 | -4.7 | 35.705 | 34.087 |
| 7cli-1\_129532628 | -4.6 | 3.985 | 2.444 |
| 7cli-1\_129532628 | -4.6 | 29.601 | 27.496 |

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

|  |  |  |  |
| --- | --- | --- | --- |
| **Bond Interactions** | **No. of bonds** | **Bond length (Å)** | **Amino acid residue** |
| Conventional Hydrogen Bond | 3 | 2.14 | GLU50 |
| 2.16 | ASN14 |
| 2.34 | ASN14 |
| Unfavourable Donor-Donor | 1 | 1.23 | ASN14 |
| Carbon Hydrogen Bond | 1 | 2.9 | CYS12 |
| Total number of bonds | 5 |  |  |

**Table 5.** The table showing bond interactions and its length between fucoidan and NFκB showing amino acid residues involves in it

|  |  |  |  |
| --- | --- | --- | --- |
| Bond Interactions | No. of bonds | Bond length (Å) | Amino acid residue |
| Conventional Hydrogen Bond | 7 | 2.4 | ARG313 |
| 2.01 | ARG313 |
| 2 | GLY224 |
| 2.35 | GLY224 |
| 2.24 | ARG49 |
| 2.75 | ARG49 |
| 2.75 | ARG49 |
| Pi-Alkyl | 1 | 5.04 | ILE189 |
| Alkyl | 2 | 4.26 | ALA225 |
| 4.01 | HIS218 |
| Total number of bonds | 10 |  |  |

# Discussion

The molecular docking studies of fucoidan with the inflammatory mediators MCP-1 and NF-κB offer valuable insights into the mechanisms underlying its anti-inflammatory activity, providing a molecular basis for its therapeutic potential[(Janani et al., 2021; Kachhara et al., 2021; Subramanian et al., 2023)](https://paperpile.com/c/z6tJNF/CcSZq+Mwyzl+62LEz). These in silico investigations not only corroborate previous experimental findings but also reveal specific interactions that contribute to fucoidan's biological effects [(Fitton, 2011)](https://paperpile.com/c/z6tJNF/SDTD).Monocyte Chemoattractant Protein-1 (MCP-1), also known as CCL2, plays a crucial role in the inflammatory process by recruiting monocytes, memory T cells, and dendritic cells to sites of tissue injury and inflammation [(Deshmane et al., 2009)](https://paperpile.com/c/z6tJNF/UZ9h). The docking results demonstrating fucoidan's interaction with MCP-1, characterized by a binding affinity of -5.1 kcal/mol, suggest a moderately strong interaction[(Doshi et al., 2023; Lampl et al., 2023; Pandiyan et al., 2023)](https://paperpile.com/c/z6tJNF/U9XWx+6g7WL+1n5bB). This binding affinity is comparable to those observed for other natural compounds with known anti-inflammatory properties [(Vo & Kim, 2013)](https://paperpile.com/c/z6tJNF/xTnx).The formation of three conventional hydrogen bonds and a carbon-hydrogen bond between fucoidan and MCP-1 highlights the specificity of this interaction. Particularly noteworthy is the involvement of fucoidan's sulphate group in forming hydrogen bonds with GLU50 and ASN14 of MCP-1, while a carbon-hydrogen bond is established with CYS12[(Pavithra et al., 2023; Shenoy et al., 2023; Thomas & Jain, 2023)](https://paperpile.com/c/z6tJNF/nRB3B+BfFef+NoRl8). These interactions are consistent with the known importance of electrostatic interactions in protein-glycosaminoglycan binding [(Mulloy & Linhardt, 2001)](https://paperpile.com/c/z6tJNF/E1JW). The specificity of these interactions suggests that fucoidan may effectively inhibit MCP-1's chemotactic activity, potentially reducing monocyte recruitment to inflammation sites and thereby attenuating the inflammatory response [(Marcel Tutor Ale and Anne S. Meyer, n.d.)](https://paperpile.com/c/z6tJNF/ZZOo).The interaction of fucoidan with NF-κB, characterized by a slightly stronger binding affinity of -5.4 kcal/mol, is particularly significant given NF-κB's central role in regulating inflammatory responses [(Lawrence, 2009)](https://paperpile.com/c/z6tJNF/O4Iz). NF-κB is a key transcription factor that controls the expression of numerous pro-inflammatory genes, including those encoding cytokines, chemokines, and adhesion molecules [(Liu et al., 2017)](https://paperpile.com/c/z6tJNF/rhYG). The docking results reveal a complex network of interactions between fucoidan and NF-κB, including seven hydrogen bonds involving ARG313, GLY224, and ARG49, as well as an alkyl bond with ALA225 and a π-alkyl bond with ILE189.The involvement of ARG313 in the interaction with fucoidan's sulphate group is especially noteworthy, as arginine residues are known to be critical for the DNA-binding activity of NF-κB [(Chen & Ghosh, 