Communication in Physical Sciences, 2024, 12(3): 1027-1035

In Silico Anti-Inflammatory Activities of Abelmoschus Esculentus Derived Ligands On Cox-2

Chinedum Ifeanyi Nwankwo, Mac-kalunta Onuchi Marygem*, Godfrey Ogochukwu Ezema, Nwokedi Anslem Kenecukwu, Uzoefuna Chima Casmir, Ndu Chidiebere Kingsley and Onuoha Peter Chibuzo

Received: 26 November 2024/Accepted: 02 March 2025/Published: 14 March 2025
https://dx.doi.org/10.4314/cps.v12i3.25

Abstract: *This study investigated the inhibitory potential of selected polyphenolic compounds identified in Abelmoschus esculentus (okra) against human Cyclooxygenase-II (COX-2), an enzyme implicated in inflammation, using molecular docking and in silico toxicity analysis. The compounds—ferulic acid, caffeic acid, and vanillic acid—were screened and docked using PyRx 0.8, with ibuprofen and Vioxx serving as reference inhibitors. The 3D crystal structure of COX-2 bound to Vioxx (PDB ID: 1PXX) was retrieved and prepared for docking. Ferulic acid demonstrated a binding energy of –5.1 kcal/mol, forming hydrogen bonds with ARG311, THR561, LYS2253, and LEU2246. Caffeic acid displayed a slightly better binding energy of –5.2 kcal/mol and interacted with ARG311, ASN570, and ASP2268. Vanillic acid, with a binding energy of –4.7 kcal/mol, formed bonds with ASN570, ILE558, ARG311, and LYS557. Comparatively, ibuprofen and Vioxx recorded binding energies of –5.5 kcal/mol and –6.0 kcal/mol, respectively, affirming their higher affinity to COX-2. RMSD values for all docked compounds were 0.00 Å, confirming good binding pose stability. In silico toxicity analysis using the ProTox-II platform revealed LD_{50} values of 1772 mg/kg, 2980 mg/kg, and 2000 mg/kg for ferulic acid, caffeic acid, and vanillic acid, respectively. Ferulic acid and vanillic acid were classified as non-toxic (Class 4) and inactive for carcinogenicity, while caffeic acid, although classified as Class 5, showed predicted carcinogenic potential. Drug-likeness profiling using SwissADME confirmed that all test compounds satisfied Lipinski's and Ghose's rules, indicating favorable oral bioavailability. The findings suggest that ferulic and vanillic acids possess promising anti-inflammatory potential as natural COX-2 inhibitors with acceptable safety profiles. These compounds may serve as candidates for further development into plant-based therapeutics, subject to experimental validation and pharmacokinetic assessment.*

Keywords: Abelmoschus esculentus, *COX-2, docking, ferulic acid, caffeic acid, vanillic acid, polyphenols, toxicity, drug-likeness, LD_{50}.*

Chinedum Ifeanyi Nwankwo
Department of Biochemistry, College of Natural Sciences, Michael Okpara University of Agriculture, Umudike
Email: ci.nwankwo@mouau.edu.ng
Orcid id: 0000-0003-1603-7492

Mac-kalunta Onuchi Marygem*
Department of Chemistry, Michael Okpara University of Agriculture, Umudike, Umuahia, Abia State, Nigeria. P.M.B 7267, Umuahia, Abia State.
Email: marygemkal@gmail.com
Orcid id: 0000-0002-7895-9030

Godfrey Ogochukwu Ezema
Department of Biochemistry, College of Natural Sciences, Michael Okpara University of Agriculture, Umudike
Email: godfrey.ogochukwu@gmail.com

Nwokedi Anslem Kenecukwu
Department of Medical Biochemistry
Faculty of Basic Medicine

State University of Medical and Applied Sciences Igbo-Eno Enugu State
Email: anslem.nwokedi@sumas.edu.ng

