IJBPAS, May, 2026, 15(5): 2388-2397

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

IN SILICO EVALUATION OF CURCUMIN-BASED ANALOGUES FOR ANALGESIC AND ANTI-INFLAMMATORY POTENTIAL VIA MOLECULAR DOCKING AGAINST COX-2 AND P2X2 RECEPTORS

WAGH HR[1*] AND MAHAJAN MP[2]

1: Department of Pharmaceutical Chemistry, Sinhgad Institute of Pharmacy, Pune, India

2: Principal and Professor, Sinhgad Institute of Pharmacy, Pune, India

***Corresponding Author: Ms. Hrutuja Rajendra Wagh: E Mail: hrutuja3196@gmail.com**

Received 16th April 2025; Revised 15th May 2025; Accepted 1st Aug. 2025; Available online 1st May 2026

https://doi.org/10.31032/IJBPAS/2026/15.5.10178

ABSTRACT

In pursuit of safer and more effective analgesic and anti-inflammatory drugs, we designed curcumin-based analogues and evaluated their binding interactions using molecular docking. Eight analogues (1A–8A) were assessed against two therapeutic targets: cyclooxygenase-2 (COX-2, PDB ID: 4PH9) and purinergic receptor P2X2 (PDB ID: 5SVL). Docking was performed using AutoDock Vina, with standard drugs ibuprofen and curcumin serving as reference ligands. Compounds 1A, 5A, and 7A demonstrated superior binding affinities and favorable interaction profiles compared to the standard drugs. These findings highlight the potential of these analogues for dual-target inhibition and warrant further experimental validation.

Keywords: In silico, Analgesic, Anti-inflammatory, PDB, Docking

INTRODUCTION

Chronic pain and inflammation are hallmark symptoms of numerous pathological conditions, including arthritis, musculoskeletal disorders, and autoimmune diseases. The primary pharmacological intervention for managing these symptoms involves the use of non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, diclofenac, and naproxen. These agents function mainly by inhibiting

cyclooxygenase (COX) enzymes, particularly COX-2, thereby reducing the synthesis of pro-inflammatory prostaglandins. However, long-term use of NSAIDs is associated with significant adverse effects, including gastrointestinal ulcers, renal dysfunction, and cardiovascular risks. Additionally, their selectivity for COX-2 over COX-1 remains suboptimal in many cases, resulting in off-target effects and limited therapeutic windows **[1]**.

Curcumin, a naturally occurring polyphenolic compound extracted from the rhizome of *Curcuma longa* (turmeric), has been extensively studied for its anti-inflammatory, antioxidant, and analgesic properties. It exerts its pharmacological activity by modulating multiple molecular targets, including COX-2, NF-κB, TNF-α, and various cytokines. Despite its broad biological potential, the clinical application of curcumin has been hindered by its poor aqueous solubility, rapid metabolism, and low systemic bioavailability. To overcome these challenges, medicinal chemists have focused on the rational design and synthesis of curcumin analogues with enhanced pharmacokinetic and pharmacodynamic properties. Structural modifications—such as bioisosteric replacement, substitution on aromatic rings, or the incorporation of heterocycles—can improve the stability, solubility, and receptor-binding efficiency of curcumin derivatives. Computational approaches, especially molecular docking, play a crucial role in early-phase drug discovery by enabling the prediction of binding affinities and interactions between drug candidates and their biological targets.

In this study, we designed a series of novel curcumin analogues and evaluated their potential as analgesic and anti-inflammatory agents through in silico docking studies. The docking simulations were performed using AutoDock Vina to predict and compare the binding affinities of the synthesized analogues against two critical targets: Cyclooxygenase-2 (COX-2, PDB ID: 4PH9), a validated target for pain and inflammation, and Purinergic Receptor P2X2 (PDB ID: 5SVL), which has emerged as a novel mediator in nociceptive signaling and inflammatory pathways.

By comparing the docking scores and interaction profiles of these analogues with standard drugs such as ibuprofen and curcumin, we aimed to identify promising lead compounds for further pharmacological development. The study also explores the structural features that contribute to enhanced receptor affinity, thereby offering insights into the structure–activity relationship (SAR) of curcumin-based therapeutics.