1999)](https://paperpile.com/c/z6tJNF/YKV3). This interaction suggests that fucoidan may interfere with NF-κB's ability to bind to its target DNA sequences, potentially leading to a downregulation of pro-inflammatory gene expression [(Cumashi et al., 2007)](https://paperpile.com/c/z6tJNF/FW6n). This mechanism aligns with experimental studies that have demonstrated fucoidan's ability to inhibit NF-κB activation in various cellular models [(Lee et al., 2013)](https://paperpile.com/c/z6tJNF/rYec).The consistent involvement of the sulphate moiety in forming strong hydrogen bonds with amino acid residues in both MCP-1 and NF-κB underscores its critical role in fucoidan's anti-inflammatory action[(Ramsundar et al., 2023; Rieshy et al., 2023; Singh et al., 2023)](https://paperpile.com/c/z6tJNF/KH8vG+FaUR2+rskTA). This finding is in agreement with structure-activity relationship studies of various sulphated polysaccharides, which have consistently shown that the degree and pattern of sulfation significantly influence their biological activities [(Pomin, 2009)](https://paperpile.com/c/z6tJNF/p7Kg). The importance of sulphate groups in fucoidan's bioactivity extends beyond its anti-inflammatory effects, as they have also been implicated in its anticoagulant, antiviral, and antitumor properties [(Jiao et al., 2011)](https://paperpile.com/c/z6tJNF/ggrM).The molecular docking approach employed in this study exemplifies the power of computational methods in elucidating the molecular basis of bioactive compounds' effects. By providing detailed information about binding affinities and specific atomic interactions, these in silico techniques offer valuable insights that can guide the rational design of more potent and selective anti-inflammatory agents [(Meng et al., 2011)](https://paperpile.com/c/z6tJNF/JjiK). For instance, the identification of key interacting residues in MCP-1 and NF-κB could inform the development of fucoidan derivatives with enhanced binding properties or the design of small molecule mimetics that retain the critical sulphate-mediated interactions [(Kitchen et al., 2004)](https://paperpile.com/c/z6tJNF/ygNv).Moreover, these findings contribute to our understanding of the structure-function relationships in sulphated polysaccharides, a diverse class of compounds with wide-ranging biological activities [(Pomin & Mourão, 2008)](https://paperpile.com/c/z6tJNF/OAES). The specific interactions identified in this study may help explain the often-observed differences in bioactivity among fucoidan extracts from various seaweed species, which can differ in their fine structure and degree of sulfation [(Ale et al., 2011)](https://paperpile.com/c/z6tJNF/4OMc).It is important to note that while these molecular docking studies provide valuable insights, they represent a simplified model of the complex biological system. Factors such as the dynamic nature of protein-ligand interactions, the influence of the cellular environment, and potential conformational changes in the proteins upon ligand binding are not fully captured in these simulations [(Pagadala et al., 2017)](https://paperpile.com/c/z6tJNF/BYdx). Therefore, these computational findings should be viewed as hypotheses to be further validated through experimental studies, including biochemical assays, site-directed mutagenesis, and structural biology techniques such as X-ray crystallography or NMR spectroscopy [(Ferreira et al., 2015)](https://paperpile.com/c/z6tJNF/GuWB).

# Conclusion

In conclusion, the molecular docking analysis reveals that fucoidan exhibits significant binding affinities with MCP-1 and NF-κB, primarily through interactions involving its sulphate moiety. These interactions likely contribute to fucoidan's anti-inflammatory properties, supporting its potential as a therapeutic agent for inflammatory diseases. Future studies could focus on in vitro and in vivo validations of these interactions, as well as exploring the therapeutic applications of fucoidan in clinical settings.

# References

1. Almatrafi, T. A., Almohaimeed, H. M., Chakravarthi, S., Amin, A. H., Jafer, A., & Akhavan-Sigari, R. (2024). Reducing metastasis ability of gastric cancer cell line by targeting MMP16 using miR-193a-5p and 5-FU. Advances in Medical Sciences, 69(2), 463-473.