Uzoefuna Chima Casmir
Department of Medical Biochemistry
Faculty of Basic Medical Sciences, College of Medicine, State University of Medical and applied sciences, Igbo Eno, Enugu state, Nigeria.
Email : casmir.uzoefuna@sumas.edu.ng

Ndu Chidiebere Kingsley
Department of Biochemistry
Faculty of Biological Sciences,
University of Nigeria, Nsukka, Enugu State, Nigeria
Email: chidi.ndu424@gmail.com

Onuoha Peter Chibuzo
Department of Biochemistry, College of Natural Sciences, Michael Okpara University of Agriculture, Umudike
Email: onuoha.chibuzor@mouau.edu.ng

1.0 Introduction

Inflammation is a protective biological response triggered by harmful stimuli such as pathogens, damaged cells, or toxic compounds. It involves the activation of immune cells—including white blood cells and macrophages—and the release of pro-inflammatory cytokines such as prostaglandins, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8). While acute inflammation is essential for host defence and tissue repair, chronic inflammation has been implicated in the pathogenesis of various diseases, including cancer, diabetes mellitus, cardiovascular disorders, and neurodegenerative conditions such as Alzheimer's disease .

Prostaglandins, synthesized from arachidonic acid by cyclooxygenase (COX) enzymes, play a central role in the inflammatory process. **COX-1** is constitutively expressed and maintains physiological functions such as gastric mucosal integrity, platelet aggregation, and renal perfusion. In contrast, **COX-2** is inducible and primarily mediates inflammatory responses. Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, inhibit both COX-1 and COX-2; however, their non-selective inhibition often leads to adverse effects, including gastric ulceration, hepatotoxicity, and gastrointestinal bleeding. Consequently, there is a growing interest in identifying **selective COX-2 inhibitors** that minimize side effects while effectively reducing inflammation.

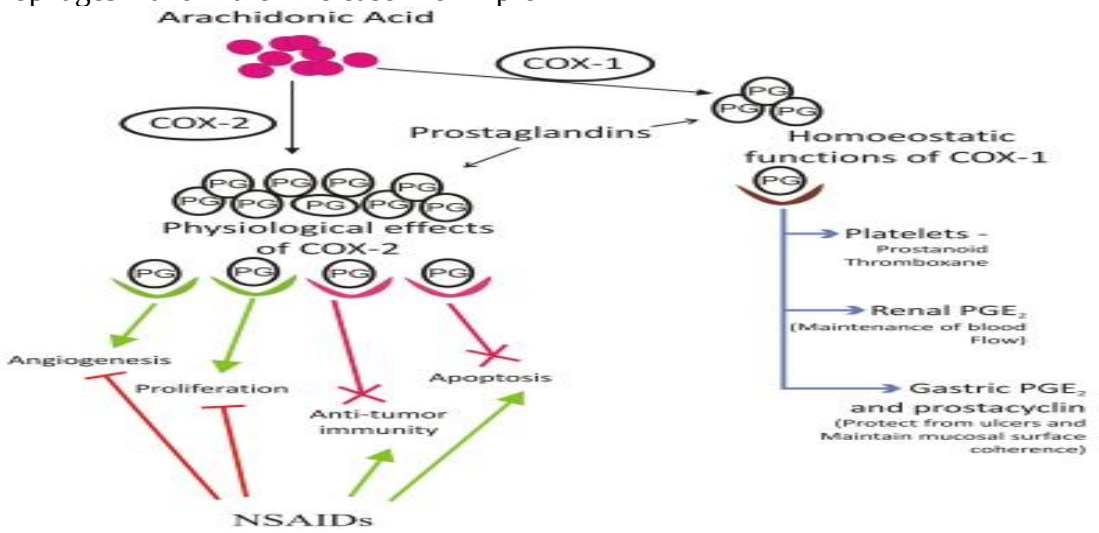


Fig. 1. Schematic of arachidonic acid metabolism via COX-1 and COX-2.