MATERIALS AND METHODS

1 Ligand Design and Preparation

Eight analogues (1A–8A) were designed via combinatorial chemistry and screened using Lipinski's rule of five. Ligands were prepared using LigPrep for geometry optimization.

2 Protein Preparation

Crystal structures of COX-2 (PDB ID: 4PH9) and P2X2 (PDB ID: 5SVL) were retrieved from the Protein Data Bank and prepared using the Protein Preparation Wizard. Hydrogen atoms were added, and energy minimization was performed. A grid box having dimension of 60, 60, and 60 points in x, y, and z directions was built with grid spacing of 0.375 Å. Distance-dependent function of the dielectric constant was used for the calculation of the energetic map **[2]**.

3 Docking Procedure

Molecular docking studies of all the compounds were carried out by taking X-ray crystal-structure data to understand the molecular interactions of the synthetic compounds within the Analgesic receptor binding site of COX2 (PDB ID 4PH9) & Anti-inflammatory receptor binding site of Purinergic Receptor P2X2 (PDB ID 5SVL). This interaction compared with standard drug ibuprofen and curcumin. The molecular docking study was used to understand the possible best binding pose of the compounds (**1A-8A**) by which they could be sorted for identifying promising leads using Auto Dock Vina **[3]**. Upon completion of docking, the best poses were screened by examination of binding energy ($\Delta G_{binding}$, kcal/mol) and number in cluster. Molecular interactions of both hydrophobic and hydrophilic types and root mean square deviation (RMSD) were studied using Biovia Discovery Studio Visualizer, LigPlot^{+} and PyMol programs. Docking scores are used to predict binding modes, binding affinity, and orientation of synthetic ligands at the active site of COX2 & P2X2 **[4]**.

RESULTS:

The molecular docking studies were performed to assess the binding affinity of the synthetic compounds (1A-8A) to the analgesic receptor COX2 (PDB ID: 4PH9) and the anti-inflammatory receptor P2X2 (PDB ID: 5SVL). The results were compared with standard drugs ibuprofen and curcumin. The docking was performed using AutoDock Vina to calculate the binding energies (ΔG), which were used to evaluate the stability and strength of the interactions between the ligands and their respective receptor binding sites **[5]**.

Table 1: Molecular Binding Affinity of Synthetic drug, Curcumin & Standard Drug for Analgesic Activity [6]

Drug Molecules	COX2 (PDB ID 4PH9) Calculated Affinity (Kcal/mol)			Higest Affinity (Kcal/mol)
	Model 1	Model 2	Model 3	
1A	-9.581	-9.342	-9.310	-9.581
2A	-9.420	-9.371	-9.132	-9.420
3A	-8.576	-8.464	-7.932	-8.576
4A	-9.402	-8.981	-8.852	-9.402
5A	-9.510	-8.948	-8.864	-9.510
6A	-9.468	-9.323	-8.923	-9.468
7A	-9.781	-9.642	-9.210	-9.781
8A	-9.410	-8.348	-8.864	-9.410
STD.Ibuprofen	-6.234	-6.109	-5.765	6.234
Curcumin	-8.321	-8.142	-7.923	-8.321

Table 2: Molecular Binding Affinity of Synthetic drug, Curcumin & Standard Drug for Anti Inflammatory Activity [7]

Drug Molecules	P2X2 (PDB ID 5SVL) Calculated Affinity (Kcal/mol)			Higest Affinity (Kcal/mol)
	Model 1	Model 2	Model 3	
1A	-8.481	-8.342	-8.110	-8.481
2A	-8.218	-8.112	-8.010	-8.218
3A	-8.381	-8.142	-8.109	-8.381
4A	-7.398	-7.138	-6.623	-7.398
5A	-7.710	-7.448	-6.864	-7.510
6A	-7.510	-7.148	-6.864	-7.510
7A	-8.118	-8.072	-7.810	-8.118
8A	-7.623	-7.456	-7.023	-7.623
STD.Ibuprofen	-5.734	-5.409	-5.364	-5.734
Curcumin	-8.121	-7.842	-7.562	-8.121