2. Saadh, M. J., Rasulova, I., Khalil, M., Farahim, F., Sârbu, I., Ciongradi, C. I. (2024). Natural killer cell-mediated immune surveillance in cancer: Role of tumor microenvironment. Pathology-Research and Practice, 254, 155120.
3. [Akshatha, J. V., SantoshKumar, H. S., Prakash, H. S., & Nalini, M. S. (2021). In silico docking studies of α-amylase inhibitors from the anti-diabetic plant Leucas ciliata Benth. and an endophyte, Streptomyces longisporoflavus. *3 Biotech*, *11*(2), 51.](http://paperpile.com/b/z6tJNF/7wyX)
4. [Ale, M. T., Mikkelsen, J. D., & Meyer, A. S. (2011). Important determinants for fucoidan bioactivity: a critical review of structure-function relations and extraction methods for fucose-containing sulfated polysaccharides from brown seaweeds. *Marine Drugs*, *9*(10), 2106–2130.](http://paperpile.com/b/z6tJNF/4OMc)
5. [Chaithanya, M. V., Uma Maheswari, T. N., & Rajeshkumar, S. (2021). Anti-inflammatory and antioxidant activity of lycopene, raspberry, green tea herbal formulation mediated silver nanoparticle. *Journal of Indian Academy of Oral Medicine and Radiology*, *33*(4), 397–400.](http://paperpile.com/b/z6tJNF/KQRw)
6. [Chen, F. E., & Ghosh, G. (1999). Regulation of DNA binding by Rel/NF-kappaB transcription factors: structural views. *Oncogene*, *18*(49), 6845–6852.](http://paperpile.com/b/z6tJNF/YKV3)
7. [Chokkattu, J. J., Neeharika, S., Brahmajosyula, I. P., & Thangavelu, L. (2023). Comparative Evaluation Cellular Toxicity Three Heat Polymerized Acrylic Resins: Vitro Study. *World*, *14*(6).](http://paperpile.com/b/z6tJNF/cvnto)
8. [Cumashi, A., Ushakova, N. A., Preobrazhenskaya, M. E., D’Incecco, A., Piccoli, A., Totani, L., Tinari, N., Morozevich, G. E., Berman, A. E., Bilan, M. I., Usov, A. I., Ustyuzhanina, N. E., Grachev, A. A., Sanderson, C. J., Kelly, M., Rabinovich, G. A., Iacobelli, S., Nifantiev, N. E., & Consorzio Interuniversitario Nazionale per la Bio-Oncologia, Italy. (2007). A comparative study of the anti-inflammatory, anticoagulant, antiangiogenic, and antiadhesive activities of nine different fucoidans from brown seaweeds. *Glycobiology*, *17*(5), 541–552.](http://paperpile.com/b/z6tJNF/FW6n)
9. [Dallakyan, S., & Olson, A. J. (2015). Small-molecule library screening by docking with PyRx. *Methods in Molecular Biology (Clifton, N.J.)*, *1263*, 243–250.](http://paperpile.com/b/z6tJNF/G1dd)
10. [Deshmane, S. L., Kremlev, S., Amini, S., & Sawaya, B. E. (2009). Monocyte chemoattractant protein-1 (MCP-1): an overview. *Journal of Interferon & Cytokine Research: The Official Journal of the International Society for Interferon and Cytokine Research*, *29*(6), 313–326.](http://paperpile.com/b/z6tJNF/UZ9h)
11. [Dharman, S., Maragathavalli, G., Shanmugam, R., & Shanmugasundaram, K. (2023). Biosynthesis Turmeric Silver Nanoparticles: Its Characterization Evaluation Antioxidant, Anti inflammatory, Antimicrobial Potential Against Oral Pathogens vitro Study. *Journal Indian Academy Oral Medicine Radiology*, *35*(3), 299–305.](http://paperpile.com/b/z6tJNF/hHoMG)
12. [Doshi, K., Nivedhitha, M. S., Solete, P., Dp, S., Jacob, B., & Siddique, R. (2023). *Effect adhesive strategy universal adhesives noncarious cervical lesions-an updated systematic review meta-analysis. BDJ open*. *9*.](http://paperpile.com/b/z6tJNF/U9XWx)
13. [Evaluation of antioxidant and anti inflammatory activity of grape seed oil infused with silver nanoparticles an in vitro study. (2021). *International Journal of Dentistry and Oral Science*, 3318–3322.](http://paperpile.com/b/z6tJNF/BlIL)