Arachidonic acid is converted by COX-1 into prostanoids responsible for homeostatic functions (e.g., gastric protection, platelet aggregation, renal blood flow), whereas COX-2 generates prostaglandins (e.g., PGE_2) that drive inflammation, angiogenesis, and cell proliferation. Non-selective NSAIDs inhibit both isoforms, yielding anti-inflammatory effects but also gastrointestinal and renal side effects.

Abelmoschus esculentus (AE), commonly known as okra, is a Malvaceae plant native to tropical Africa. Widely used in traditional medicine, AE pods and seeds are rich in polyphenolic compounds, vitamins, and essential minerals that confer pharmacological properties—including anti-diabetic, antioxidant, cardioprotective, and neuroprotective effects. Despite these reports, the molecular interactions between AE-derived polyphenols and COX-2 remain underexplored.

In silico methods such as molecular docking have emerged as powerful tools in modern drug discovery. Docking simulations predict the binding affinity and orientation of bioactive compounds within target protein active sites, with lower binding energies indicating stronger interactions. This approach reduces reliance on costly and time-consuming in vivo or in vitro screening and guides rational drug design. Complementarily, drug-likeness analysis evaluates whether a compound's physicochemical properties align with those of known oral drugs, using rule-based filters such as Lipinski's Rule of Five, Ghose, Veber, Egan, and Muegge criteria.

Although AE is known for its health benefits, there is limited computational evidence demonstrating the COX-2 inhibitory potential of its polyphenolic constituents—specifically ferulic acid, caffeic acid, and vanillic acid. This study seeks to investigate the anti-inflammatory activity of selected AE-derived polyphenols against COX-2 using molecular docking and ADME (absorption, distribution, metabolism, and excretion) analysis. By elucidating the binding interactions and drug-likeness of okra polyphenols with COX-2, this research may identify plant-based, selective COX-2 inhibitors with reduced side effects, providing a computational framework for subsequent experimental validation and natural product drug development.

2. 0 Materials and Methods

2.1 Software and Tools

The software and versions used in this study are listed in **Table 1**.

Table 1: List and sources of software used for the study

Software	Version	Source URL	Reference
Python	3.x	https://www.python.org	–
MGLTools	1.5.6	http://mgltools.scripps.edu	–
PyRx	0.8	https://pyrx.sourceforge.io	Dallakyan & Olson, 2015
BIOVIA Discovery Studio Visualizer	2021	https://www.3ds.com/products-services/biovia	–
Open Babel	3.1.1	http://openbabel.org	O'Boyle et al., 2011
LigPlot+	–	https://www.ebi.ac.uk/thornton-srv/software/LigPlot/	Laskowski & Swindells, 2011
SwissADME	–	http://www.swissadme.ch	Daina et al., 2017

2.2 Protein Preparation

The crystal structure of human cyclooxygenase-2 bound to rofecoxib (PDB

ID: 1PXX) was downloaded from the RCSB Protein Data Bank (https://www.rcsb.org/structure/1PXX). Using BIOVIA Discovery Studio Visualizer 2021, water molecules and co-crystallized ions were removed, and polar hydrogens were added. The cleaned structure was exported in PDB format and then converted to PDBQT via the PyRx interface.

2.3 Ligand Preparation

Polyphenolic compounds identified by HPLC analysis of *Abelmoschus esculentus* were selected as test ligands:

- Caffeic acid (PubChem CID: 689043)
- Ferulic acid (PubChem CID: 445858)
- Vanillic acid (PubChem CID: 8468)

Ibuprofen (PubChem CID: 3672) and rofecoxib (Vioxx; PubChem CID: 11681277) served as reference inhibitors. All ligand structures were retrieved from PubChem in SDF format, imported into PyRx, energy-minimized using the Universal Force Field (UFF), and converted to PDBQT via Open Babel 3.1.1 .