Table 3: Visualization of Molecular Interactions between Amino Acids and Curcumin, as well as a Standard Drug, in Binding to Protein Surfaces for Anti Analgesic Activity [8]

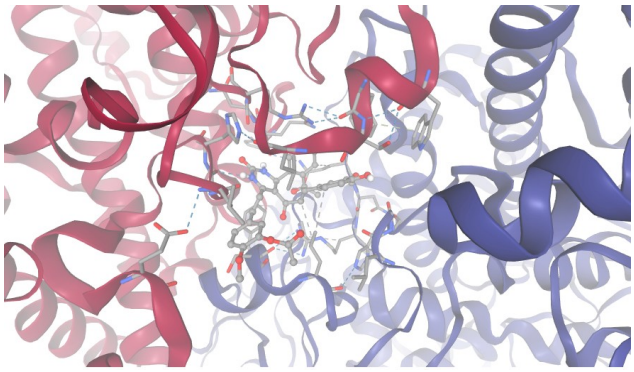
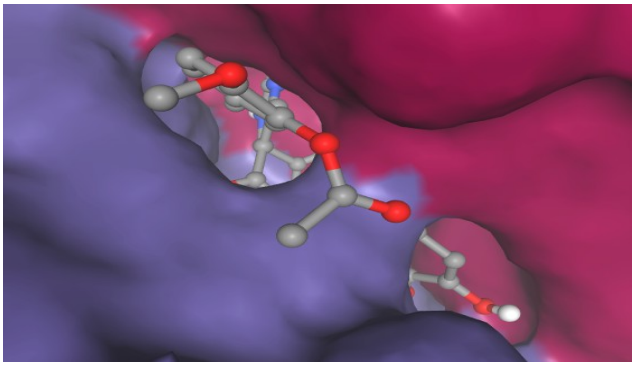
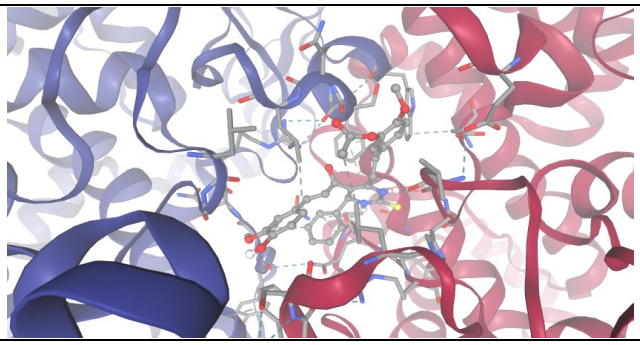