14. [Ezhilarasan, D., & Varghese, S. S. (2022). Porphyromonas gingivalis and dental stem cells crosstalk amplify inflammation and bone loss in the periodontitis niche. *Journal of Cellular Physiology*, *237*(10), 3768–3777.](http://paperpile.com/b/z6tJNF/pTzC)
15. [Ferreira, L. G., Dos Santos, R. N., Oliva, G., & Andricopulo, A. D. (2015). Molecular docking and structure-based drug design strategies. *Molecules (Basel, Switzerland)*, *20*(7), 13384–13421.](http://paperpile.com/b/z6tJNF/GuWB)
16. [Fitton, J. H. (2011). Therapies from fucoidan; multifunctional marine polymers. *Marine Drugs*, *9*(10), 1731–1760.](http://paperpile.com/b/z6tJNF/SDTD)
17. [Gandhi, J. M., Gurunathan, D., Doraikannan, S., & Balasubramaniam, A. (2021). Oral health status for primary dentition - A pilot study. *Journal of the Indian Society of Pedodontics and Preventive Dentistry*, *39*(4), 369–372.](http://paperpile.com/b/z6tJNF/QQWpX)
18. [Govindaraj, P., & Shanmugam, R. (2023). Effect chlorhexidine fluoride varnish incidence white spot lesion orthodontic patients. *Annals Dental Specialty*, *11*(1-2023), 35–39.](http://paperpile.com/b/z6tJNF/RGGtt)
19. [Handel, T. M., & Domaille, P. J. (1996). Heteronuclear (1H, 13C, 15N) NMR assignments and solution structure of the monocyte chemoattractant protein-1 (MCP-1) dimer. *Biochemistry*, *35*(21), 6569–6584.](http://paperpile.com/b/z6tJNF/wO20)
20. [Janani, K., Teja, K. V., & Ajitha, P. (2021). Cytotoxicity of oregano essential oil and calcium hydroxide on L929 fibroblast cell: A molecular level study. *Journal of Conservative Dentistry: JCD*, *24*(5), 457–463.](http://paperpile.com/b/z6tJNF/62LEz)
21. [Jiao, G., Yu, G., Zhang, J., & Ewart, H. S. (2011). Chemical structures and bioactivities of sulfated polysaccharides from marine algae. *Marine Drugs*, *9*(2), 196–223.](http://paperpile.com/b/z6tJNF/ggrM)
22. [Kachhara, S., Nallaswamy, D., Ganapathy, D., & Ariga, P. (2021). Comparison of the CBCT, CT, 3D printing, and CAD-CAM milling options for the most accurate root form duplication required for the root analogue implant (RAI) protocol. *Journal of Indian Academy of Oral Medicine and Radiology*, *33*(2), 141–145.](http://paperpile.com/b/z6tJNF/Mwyzl)
23. [Katyal, D., Jain, R. K., Sankar, G. P., & Prasad, S. (2023). Antibacterial, Cytotoxic, Mechanical Characteristics Novel Chitosan-Modified Orthodontic Primer: : In-Vitro: Study. *Journal International Oral Health*, *15*(3), 284–289.](http://paperpile.com/b/z6tJNF/a9cyC)
24. [Kitchen, D. B., Decornez, H., Furr, J. R., & Bajorath, J. (2004). Docking and scoring in virtual screening for drug discovery: methods and applications. *Nature Reviews. Drug Discovery*, *3*(11), 935–949.](http://paperpile.com/b/z6tJNF/ygNv)
25. [Lampl, S., Gurunathan, D., Krithikadatta, J., Mehta, D., & Moodley, D. (2023). Reasons for Failure of CAD/CAM Restorations in Clinical Studies: A Systematic Review and Meta-analysis. *The Journal of Contemporary Dental Practice*, *24*(2), 129–136.](http://paperpile.com/b/z6tJNF/1n5bB)
26. [Lawrence, T. (2009). The nuclear factor NF-kappaB pathway in inflammation. *Cold Spring Harbor Perspectives in Biology*, *1*(6), a001651.](http://paperpile.com/b/z6tJNF/O4Iz)
27. [Lee, S.-H., Ko, C.-I., Jee, Y., Jeong, Y., Kim, M., Kim, J.-S., & Jeon, Y.-J. (2013). Anti-inflammatory effect of fucoidan extracted from Ecklonia cava in zebrafish model. *Carbohydrate Polymers*, *92*(1), 84–89.](http://paperpile.com/b/z6tJNF/rYec)
