ORIGINAL PAPER

COMPUTATIONAL INVESTIGATION OF THE BINDING INTERACTIONS OF PARACETAMOL, IBUPROFEN, AND THEIR COMPLEXES WITH CYCLOOXYGENASE ENZYMES

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Abstract. *The combination of paracetamol and ibuprofen is widely used in clinical practice for the management of acute pain and fever. Paracetamol exerts its analgesic and antipyretic effects primarily through central mechanisms, whereas ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID), acts by inhibiting cyclooxygenase enzymes and reducing prostaglandin synthesis. The concurrent administration of these agents provides complementary mechanisms of action, resulting in enhanced analgesic efficacy compared with either drug alone. Numerous clinical studies have demonstrated that this combination is effective in postoperative pain, musculoskeletal disorders, and febrile conditions. This multimodal approach can enhance therapeutic efficacy while allowing lower doses of each medication. When administered appropriately, the combination is generally well tolerated and has a favorable safety profile. The primary aim of this study was to investigate whether the interactions of paracetamol and ibuprofen with cyclooxygenase (COX) enzymes are affected when the two drugs are administered in combination. Molecular docking simulations were performed using the HEX 8.0 docking software, with binding energy serving as an indicator of interaction strength and complex stability. The results demonstrated that the ibuprofen–paracetamol complex exhibited the strongest affinity for COX-2, with a binding energy of –290.80 kcal/mol. This finding suggests that, when ibuprofen functions as the receptor and paracetamol as the ligand, the resulting complex achieves the most favorable accommodation within the COX-2 binding site. These observations underscore the significance of evaluating drug–drug interactions at the molecular level, as such interactions may influence therapeutic outcomes. Consequently, a comprehensive understanding of these mechanisms is essential for optimizing the efficacy and safety of combination therapies.*

Keywords: *Paracetamol; ibuprofen; cyclooxygenase.*

1. INTRODUCTION

Pain and fever represent two of the most common symptoms encountered in clinical practice, often necessitating therapeutic agents with both analgesic and antipyretic properties.

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Paracetamol is extensively used because of its favorable safety profile and its centrally mediated analgesic and antipyretic actions, while ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID), exerts analgesic, antipyretic, and anti-inflammatory effects primarily through the inhibition of cyclooxygenase enzymes. The concomitant administration of paracetamol and ibuprofen is intended to capitalise on their complementary mechanisms of action, thereby potentially improving therapeutic efficacy and optimising symptom control. This combination may provide enhanced pain relief and fever reduction compared with either agent used alone, supporting its widespread application in clinical practice [1-3].

Paracetamol, also known as acetaminophen, is one of the most widely used analgesic and antipyretic agents worldwide [1]. Unlike nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol possesses minimal anti-inflammatory activity while maintaining effective pain-relieving and fever-reducing properties [4]. Despite its extensive clinical use for more than a century, the precise mechanism of action of paracetamol has long remained incompletely understood [5]. Contemporary pharmacological research suggests that its effects result from a combination of central nervous system actions involving cyclooxygenase inhibition, modulation of serotonergic pathways, and interactions with the endocannabinoid system [6,7].

The primary mechanism traditionally associated with paracetamol is the inhibition of prostaglandin synthesis in the central nervous system [5]. Prostaglandins are lipid mediators involved in pain perception and thermoregulation. Their synthesis depends on cyclooxygenase (COX) enzymes, particularly COX-1 and COX-2 [8]. Paracetamol acts predominantly within the brain, where it inhibits the peroxidase function of COX enzymes, thereby reducing the production of prostaglandin E2 (PGE2), a mediator implicated in fever and nociception [1,4,9]. This central inhibition explains the strong antipyretic and analgesic properties of paracetamol. Unlike classical NSAIDs, however, paracetamol exerts only weak peripheral COX inhibition because inflammatory tissues contain high concentrations of peroxides that diminish its inhibitory activity [4,10].