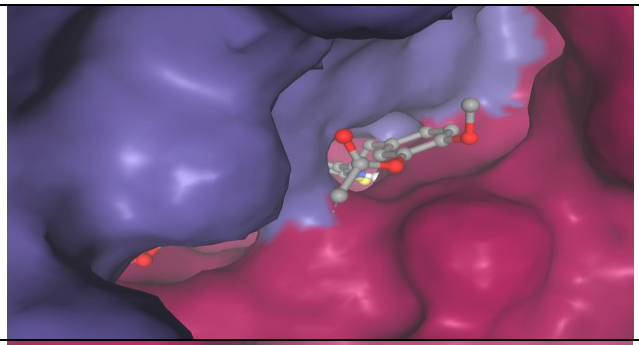
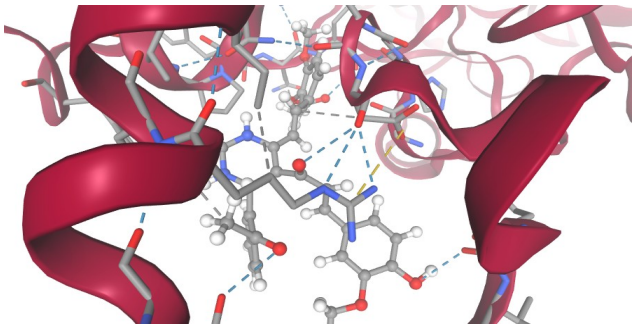
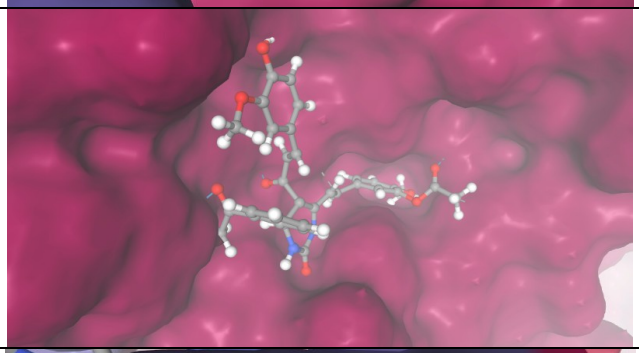
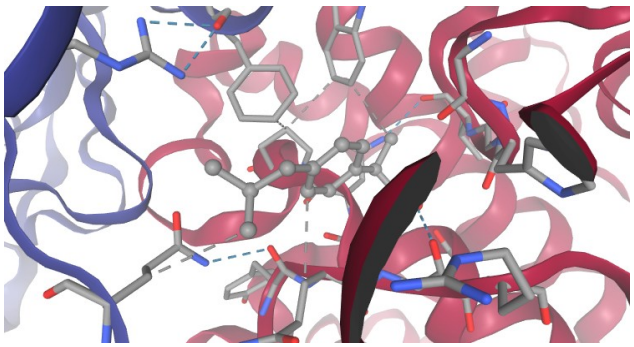
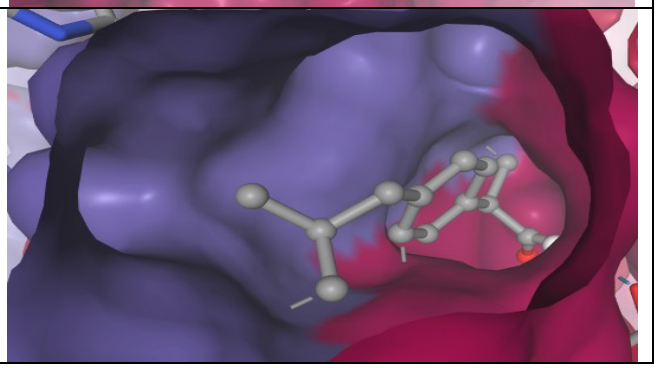
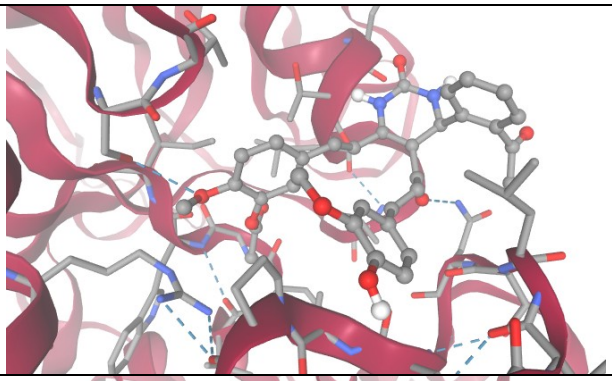
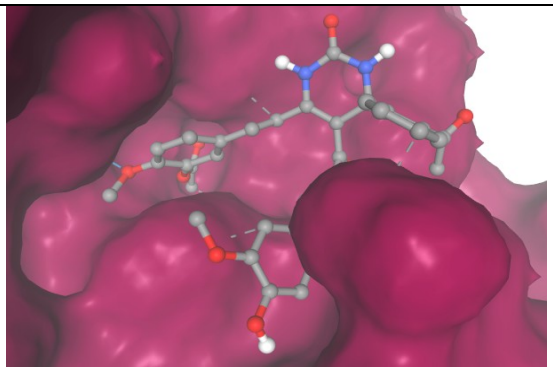
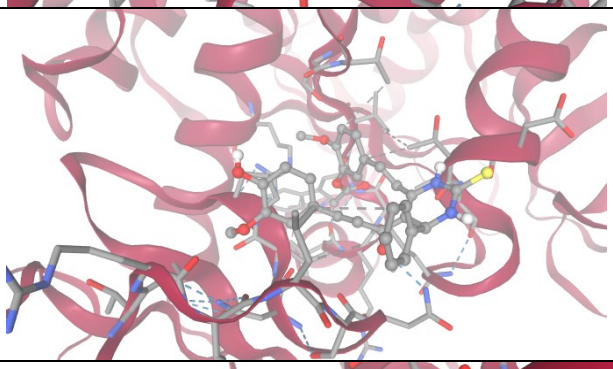