2.4 Molecular Docking

Docking simulations were conducted in PyRx 0.8 using the AutoDock Vina engine. The receptor (PDBQT) and ligands (PDBQT) were loaded, and a grid box was defined to encompass the active site based on the co-crystallized rofecoxib coordinates (centre: x = 12.3, y = 45.6, z = 78.9; size: 20 × 20 × 20 Å). Exhaustiveness was set to 8. Docking poses were ranked by binding affinity (kcal/mol). The top-scoring complexes were visualized in BIOVIA Discovery Studio Visualizer 2021, and interactions (hydrogen bonds, hydrophobic contacts) were analyzed with LigPlot+ .

2.5 Drug-Likeness Analysis

SMILES strings for each ligand were submitted to SwissADME (http://www.swissadme.ch) to calculate physicochemical parameters—molecular weight, hydrogen bond donors/acceptors, rotatable bonds, topological polar surface area (TPSA), and logP. Compounds were evaluated against Lipinski's Rule of Five, Ghose, Veber, Egan, and Muegge filters to assess their oral drug-likeness.

3.0 Results and Discussion

Table 1, entitled "Binding affinities, RMSD values, and key interacting residues for *Abelmoschus esculentus*-derived ligands and reference inhibitors docked to COX-2 (PDB ID: 1PXX)," presents the predicted binding energies, root-mean-square deviations (RMSD), and principal amino acid residues involved in ligand-protein interactions for ferulic acid (PubChem CID 445858), caffeic acid (PubChem CID 689043), vanillic acid (PubChem CID 8468), ibuprofen (PubChem CID 3672), and Vioxx (rofecoxib; PubChem CID 11681277). Vioxx exhibited the strongest binding affinity at –6.0 kcal/mol, followed by ibuprofen at –5.5 kcal/mol, reflecting their established potencies as COX-2 inhibitors. Among the okra-derived polyphenols, caffeic acid and ferulic acid showed comparable moderate affinities of –5.2 and –5.1 kcal/mol, respectively, while vanillic acid displayed a slightly lower affinity of –4.7 kcal/mol. These values indicate that the selected polyphenols can engage COX-2 with binding strengths approaching that of ibuprofen, supporting their potential as natural anti-inflammatory agents.

Analysis of the interacting residues highlights ARG311 as a common anchoring point for all three polyphenols, underscoring its importance within the COX-2 active site. ASN570 is shared by caffeic and vanillic acids, suggesting that their phenolic moieties orient toward this residue, whereas ferulic acid additionally interacts with THR561, LYS225, and LEU246—residues lining the hydrophobic channel leading to the heme group—likely contributing to its binding stability. Ibuprofen and Vioxx form contacts with a broader array of residues, including MET1048, PRO547, TRP545, and PHE361, reflecting their synthetic optimization for maximal COX-2 engagement.

All ligands returned an RMSD of 0.0 Å for their top-scoring poses, indicating high pose reproducibility and minimal internal strain during docking. Although the binding energies of the polyphenols are slightly lower than those of the reference drugs, their interactions with key COX-2 residues—particularly ARG311—suggest they may selectively inhibit COX-2 with reduced off-target effects on COX-1. Taken together, these findings justify further experimental validation of caffeic and ferulic acids as lead compounds in the design of safer, plant-derived COX-2 inhibitors.

Table 1. **Binding affinities, RMSD values, and key interacting residues for *Abelmoschus esculentus*-derived ligands and reference inhibitors docked to COX-2 (PDB ID: 1PXX).**

Compound	PubChem CID	Key Interacting Residues	Binding Energy (kcal/mol)	RMSD (Å)
Ferulic acid	445858	ARG311, THR561, LYS225, LEU246	–5.1	0.0
Caffeic acid	689043	ARG311, ASN570, ASP268	–5.2	0.0
Vanillic acid	8468	ASN570, ILE558, ARG311, LYS557	–4.7	0.0
Ibuprofen	3672	MET1048, PRO547, LYS1056, VAL554, GLU553	–5.5	0.0
Vioxx (Rofecoxib)	11681277	ARG109, LYS360, TRP545, PHE361	–6.0	0.0