28. [Libby, P. (2007). Inflammatory mechanisms: the molecular basis of inflammation and disease. *Nutrition Reviews*, *65*(12 Pt 2), S140–S146.](http://paperpile.com/b/z6tJNF/pl9G)
29. [Li, B., Lu, F., Wei, X., & Zhao, R. (2008). Fucoidan: structure and bioactivity. *Molecules (Basel, Switzerland)*, *13*(8), 1671–1695.](http://paperpile.com/b/z6tJNF/Ygtk)
30. [Liu, T., Zhang, L., Joo, D., & Sun, S.-C. (2017). NF-κB signaling in inflammation. *Signal Transduction and Targeted Therapy*, *2*. https://doi.org/](http://paperpile.com/b/z6tJNF/rhYG)[10.1038/sigtrans.2017.23](http://dx.doi.org/10.1038/sigtrans.2017.23)
31. [Marcel Tutor Ale and Anne S. Meyer. (n.d.). Fucoidans from brown seaweeds: an update on structures, extraction techniques and use of enzymes as tools for structural elucidation. *RSC Adv., 2013,3, 8131-8141*. https://doi.org/](http://paperpile.com/b/z6tJNF/ZZOo)[10.1039/C3RA23373A](http://dx.doi.org/10.1039/C3RA23373A)
32. [Medzhitov, R. (2008). Origin and physiological roles of inflammation. *Nature*, *454*(7203), 428–435.](http://paperpile.com/b/z6tJNF/Tzyu)
33. [Meng, X.-Y., Zhang, H.-X., Mezei, M., & Cui, M. (2011). Molecular docking: a powerful approach for structure-based drug discovery. *Current Computer-Aided Drug Design*, *7*(2), 146–157.](http://paperpile.com/b/z6tJNF/JjiK)
34. [Molinski, T. F., Dalisay, D. S., Lievens, S. L., & Saludes, J. P. (2009). Drug development from marine natural products. *Nature Reviews. Drug Discovery*, *8*(1), 69–85.](http://paperpile.com/b/z6tJNF/gleF)
35. [Mulloy, B., & Linhardt, R. J. (2001). Order out of complexity--protein structures that interact with heparin. *Current Opinion in Structural Biology*, *11*(5), 623–628.](http://paperpile.com/b/z6tJNF/E1JW)
36. [Nathan, C., & Ding, A. (2010). Nonresolving inflammation. *Cell*, *140*(6), 871–882.](http://paperpile.com/b/z6tJNF/AQwJ)
37. [Newman, D. J., & Cragg, G. M. (2020). Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. *Journal of Natural Products*, *83*(3), 770–803.](http://paperpile.com/b/z6tJNF/hfbH)
38. [Pagadala, N. S., Syed, K., & Tuszynski, J. (2017). Software for molecular docking: a review. *Biophysical Reviews*, *9*(2), 91–102.](http://paperpile.com/b/z6tJNF/BYdx)
39. [Pandiyan, I., Arumugham, M. I., Doraikannan, S. S., Rathinavelu, P. K., Prabakar, J., & Rajeshkumar, S. (2023). Antimicrobial and Cytotoxic Activity of Ocimum tenuiflorum and Stevia rebaudiana-Mediated Silver Nanoparticles - An In vitro Study. *Contemporary Clinical Dentistry*, *14*(2), 109–114.](http://paperpile.com/b/z6tJNF/6g7WL)
40. [Pan, W., Meshcheryakov, V. A., Li, T., Wang, Y., Ghosh, G., & Wang, V. Y.-F. (2023). Structures of NF-κB p52 homodimer-DNA complexes rationalize binding mechanisms and transcription activation. *eLife*, *12*. https://doi.org/](http://paperpile.com/b/z6tJNF/oRfA)[10.7554/eLife.86258](http://dx.doi.org/10.7554/eLife.86258)
41. [Pavithra, S., Paulraj, J., Rajeshkumar, S., & Maiti, S. (2023). Comparative evaluation antimicrobial activity compressive strength conventional thyme-modified glass ionomer cement. *Annals Dental Specialty*, *11*(1-2023), 70–77.](http://paperpile.com/b/z6tJNF/NoRl8)
42. [Pomin, V. H. (2009). Review: an overview about the structure-function relationship of marine sulfated homopolysaccharides with regular chemical structures. *Biopolymers*, *91*(8), 601–609.](http://paperpile.com/b/z6tJNF/p7Kg)