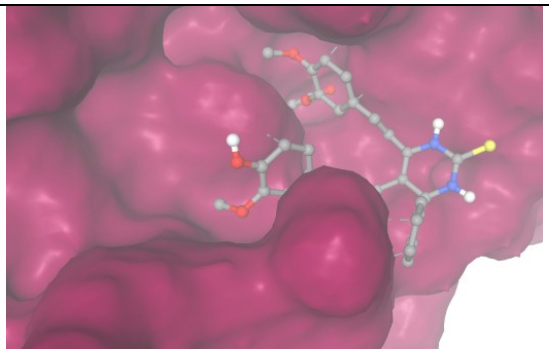
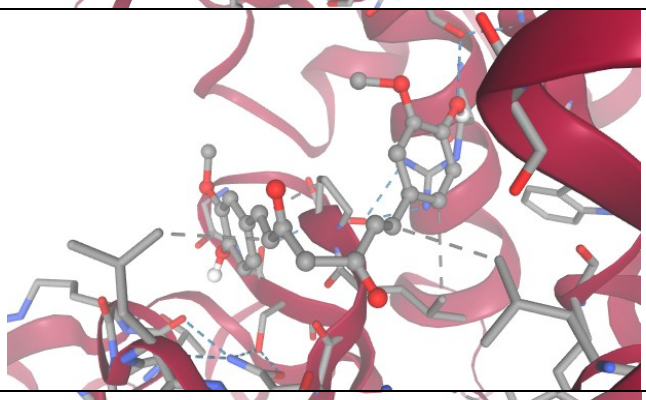
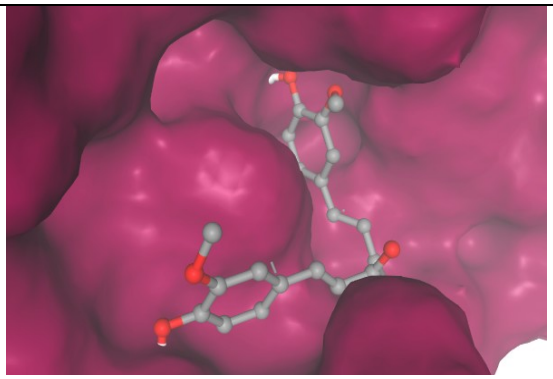
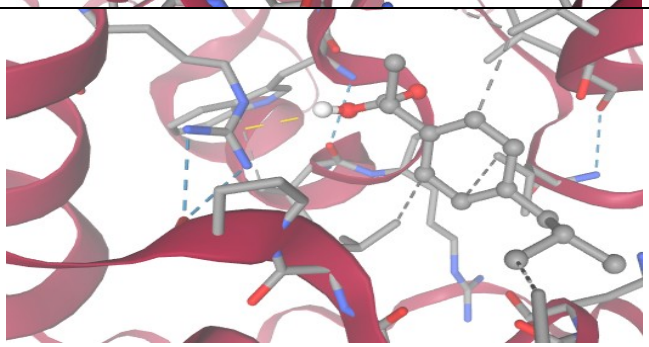
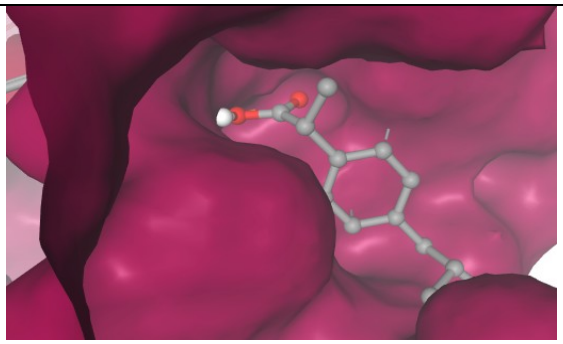
Name of Mol.	Molecule Interaction with Amino Acids	Binding to the Protein surface
1A		
7A		
CUR		
STD.		