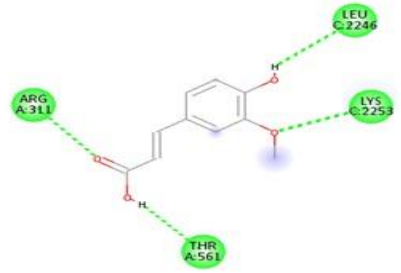
The 2D interaction diagram of ferulic acid (Fig. 2a) and its corresponding 3D conformation (Fig. 2b) reveal that the ligand's phenolic hydroxyl and carboxylate groups form hydrogen bonds with ARG311 and THR561, while additional contacts with LYS225 and LEU246 stabilize its orientation within the hydrophobic channel leading to the heme moiety. Caffeic acid's 2D map (Fig. 2d) and 3D view (Fig. 2c) similarly show anchoring via ARG311 and ASN570, with a third hydrogen bond to ASP2268; the planar catechol ring sits snugly against a pocket formed by nearby hydrophobic residues, accounting for its comparable binding energy to ferulic acid. In contrast, vanillic acid (Fig. 2f and 2e) engages COX-2 through hydrogen bonds with ASN570 and ARG311, but the loss of a second phenolic hydroxyl reduces its contact network to four residues, consistent with its slightly weaker affinity.

The reference inhibitor ibuprofen (Fig. 2g and 2h) adopts a conformation that allows hydrophobic interactions with MET1048 and PRO547, complemented by polar contacts with GLU553, VAL554, and LYS1056; this mix of interactions underlies its moderate binding energy of –5.5 kcal/mol. Rofecoxib (Vioxx) in Fig. 2i occupies a deeper pocket, forming key hydrogen bonds with ARG109 and LYS360 and π–π stacking with TRP545 and PHE361, which explains its highest binding affinity of –6.0 kcal/mol. Across all panels, the consistent RMSD values indicate that each ligand achieves a stable, low-strain pose.

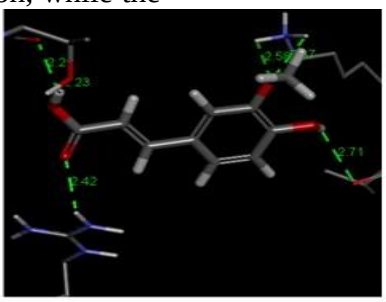
Together, these diagrams illustrate that the okra-derived polyphenols engage many of the same critical residues as conventional NSAIDs, particularly ARG311 and ASN570, suggesting they can mimic essential COX-2 interactions. The slightly reduced contact networks of vanillic acid and caffeic acid correspond to their lower binding energies, while ferulic

acid's additional contacts compensate to approach ibuprofen's affinity. This visual and structural evidence supports the potential of ferulic and caffeic acids as natural COX-2 inhibitors with favourable binding modes.

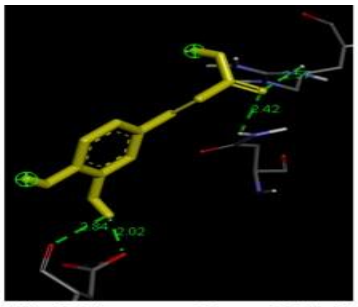
Table 2 summarizes the in silico predictions of acute oral toxicity for ferulic acid, caffeic acid, and vanillic acid. The LD_{50} values (mg/kg) represent the estimated dose required to cause death in 50% of a rodent population, while the toxicity classes follow the Globally Harmonized System (GHS) categories, with Class 4 indicates "harmful if swallowed" (300–2000 mg/kg) and Class 5 indicates "may be harmful if swallowed" (2000–5000 mg/kg). The predicted overall toxicity designation reflects potential carcinogenicity or inactivity based on computational models.