Paracetamol also enhances the activity of serotonin-mediated pain-control systems in the spinal cord and brainstem, thereby reducing nociceptive transmission and amplifying analgesic effects [11,12]. More recent research has also highlighted the role of paracetamol metabolites in the endocannabinoid system. In the brain and spinal cord, paracetamol is metabolized to p-aminophenol, which subsequently conjugates with arachidonic acid to form AM404 [13]. This metabolite inhibits the reuptake of endogenous cannabinoids and activates transient receptor potential vanilloid 1 (TRPV1) receptors and indirectly modulates cannabinoid signalling, contributing further to analgesia [14].

The favorable safety profile of paracetamol at therapeutic doses contributes to its widespread use in clinical practice [12]. Nevertheless, overdose may result in severe hepatotoxicity due to the accumulation of the toxic metabolite N-acetyl-p-benzoquinone imine (NAPQI) [15]. Under normal conditions, NAPQI is detoxified by glutathione, but excessive doses deplete hepatic glutathione stores, leading to liver cell necrosis. Therefore, although paracetamol is generally considered safe, appropriate dosing remains essential [5].

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) used for its antipyretic, analgesic, and anti-inflammatory properties [16]. Since its introduction into clinical practice in the 1960s, ibuprofen has become one of the most frequently administered medications worldwide for the treatment of pain, fever, and inflammatory disorders such as rheumatoid arthritis and osteoarthritis [17].

Ibuprofen exerts its therapeutic effects primarily through the reversible inhibition of cyclooxygenase enzymes (COX-1 and COX-2), thereby decreasing prostaglandin production, particularly prostaglandin E2 (PGE2) [16]. Reduced prostaglandin synthesis lowers the sensitivity of peripheral pain receptors and suppresses inflammatory processes [9].

Its analgesic action is mainly due to decreased prostaglandin levels at sites of tissue injury, which reduces pain receptor sensitization and limits the transmission of pain signals to the central nervous system. As a result, ibuprofen is effective in relieving mild to moderate pain, including headaches, musculoskeletal pain, dysmenorrhea, and postoperative pain [16]. By inhibiting COX-2, which is upregulated during inflammation, ibuprofen reduces prostaglandin-mediated vasodilation, vascular permeability, and leukocyte infiltration. This leads to decreased swelling, redness, and edema. Because ibuprofen inhibits both COX-1 and COX-2, it provides broad therapeutic benefits but may also cause adverse effects associated with nonselective COX inhibition [9,16]. The antipyretic effect of ibuprofen results from inhibition of prostaglandin synthesis in the hypothalamus. By restoring the normal temperature set point and promoting heat loss through vasodilation and sweating, ibuprofen effectively reduces fever [16,17].

Although generally well tolerated at therapeutic doses, ibuprofen may produce adverse reactions due to COX-1 inhibition. Prostaglandins generated by COX-1 play a protective role in the gastric mucosa by stimulating mucus and bicarbonate secretion and maintaining adequate blood flow. Inhibition of these protective prostaglandins can lead to gastrointestinal irritation, ulceration, and bleeding. Additionally, prolonged use may impair renal function because renal prostaglandins help maintain renal perfusion, particularly under conditions of reduced blood flow [16,18].

The combination of paracetamol (acetaminophen) and ibuprofen is a widely used therapeutic strategy for managing pain and fever [19]. Both drugs possess analgesic and antipyretic properties, yet they differ significantly in their mechanisms of action, pharmacological profiles, and adverse effects [6,17]. The concomitant administration of paracetamol and ibuprofen has attracted considerable clinical interest because the combination may provide superior analgesic efficacy compared with either drug alone, while maintaining an acceptable safety profile when used appropriately [2].