Table 4: Visualization of Molecular Interactions between Amino Acids and Curcumin, as well as a Standard Drug, in Binding to Protein Surfaces for Antiinflammatory Activity [9]

Name of Mol.	Molecule Interaction with Amino Acids	Binding to the Protein surface
1A		
7A		
CUR		
STD		

DISCUSSION:

The results are summarized below:

COX2 (PDB ID: 4PH9) Binding Affinity: [10]

The binding affinities of the synthesized compounds at the COX2 receptor are shown in **Table 1**.

- **Compounds 7A and 5A** exhibited the best binding affinities at COX2 with docking scores of -9.781 kcal/mol and -9.510 kcal/mol, respectively. These compounds had consistently high binding energies across all models, suggesting a strong interaction with the COX2 active site.
- **Compound 1A** also showed a high affinity of -9.581 kcal/mol, which was the highest among the tested compounds in all three docking models, indicating that it binds effectively to the COX2 receptor.
- **Ibuprofen**, the standard analgesic drug, displayed a significantly lower binding affinity (-6.234 kcal/mol), indicating that while it does bind to the COX2 receptor, its interaction is not as favorable as that of the synthesized compounds.
- **Curcumin** exhibited a moderate binding affinity (-8.321 kcal/mol), which is higher than ibuprofen but lower than compounds such as 1A, 7A, and 5A. This suggests curcumin has a relatively weaker interaction with the COX2 receptor compared to the synthesized compounds.

P2X2 (PDB ID: 5SVL) Binding Affinity:

The binding affinities of the compounds at the P2X2 receptor are summarized in **Table 2**.

- **Compound 1A** showed the best docking score for P2X2 with -8.481 kcal/mol, which was the highest binding affinity among all compounds tested for P2X2. This indicates that 1A has a strong affinity for the P2X2 receptor.
- **Compound 7A** also showed a notable binding affinity of -8.118 kcal/mol, suggesting that it could interact effectively with the P2X2 receptor.
- **Curcumin**, with a docking score of -8.121 kcal/mol, exhibited a comparable binding affinity to 7A, indicating a moderate interaction with the P2X2 receptor.
- **Ibuprofen**, with a docking score of -5.734 kcal/mol, showed significantly weaker binding to P2X2 compared to the synthetic compounds and curcumin. This reinforces the idea that ibuprofen may be less effective against

P2X2-mediated inflammatory responses.

Binding Mode and Interactions:

The best poses from the docking analysis were analyzed to determine the binding modes and interactions of the compounds with the respective receptors. The docking results were visualized using Biovia Discovery Studio Visualizer, LigPlot+, and PyMol programs **[11]**.

COX2 (PDB ID: 4PH9):

- The interactions of the top compounds (1A, 5A, and 7A) with the COX2 receptor involved key hydrophobic interactions, particularly with the aromatic residues in the binding pocket, which may contribute to the observed high binding affinity.
- Compound 1A formed stable interactions with the hydrophobic residues of the COX2 receptor, such as Val523 and Leu531, which are crucial for the receptor's activity.
- Hydrophilic interactions, including hydrogen bonding with Ser530 and Arg120, were also observed in several compounds, further stabilizing the ligand-receptor complex.

P2X2 (PDB ID: 5SVL):

- The best scoring compounds (1A, 7A, and 6A) interacted with the P2X2 receptor through both hydrophobic and hydrophilic interactions. Hydrophobic interactions with residues such as Phe311 and Tyr314 were prominent, which could enhance the stability of the complex.
- Compound 1A showed a well-formed hydrogen bond with Asp317, contributing to its strong binding affinity to the P2X2 receptor.

Root Mean Square Deviation (RMSD):

To ensure that the docking results were consistent, the root mean square deviation (RMSD) was calculated for the best poses across the three models. The RMSD values indicated that the compounds 1A and 7A exhibited low RMSD values, suggesting that the docking results were stable and reproducible, further supporting the reliability of the predicted binding modes **[12]**.