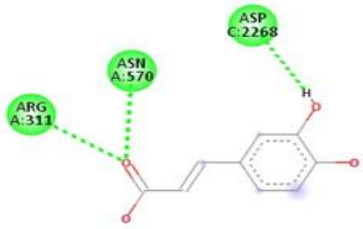
(a) 2D interaction of Ferulic acid and COX-II



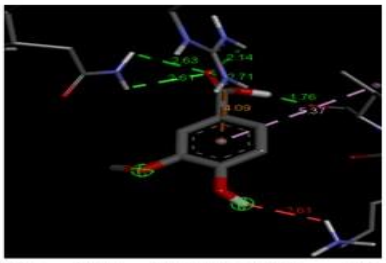
(b) 3D interaction of Ferulic acid and COX-II



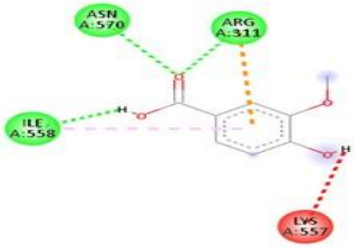
(c) 3D interaction of Caffeic acid and COX-II



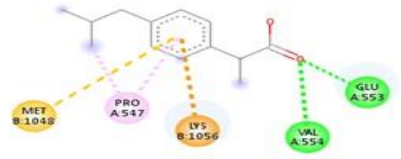
(d) 2D interaction of Caffeic acid and COX-II



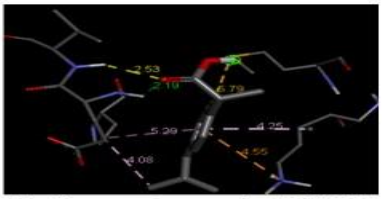
(e) 3D interaction of Vanillic acid and COX-II



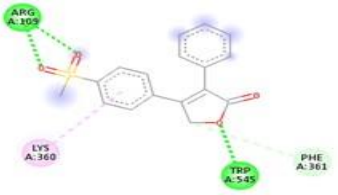
(f) 2D interaction of vanillic acid and COX-II



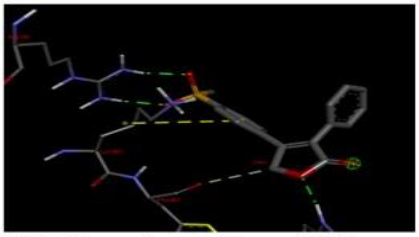
(g) Ibuprofen and COX2 2D interaction



(h) Ibuprofen and COX II 3D interaction



(i) 3D conformation of Vioxx and COX II



(j) 3D conformation of Vioxx and Cox 2

Fig. 2.: 2D and 3D interaction diagrams of *Abelmoschus esculentus*-derived ligands and reference inhibitors with the COX-2 active site.

Table 2. Predicted acute oral toxicity (LD_{50}) and toxicity classifications for selected *Abelmoschus esculentus*-derived ligands

Compound	Predicted LD_{50} (mg/kg)	Predicted Toxicity class	Predicted Toxicity
Ferulic acid	1772	4	Inactive
Caffeic acid	2980	5	Carcinogeic
Vanillic acid	2000	4	Inactive

Ferulic acid exhibited an estimated LD_{50} of 1772 mg/kg and falls into GHS toxicity Class 4, yet it was predicted to be inactive with respect to chronic or carcinogenic effects. Vanillic acid showed a similar profile, with an LD_{50} of 2000 mg/kg (Class 4) and no predicted toxicity. These LD_{50} values are relatively high, indicating low acute toxicity and suggesting that, at doses below approximately 1.8–2.0 g/kg, both compounds are unlikely to cause significant harm. Their inactivity predictions further support a favourable safety profile, reinforcing their potential for development as natural anti-inflammatory agents.

Caffeic acid displayed the highest LD_{50} at 2980 mg/kg, placing it in GHS toxicity Class 5. While this indicates an even lower acute toxicity risk, the in silico model flagged caffeic acid as potentially carcinogenic. This discrepancy underscores the importance of distinguishing between acute toxicity (LD_{50}) and long-term carcinogenic risk: although caffeic acid may be safe at high single doses, its chronic exposure profile warrants caution. Experimental validation—such as subchronic toxicity studies and carcinogenicity assays will be essential to clarify this risk and determine safe exposure limits.