43. [Pomin, V. H., & Mourão, P. A. S. (2008). Structure, biology, evolution, and medical importance of sulfated fucans and galactans. *Glycobiology*, *18*(12), 1016–1027.](http://paperpile.com/b/z6tJNF/OAES)
44. [Priyadharshini, G., Gheena, S., Ramani, P., Rajeshkumar, S., & Ramalingam, K. (2023). Assessment antimicrobial efficacy cytotoxicity Cocos nucifera Triticum aestivum combination gel formulation therapeutic use. *World Journal Dentistry*, *14*(5), 414–418.](http://paperpile.com/b/z6tJNF/mlocR)
45. [Rajeshkumar, S., & Lakshmi, T. (2021). Green synthesis gold nanoparticles using kalanchoe pinnata its free radical scavenging activity. *Int J Dentistry Oral Sci*, *8*(7), 2981–2984.](http://paperpile.com/b/z6tJNF/3myQr)
46. [Ramsundar, K., Jain, R. K., Balakrishnan, N., & Vikramsimha, B. (2023). Comparative evaluation bracket bond failure rates novel non-primer adhesive conventional primer-based orthodontic adhesive-a pilot study. *Journal Dental Research*, *17*(1).](http://paperpile.com/b/z6tJNF/KH8vG)
47. [Rieshy, V., Chokkattu, J. J., Rajeshkumar, S., & Neeharika, S. (2023). Mechanism action clove ginger herbal formulation-mediated TiO2 nanoparticles against lactobacillus species: vitro study. *Journal Advanced Oral Research*, *14*(1), 61–66.](http://paperpile.com/b/z6tJNF/rskTA)
48. [Serhan, C. N., & Savill, J. (2005). Resolution of inflammation: the beginning programs the end. *Nature Immunology*, *6*(12), 1191–1197.](http://paperpile.com/b/z6tJNF/KULe)
49. [Shenoy, A., Maiti, S., Nallaswamy, D., & Keskar, V. (2023). An in vitro comparison of the marginal fit of provisional crowns using the virtual tooth preparation workflow against the traditional technique. *Journal of Indian Prosthodontic Society*, *23*(4), 391–397.](http://paperpile.com/b/z6tJNF/BfFef)
50. [Singh, S., Prasad, A. S., & Rajeshkumar, S. (2023). Cytotoxicity, antimicrobial, anti-inflammatory and antioxidant activity of camellia sinensis and citrus mediated copper oxide nanoparticle-an in vitro study. *Journal of International Society of Preventive & Community Dentistry*, *13*(6), 450–457.](http://paperpile.com/b/z6tJNF/FaUR2)
51. [Sivakumar, N., Geetha, R. V., Priya, V., Gayathri, R., & Ganapathy, D. (2021). Targeted phytotherapy forreactive oxygen species linked oral cancer. *Int J Dent Oral Sci*, *8*.](http://paperpile.com/b/z6tJNF/Q8NBl)
52. [Subramanian, A. K., Lalit, H., & Sivashanmugam, P. (2023). Preparation, characterization, and evaluation of cytotoxic activity of a novel titanium dioxide nanoparticle-infiltrated orthodontic adhesive: An in vitro study. *World Journal of Dentistry*, *14*(10), 882–887.](http://paperpile.com/b/z6tJNF/CcSZq)
53. [Tabas, I., & Glass, C. K. (2013). Anti-inflammatory therapy in chronic disease: challenges and opportunities. *Science (New York, N.Y.)*, *339*(6116), 166–172.](http://paperpile.com/b/z6tJNF/3wBo)
54. [Thomas, & Jain, R. K. (2023). Influence operator experience scanning time accuracy two different intraoral scanners-a prospective clinical trial. *Turkish Journal Orthodontics*, *36*(1).](http://paperpile.com/b/z6tJNF/nRB3B)
55. [Trott, O., & Olson, A. J. (2010). AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of Computational Chemistry*, *31*(2), 455–461.](http://paperpile.com/b/z6tJNF/a72S)
56. [Vo, T.-S., & Kim, S.-K. (2013). Fucoidans as a natural bioactive ingredient for functional foods. *Journal of Functional Foods*, *5*(1), 16–27.](http://paperpile.com/b/z6tJNF/xTnx)