Comparison with Standard Drugs:

When comparing the synthetic compounds to the standard drugs, ibuprofen and curcumin, the synthesized compounds (especially 1A and 7A) showed superior binding affinity to both COX2 and P2X2 receptors. This suggests that these compounds may have better efficacy in managing pain and inflammation compared to ibuprofen. Moreover, the results indicate

that some of the synthesized compounds could have dual-target activity, interacting with both the COX2 and P2X2 receptors, which might provide a broader spectrum of therapeutic benefits.

CONCLUSION

The molecular docking studies suggest that the synthesized compounds, particularly 1A, 7A, and 5A, exhibit favorable binding affinities for both COX2 and P2X2 receptors, outperforming ibuprofen and curcumin in most cases. These compounds may represent promising leads for the development of new analgesic and anti-inflammatory drugs with improved efficacy. Further experimental validation, including in vitro and in vivo studies, is recommended to confirm their potential as therapeutic agents **[13]**.

REFERENCES

[1] Wagh M, Dupade M, Girbane V, Bhosale M, Deshmukh M, Tilak P. Ashtasudaya Churn: To Give Relief from Congestion Due to Airborne Diseases. *Int J Res Appl Sci Eng Technol*. 2023;11:1133-1140. doi:10.22214/ijraset.2023.56146

[2] Girbane V. Molecular Docking and Admet Study of Selective Phytochemicals and Synthetic Drugs Against Respiratory Syncytial Virus, 7LVW Fusion Protein. *Int J Biol Pharm Allied Sci*. 2025;14:53-66. doi:10.31032/IJBPAS/2025/14.3.1006

[3] Ugwu DI, Okoro UC, Ukoha PO, Gupta A, Okafor SN. Novel anti-inflammatory and analgesic agents: synthesis, molecular docking and in vivo studies. *J Enzyme Inhib Med Chem*. 2018;33(1):405-415. doi:10.1080/14756366.2018.1426573

[4] Muhammad N, Khan R, Seraj F, *et al*. In vivo analgesic, anti-inflammatory and molecular docking studies of S-naproxen derivatives. *Heliyon*. 2024;10(2):e24267. doi:10.1016/j.heliyon.2024.e24267

[5] Sherwood ER, Toliver-Kinsky T. Mechanisms of the inflammatory response. *Best Pract Res Clin Anaesthesiol*. 2004;18(3):385-405. doi:https://doi.org/10.1016/j.bpa.2003.12.002

[6] Schrödinger LLC. *The PyMOL Molecular Graphics System, Version~1.8*.; 2015.

[7] Schrödinger LLC. *The AxPyMOL Molecular Graphics Plugin for Microsoft PowerPoint, Version~1.8*.; 2015.

[8] Sachin Parmar, Amit Gangwal NSD. *Scholars Research Library*. 2011;2(4):373-383.

[9] Press D. Docking Studies of Hybrid Pyrazole Analogues. Published online 2016:3529-3543.

[10] Eberhardt J, Santos-Martins D, Tillack AF, Forli S. AutoDock Vina 1.2.0: New Docking Methods, Expanded Force Field, and Python Bindings. *J Chem Inf Model*. 2021;61(8):3891-3898. doi:10.1021/acs.jcim.1c00203

[11] Soyer Z, Uysal S, Parlar S, Dogan AHT, Alptuzun V. Synthesis and molecular docking studies of some 4-phthalimidobenzenesulfonamide derivatives as acetylcholinesterase and butyrylcholinesterase inhibitors. *J Enzyme Inhib Med Chem*. 2017;32(1):13-19. doi:10.1080/14756366.2016.1226298

[12] Wagh H, Bhosale A, Girbane V, *et al*. Popping balls papaya extract: Preparation of pediatric dosages in therapeutic formulations for therapeutic usage in dengue and malaria. *International Journal of Experimental Research and Review*. 2023;32:188-194. doi:10.52756/ijerr.2023.v32.016

[13] Pokhrel S. No TitleΕΛΕΝΗ. *Αγαη*. 2024;15(1):37-48.