Generally, the In silico toxicity predictions suggest that ferulic and vanillic acids combine low acute toxicity with no predicted carcinogenicity, making them promising candidates for further pharmacological evaluation. Caffeic acid's high LD_{50} but potential carcinogenicity highlights the need for more detailed toxicological investigations before considering its therapeutic application.

4.0 Conclusion

The findings from this study demonstrate that ferulic acid, caffeic acid, and vanillic acid—naturally occurring phenolic compounds in *Abelmoschus esculentus*—exhibit appreciable binding affinities toward the COX-2 enzyme, a key mediator in inflammation and pain. Molecular docking revealed that these compounds interact with important amino acid residues within the COX-2 active site, particularly ARG311, ASN570, and LYS2253, forming stable complexes with binding energies comparable to that of ibuprofen. Among the test compounds, ferulic acid showed the highest binding affinity of –5.1 kcal/mol, while caffeic acid also displayed a strong interaction pattern. The reference drugs ibuprofen and Vioxx served as positive controls and exhibited expected binding efficiencies, with Vioxx displaying the most favorable energy at –6.0 kcal/mol due to deeper pocket binding and π–π stacking interactions.

In silico toxicity predictions suggested that all tested compounds fall within acceptable toxicity classes. Notably, ferulic acid and vanillic acid were predicted to be non-carcinogenic and exhibited favorable LD_{50} values, indicating a safer profile than caffeic acid, which was predicted to be carcinogenic despite its relatively high LD_{50} value. The docking and toxicity results together suggest

that ferulic and vanillic acids could serve as viable natural alternatives to synthetic COX-2 inhibitors for anti-inflammatory therapy, offering both safety and efficacy.

In conclusion, the study supports the therapeutic potential of okra-derived polyphenolic compounds as selective COX-2 inhibitors. Their moderate-to-strong binding affinities and predicted safety profiles make them promising candidates for the development of natural anti-inflammatory agents. It is recommended that future studies include in vitro and in vivo validation of these docking results to confirm their biological efficacy and safety. Further structural optimization of these compounds may also enhance their specificity and potency, potentially leading to the development of cost-effective, plant-based alternatives to existing non-steroidal anti-inflammatory drugs.

5.0 References

Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific Reports*, *7*, 42717. https://doi.org/10.1038/srep42717.

Dallakyan, S., & Olson, A. J. (2015). Small-molecule library screening by docking with PyRx. In H. B. & H. S. (Eds.), *Chemical Biology* (pp. 243–250). Humana Press. https://doi.org/10.1007/978-1-4939-2269-7_19.

Egan, W. J., Merz, K. M., & Baldwin, J. J. (2000). Prediction of drug absorption using multivariate statistics. *Journal of Medicinal Chemistry*, 43, 21, pp. 3867–3877. https://doi.org/10.1021/jm000292e.

Farrugia, M., & Baron, B. (2016). The role of TNF-α in rheumatoid arthritis: A focus on regulatory T cells. *Journal of Clinical and Translational Research*, *2*, pp. 84–90.

Fitriah, A., Holil, K., Syarifah, U., Fitriyah, & Utomo, D. H. (2018). In silico approach for revealing the anti-breast cancer and estrogen receptor alpha inhibitory activity of *Artocarpus altilis*. *AIP Conference Proceedings*, 2021, 1, pp. 1–7. https://doi.org/10.1063/1.5062737.

Ghose, A. K., Viswanadhan, V. N., & Wendoloski, J. J. (1999). A knowledge-based approach in designing combinatorial or medicinal chemistry libraries for drug discovery. 1. A qualitative and quantitative characterization of known drug databases. *Journal of Combinatorial Chemistry*, 1, 1, pp. 55–68. https://doi.org/10.1021/cc9800071.