The pharmacological rationale for combining paracetamol and ibuprofen lies in the simultaneous targeting of central and peripheral pathways involved in pain perception and inflammation [19]. Paracetamol predominantly modulates nociceptive transmission at the central level, whereas ibuprofen reduces inflammatory mediator synthesis at peripheral sites of tissue injury. As a result, the association is particularly effective in acute pain conditions such as postoperative pain, dental pain, musculoskeletal disorders, headaches, and febrile illnesses. Clinical studies have demonstrated that this combined therapy often provides more rapid and prolonged pain relief than monotherapy with either agent [12]. Another important advantage of the paracetamol–ibuprofen combination is the option to reduce the dose of each drug. By achieving improved analgesia through complementary mechanisms, lower doses may be sufficient to obtain therapeutic effects, potentially reducing the incidence of adverse reactions. This strategy is especially relevant in pediatric and postoperative settings, where optimizing pain control while minimizing toxicity is essential [20].

Despite its therapeutic benefits, the combined use of paracetamol and ibuprofen requires careful consideration of safety issues. Paracetamol overdose remains associated with hepatotoxicity, particularly in individuals with liver disease, chronic alcohol consumption, or malnutrition [5]. Ibuprofen, on the other hand, may cause gastrointestinal irritation, peptic ulceration, renal impairment, and, in some cases, cardiovascular complications because of cyclooxygenase inhibition [16]. Although short-term combined use is generally considered safe in healthy individuals, prolonged administration or excessive dosing increases the risk of cumulative toxicity [16,21].

Pharmacokinetic interactions between paracetamol and ibuprofen are relatively limited, which contributes to the practicality of their coadministration. Both drugs are rapidly absorbed after oral administration and exhibit different metabolic pathways, reducing the

likelihood of clinically significant metabolic interference. This favorable pharmacokinetic compatibility supports their frequent use in multimodal analgesic protocols [2].

2. MATERIALS AND METHODS

2.1. MATERIALS

A computational chemistry framework was employed to investigate the structural and interactional properties of paracetamol and ibuprofen. Initial molecular modelling and geometry optimisation were performed using the HyperChem software package [22], thereby generating energy-minimized three-dimensional conformations and evaluating relevant electronic and physicochemical parameters. The optimized molecular geometries obtained from these calculations were subsequently used as input structures for docking simulations.

To evaluate potential intermolecular interactions between the two analgesic compounds, docking studies were carried out using the Hex docking program [23]. This software enables the assessment of molecular shape complementarity, electrostatic interactions, and steric compatibility, parameters that are essential for predicting the formation and stability of supramolecular complexes. The docking methodology implemented in Hex has been widely applied in molecular recognition and protein–ligand interaction studies [24].

For the biological component of the study, the three-dimensional structures of the selected receptor targets were retrieved from the RCSB Protein Data Bank [25,26]. Only high-resolution crystallographic structures containing complete active-site information were selected to ensure reliable docking simulations. Prior to molecular docking, receptor structures were prepared by removing crystallographic water molecules, adding missing hydrogen atoms, and optimizing protonation states as needed.

2.2. METHODS

The methodological protocol consisted of two sequential stages: intermolecular complex generation and protein–ligand docking analysis. In the first stage, the influence of docking orientation on intermolecular complex formation was investigated. Paracetamol and ibuprofen were docked against each other in both possible orientations using Hex 8.0.0. In each simulation, one molecule was assigned as the ligand (mobile component), while the second acted as the receptor (stationary component). This bidirectional docking strategy enabled the evaluation of potential differences in binding geometry, interaction energy, and predicted complex stability resulting from docking asymmetry.

Following the formation of the intermolecular complexes, the optimized structures of paracetamol, ibuprofen, and the preformed paracetamol–ibuprofen complexes were individually docked into the selected biological receptors. The purpose of these simulations was to determine whether the supramolecular complexes exhibit interaction patterns distinct from those of the isolated compounds.

To ensure consistency and comparability between simulations, identical docking parameters were applied throughout the study. Both shape-based and electrostatic scoring functions available in Hex were included during the docking calculations, and multiple binding poses were generated for each ligand–receptor pair. The best-ranked conformations

were subsequently analyzed according to binding energy, spatial orientation within the receptor active site, hydrogen-bond formation, hydrophobic contacts, and possible steric interactions.

This two-stage computational approach, involving both drug–drug and drug–receptor interaction analyses, provides a more comprehensive perspective on the molecular behavior of combination analgesic therapies and may offer insight into possible synergistic or competitive binding mechanisms [27–36].

3. RESULTS AND DISCUSSION

Following the molecular modeling and geometry optimization procedures, the investigated compounds (Table 1) were assembled into intermolecular complexes using the Hex 8.0.0 docking software. The main objective of this stage was to evaluate whether the order in which paracetamol and ibuprofen are assigned as ligand or receptor influences the resulting interaction geometry and binding affinity (Table 2, Figs. 1 and 2).

Table 1. Chemical structure of the studied compounds.

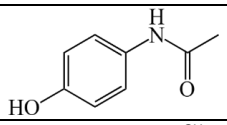
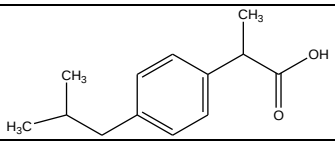
Compound	Structure
Paracetamol	
Ibuprofen	

Table 2. Docking order and docking energies for the drugs paracetamol and ibuprofen.

Receptor	Ligand	Energy [kcal/mol]
Paracetamol	Ibuprofen	-111.35
Ibuprofen	Paracetamol	-115.45

The obtained results indicate that the docking orientation slightly affects the predicted stability of the supramolecular complexes. Although both configurations exhibited favorable interaction energies, the complex generated using ibuprofen as the receptor and paracetamol as the ligand displayed a slightly lower docking energy, suggesting a more stable intermolecular association.

In the subsequent stage of the study, the generated complexes were subjected to molecular docking simulations against selected biological targets retrieved from the Protein Data Bank (PDB) [25,26]. Specifically, PDB structure 3KK6 was selected for cyclooxygenase-1 (COX-1), while PDB structure 3LN1 was employed for cyclooxygenase-2 (COX-2). These enzymes are directly involved in prostaglandin biosynthesis and represent major pharmacological targets for the studied drugs [25,26].

The docking simulations were designed to investigate the binding orientations, interaction energies, and molecular interaction patterns formed between the investigated ligands or ligand complexes and the active sites of the COX enzymes. Particular attention was given to hydrogen-bond formation, hydrophobic interactions, steric complementarity, and interactions with key amino acid residues located within the catalytic pocket. Through this analysis, we aimed to evaluate whether the formation of paracetamol–ibuprofen complexes could influence receptor binding behavior and potentially modify the pharmacological profile

of the individual compounds. These findings provide additional insight into the molecular mechanisms governing the activity and selectivity of combination analgesic systems.

Table 3. Values of binding energy with COX-1.

Complex/Compound	Energy [kcal/mol]
Ibuprofen–Paracetamol	-268.42
Paracetamol–Ibuprofen	-260.56
Ibuprofen	-247.19
Paracetamol	-192.34

The docking results presented in Table 3 indicate that both ibuprofen–paracetamol complexes exhibit lower binding energies than the individual compounds, suggesting the formation of more stable intermolecular systems. The Ibuprofen–Paracetamol complex showed the lowest interaction energy (−268.42 kcal/mol), followed closely by the Paracetamol–Ibuprofen complex (−260.56 kcal/mol). In comparison, ibuprofen alone presented a binding energy of −247.19 kcal/mol, while paracetamol displayed the weakest interaction energy (−192.34 kcal/mol).

These findings suggest that the formation of supramolecular complexes between ibuprofen and paracetamol may enhance the overall stability of the interacting system relative to the isolated drugs. The lower docking energies obtained for the complexes may result from the establishment of additional intermolecular interactions, including hydrogen bonding, hydrophobic contacts, and steric complementarity between the two molecules. Such interactions could contribute to a more favorable spatial arrangement and increased stabilization of the complex.

An important observation is the slight difference between the two docking orientations. The Ibuprofen–Paracetamol configuration exhibited a lower binding energy than the reverse orientation, indicating that the order in which the molecules are arranged influences the predicted interaction stability. This behavior suggests that the relative positioning of the functional groups within the complex affects the interaction geometry and may alter the accessibility of hydrogen bond donor and acceptor sites.