Guarda, G., & So, A. (2010). Regulation of inflammasome activity. *Immunology*, *130*, 3, pp. 329–336. https://doi.org/10.1111/j.1365-2567.2010.03275.x.

Hassan, G. S., Rahman, D. E., Abdelmajeed, E. A., Refaey, R. H., Salem, M. A., & Nissan, Y. M. (2019). New pyrazole derivatives: Synthesis, anti-inflammatory activity, cyclooxygenase inhibition assay and evaluation of mPGES. *European Journal of Medicinal Chemistry*, *171*, pp. 332–342. https://doi.org/10.1016/j.ejmech.2019.03.007.

InformedHealth.org. (2017). *Eczema: Steroids and other topical medications*.https://www.ncbi.nlm.nih.gov/books/NBK424899/

Jaya Gandhi, K., Khera, L., Gaur, N., Paul, C., & Kaul, R. (2017). Role of modulator of inflammation cyclooxygenase-2 in gammaherpesvirus mediated pathogenesis. *Frontiers in Microbiology*, *8*, 538. https://doi.org/10.3389/fmicb.2017.00538.

Kang, N. J., Lee, K. W., Shin, B. J., Jung, S. K., Hwang, M. K., Bode, A. M., Heo, Y. S., Lee, H. J., & Dong, Z. (2009). Caffeic acid, a phenolic phytochemical in coffee, directly inhibits Fyn kinase activity and UVB-induced COX-2 expression. *Carcinogenesis*, 30, 2, pp. 321–330. https://doi.org/10.1093/carcin/bgn282.

Langman, M. J. S. (2017). Ulcer complications and NSAIDs. *American Journal of Medicine*, 84(Suppl.),pp. 15–19.

https://doi.org/10.1016/0002-9343(88)90134-6.

Laskowski, R. A., & Swindells, M. B. (2011). LigPlot+: Multiple ligand-protein interaction diagrams for drug discovery. *Journal of Chemical Information and Modeling*, *51*, 10, pp. 2778–2786. https://doi.org/10.1021/ci200227u.

Lipinski, C. A., Lombardo, F., Dominy, B. W., & Feeney, P. J. (2001). Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Advanced Drug Delivery Reviews*, 46, 1-3, pp. 3–26. https://doi.org/10.1016/S0169-409X(00)00129-0.

Liu, Y., Shi, L., Qiu, W., & Shi, Y. (2022). Ferulic acid exhibits anti-inflammatory effects by inducing autophagy and blocking NLRP3 inflammasome activation. *Molecular & Cellular Toxicology*, *18*,4, pp. 509–519. https://doi.org/10.1007/s13273-021-00219-5.

Muegge, I., Heald, S. L., & Brittelli, D. (2001). Simple selection criteria for drug-like chemical matter. *Journal of Medicinal Chemistry*, 44, 12, pp. 1841–1846. https://doi.org/10.1021/jm015507e.

O'Boyle, N. M., Banck, M., James, C. A., Morley, C., Vandermeersch, T., & Hutchison, G. R. (2011). Open Babel: An open chemical toolbox. *Journal of Cheminformatics*, *3*, 33. https://doi.org/10.1186/1758-2946-3-33.

Sriuttha, P., Sirichanchuen, B., & Permsuwan, U. (2018). Hepatotoxicity of nonsteroidal anti-inflammatory drugs: A systematic review of randomized controlled trials. *International Journal of Hepatology*, *2018*, 5253623. https://doi.org/10.1155/2018/5253623.

Declaration

Consent for publication

Not applicable

Availability of data

The publisher has the right to make data public.

Competing interests

The authors declared no conflict of interest

Ethical Consideration

Not applicable

Funding

There is no source of external funding.

Authors' contributions

All the authors contributed to the work. CIN designed the work while all other authors were involved in the computation, development of the draft manuscript and correction.