Furthermore, the stronger interaction energies observed for the complexes compared with paracetamol alone may indicate that ibuprofen contributes significantly to the stabilization of the supramolecular assembly, likely due to its larger hydrophobic region and greater conformational flexibility. These results support the hypothesis that intermolecular drug–drug interactions may influence the physicochemical and potentially pharmacological behavior of combination analgesic systems.

Overall, the docking analysis demonstrates that paracetamol and ibuprofen can form stable intermolecular complexes and that the docking orientation has a measurable effect on interaction strength. These findings may provide useful insight into the molecular basis of combined analgesic formulations and justify further investigations using molecular dynamics simulations and receptor-binding studies [27-36].

Table 4. Values of binding energy with COX-2.

Complex/Compound	Energy [kcal/mol]
Paracetamol–Ibuprofen	-40.45
Ibuprofen–Paracetamol	-29.53
Ibuprofen	-23.58
Paracetamol	-19.8

The binding energy values presented in Table 4 indicate that both paracetamol–ibuprofen complexes exhibit stronger interactions with the COX-2 receptor compared with the individual compounds. Among the studied systems, the Paracetamol–Ibuprofen complex

showed the lowest binding energy (−40.45 kcal/mol), followed by the Ibuprofen–Paracetamol complex (−29.02 kcal/mol). In contrast, ibuprofen alone displayed a binding energy of −23.58 kcal/mol, while paracetamol showed the weakest interaction with the receptor (−19.8 kcal/mol).

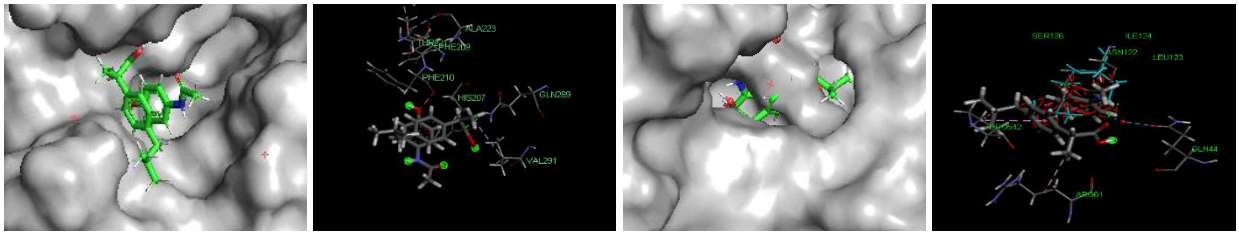
These results suggest that intermolecular complexes between paracetamol and ibuprofen enhance the compounds' affinity for the COX-2 active site. The significantly lower binding energy of the Paracetamol–Ibuprofen complex indicates a more stable ligand–receptor interaction, likely due to cooperative effects between the two molecules. Such effects could include complementary hydrogen bonding, improved hydrophobic interactions, or a more favorable occupation of the binding pocket.

An important aspect highlighted by these findings is the influence of docking orientation on receptor binding. Although both complexes showed stronger affinities than the isolated drugs, the Paracetamol–Ibuprofen configuration had substantially lower binding energy than the reverse arrangement. This difference suggests that the spatial orientation of the molecules within the complex affects the exposure and positioning of key functional groups involved in receptor interactions. Consequently, distinct docking geometries may alter the interaction network established with amino acid residues in the COX-2 catalytic site.

The greater affinity of the complexes compared with paracetamol alone is expected, given ibuprofen's known anti-inflammatory activity and its higher intrinsic affinity for cyclooxygenase enzymes. However, the improved interaction energy observed for the complexes compared with ibuprofen alone may indicate that paracetamol contributes indirectly to receptor stabilization by modifying the overall conformation of the supramolecular assembly.

Overall, these results support the hypothesis that intermolecular complex formation between paracetamol and ibuprofen can influence receptor binding behavior and potentially enhance interaction stability at the COX-2 active site. Such findings may help explain the pharmacological benefits observed in combination analgesic therapies and provide a basis for further molecular dynamics and structure–activity relationship studies.

Molecular docking studies provide valuable information regarding the orientation of ligands within the active site of the enzyme and identify the amino acid residues responsible for stabilizing ligand–receptor complexes [27–38]. In supramolecular drug assemblies, the order of molecular association may influence not only the overall binding affinity but also the location of the binding site and the pattern of interactions with the receptor [27,28,30,32-38]. Therefore, the interaction of the Paracetamol–Ibuprofen and Ibuprofen–Paracetamol complexes with COX-1 was investigated to evaluate possible differences in binding mode, amino acid recognition, and receptor occupancy.



A. Paracetamol–Ibuprofen B. Ibuprofen–Paracetamol

Figure 1. Predicted binding poses of the binary supramolecular complexes within the active site of COX-1. The docking simulations reveal the spatial orientation of the complexes and the amino acid residues involved in ligand stabilization. Differences in binding positions and interaction patterns indicate that the order of molecular assembly influences receptor recognition and the formation of intermolecular contacts within the enzyme cavity [37,38].

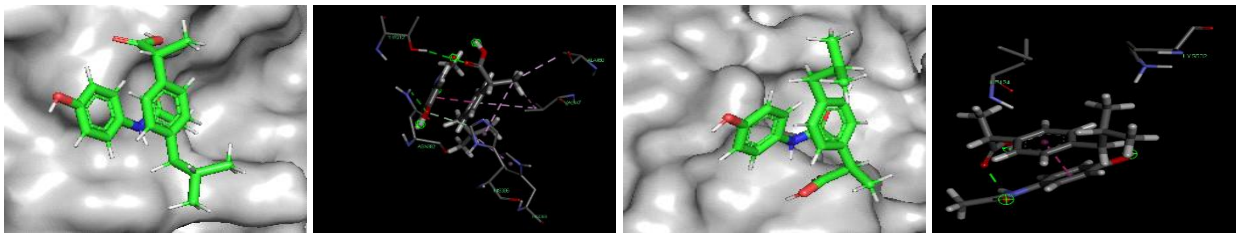
The docking results indicate that the two supramolecular complexes interact differently with COX-1 despite being composed of the same molecular components (Fig. 1). The Paracetamol–Ibuprofen and Ibuprofen–Paracetamol assemblies adopt distinct orientations within the receptor cavity, suggesting that the sequence of molecular association affects the three-dimensional arrangement of the complex and consequently its interaction with the enzyme.

An important observation is that the complexes appear to occupy distinct regions of the COX-1 binding pocket and interact with different amino acid residues. This finding suggests that supramolecular organization modifies the distribution of hydrogen-bond donor and acceptor groups as well as hydrophobic surfaces exposed to the receptor environment. Therefore, each complex is recognized differently by the enzyme and follows a distinct binding pathway.

The interaction of the complexes with different amino acid residues may have important pharmacological implications. Amino acids located within the catalytic channel of COX-1 contribute differently to ligand stabilization through hydrogen bonding, electrostatic interactions, van der Waals contacts, and hydrophobic interactions. Therefore, changes in the interaction pattern may alter binding affinity, residence time, and inhibitory potency. The ability of the two complexes to recognize distinct binding regions further suggests that intermolecular association between paracetamol and ibuprofen modifies the molecular surface available for receptor recognition.

These findings support the hypothesis that drug–drug complexes may exhibit biological properties that differ from those of the individual compounds and highlight the importance of considering supramolecular organization when investigating combination therapies at the molecular level.

The next steps are the interaction profiles of the Paracetamol–Ibuprofen and Ibuprofen–Paracetamol supramolecular complexes with COX-2, which were investigated to determine whether the sequence of molecular association influences receptor binding and amino acid recognition within the enzyme's active site (Fig. 2).



A. Paracetamol–Ibuprofen B. Ibuprofen–Paracetamol

Figure 2. Interaction maps of the supramolecular complexes with COX-2. The diagrams illustrate the amino acid residues involved in the stabilization of the complexes within the receptor binding cavity through hydrogen bonding, hydrophobic interactions, electrostatic contacts, and van der Waals interactions. Differences in the interaction patterns reveal that the two supramolecular assemblies adopt distinct binding orientations and interact with different regions of the COX-2 active site [39,40].

The interaction analysis indicates that the two supramolecular complexes exhibit different binding behaviors toward COX-2 despite containing the same molecular components. The Paracetamol–Ibuprofen and Ibuprofen–Paracetamol complexes interact with distinct groups of amino acid residues, suggesting that the order of molecular association significantly affects the spatial arrangement of the supramolecular system within the enzyme binding pocket.

The observed differences in residue participation indicate that the two complexes are likely accommodated in different regions of the COX-2 cavity or adopt alternative

orientations within the same binding channel. Such variations are expected because reversing the positions of the constituent molecules alters the overall molecular geometry, surface polarity, and the distribution of functional groups available for receptor recognition. Consequently, different hydrogen-bond donor and acceptor sites, aromatic regions, and hydrophobic domains become exposed to the protein environment.

The interaction maps suggest that each complex establishes a unique network of stabilizing contacts with COX-2. Variations in hydrogen bonding and hydrophobic interactions may contribute to differences in calculated docking energies and binding affinities. Since ligand stabilization within the active site depends strongly on the nature and number of amino acid contacts, even relatively small changes in binding orientation can significantly influence the predicted strength of interaction.

An important observation is that the two complexes are not merely shifted versions of one another but appear to recognize different amino acid environments within the receptor. This finding supports the hypothesis that supramolecular organization influences molecular recognition processes and may affect the pharmacological profile of drug combinations. The ability of the complexes to interact with distinct residue subsets could potentially alter selectivity, binding stability, and inhibitory efficiency toward COX-2.

Overall, the results demonstrate that the sequence of association between paracetamol and ibuprofen has a measurable impact on receptor recognition. Although both assemblies can interact with COX-2, they do so through distinct amino acid interaction networks and binding-site arrangements. These findings highlight the importance of considering supramolecular organization when investigating combination therapies, as subtle structural differences may translate into distinct biological and pharmacological outcomes.

4. CONCLUSIONS

The combination of paracetamol and ibuprofen is an effective multimodal approach for treating pain and fever. By combining central and peripheral mechanisms of action, this strategy may enhance clinical efficacy and reduce the need for higher doses of individual drugs. However, careful attention to dosage, duration of therapy, and patient-specific risk factors remains essential to ensure safe and effective use.

The present study investigated the molecular interactions between paracetamol and ibuprofen using a combination of molecular modelling, lipophilicity analysis, supramolecular complex formation, and molecular docking simulations against the pain-related biological targets COX-1 and COX-2. The results demonstrated that the two drugs can form stable supramolecular assemblies whose physicochemical and biological properties differ from those of the individual compounds.

Molecular docking simulations showed that the supramolecular complexes generally exhibited stronger binding affinities toward both COX-1 and COX-2 than paracetamol or ibuprofen alone. Moreover, the Paracetamol–Ibuprofen and Ibuprofen–Paracetamol assemblies displayed different interaction patterns and engaged different amino acid residues within the receptor binding sites, indicating that the sequence of molecular association influences receptor recognition and binding orientation.

Overall, the findings indicate that paracetamol and ibuprofen may interact cooperatively at the molecular level through the formation of stable supramolecular complexes. These complexes exhibit modified physicochemical properties, distinct electronic characteristics, and enhanced receptor interactions compared with the individual drugs. The proposed approach provides new insights into the molecular basis of combination analgesic

therapy and highlights the importance of considering drug–drug interactions during the design and optimization of multi-component therapeutic formulations.

Further investigations using molecular dynamics simulations, free-energy analyses, and experimental approaches are required to establish the pharmacological relevance of computational predictions.

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