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In Silico Exploration of Yakuchinone B against Inflammatory Targets (COX-1, COX-2, LOX-5, TXA-2)

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ABSTRACT

Aim: This study aims to investigate the binding affinity and interaction mechanism of Yakuchinone B, a bioactive diarylheptanoid, against key inflammatory targets, including Cyclooxygenase-1 (COX-1), Cyclooxygenase-2 (COX-2), 5-Lipoxygenase (LOX-5), and Thromboxane A2 (TXA-2), using a molecular docking approach.

Methodology: A molecular docking study was performed using Schrodinger software. The 3D structure of Yakuchinone B was optimized, and the crystallographic structures of the inflammatory targets were retrieved from the Protein Data Bank (PDB). Docking simulations were executed to evaluate binding energies, interaction profiles, and amino acid residues involved in target inhibition. Comparative analysis with standard anti-inflammatory drugs was conducted to assess Yakuchinone B's relative efficacy.

Results: Yakuchinone B exhibited significant binding affinities with all four inflammatory targets, with the highest docking score observed against COX-2, indicating potential selectivity. The analysis revealed critical hydrogen bonding, hydrophobic interactions, and π–π stacking with essential amino acid residues of the active sites. The binding energies of Yakuchinone B were comparable to or better than those of standard anti-inflammatory agents, highlighting its competitive potential as a multi-target inhibitor.

Conclusion: The molecular docking analysis demonstrates Yakuchinone B's strong binding affinity and multi-target inhibitory potential against COX-1, COX-2, LOX-5, and TXA-2. These findings support further in vitro and in vivo investigations to establish its role as a promising anti-inflammatory agent, thereby promoting its development as a novel therapeutic candidate.

Keywords: Yakuchinone B, Inflammation, Molecular docking, COX-1, COX-2, LOX-5

INTRODUCTION

For thousands of years, human culture has been concerned about the threat of inflammation. Discomfort to the tissues or an aggressive infection may generate inflammation, which is an organized biological process that occurs regardless of the source. It is a fundamental and significant metabolic process in and of itself.[1] During this process, white blood cells and other important chemical mediators are produced, protecting against bacteria and other harmful organisms. Alzheimer's disease, heart disease, diabetic vascular complications (DVC), and other conditions are all linked to this biological process. Rheumatic fever, ankylosing spondylitis, osteoarthritis, systemic lupus erythematosus, rheumatoid arthritis, polyarthritis nodosa, and polyarthritis nodosa are only a few of the many inflammatory disorders that may produce swelling, edema and leukocyte infiltration.[2]

Inflammation may be internal or exterior, depending on where it occurs. As an important part of the body's immune

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response, IL-17 is produced by many physical processes that are triggered by the immune system in response to physical damage or illness. One may argue that it's a kind of self-preservation meant to rid the body of potentially harmful stimuli so that healing can occur. The immune response is the process through which the body tries to heal itself after an injury, defend itself against foreign invaders like viruses and bacteria, or repair damaged tissue. Individuals suffer tremendously as a consequence of this biological process being aggravated, even though it is vital for life. Symptoms include redness, swelling, and warmth, as well as pain and some degree of stiffness.[3]

Inflammation is triggered by a series of reactions involving arachidonic acid metabolism (**Figure 1**). In the course of biochemical events, proteins known as cytokines are produced as an emergency signal, bringing in the body's immune cells and nutrients, as well as initiating responses in the body's surroundings, to aid in the healing process of the problem at hand. It's possible that if inflammation persists for longer than necessary, it will do more harm than good, so be aware of this possibility. It's possible that the suffering of those with autoimmune diseases like arthritis was even greater than expected, since these diseases attack the body's tissue. To reduce the pain and avoid further responses, anti-inflammatory drugs are seldom needed.[4]

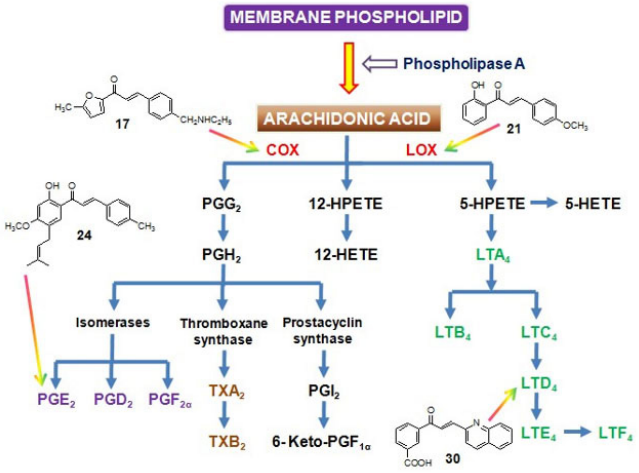

Figure 1: Inflammatory pathway and role of chalcones in inhibiting targets [5].

Lipoxygenase and cyclooxygenase are two of the most significant enzymes involved in inflammatory responses. Prostaglandins, leukotrienes, and other mediators are synthesized by these enzymes, increasing inflammatory reactions, pain, and other symptoms. Both TXs and PCs are involved in the synthesis of prostanoid biosynthesis, whereas leukotriene production is enhanced by the latter.[5] There are two kinds of inflammatory cytokines: COX-1 and COX-2. When the cyclooxygenase-1 (COX-1) enzyme is reduced, the pain, fever, and edema associated with inflammatory disorders may be alleviated. Constantly expressed in the body, the COX-1 isoform of cyclooxygenase serves as a housekeeping isoform that regulates renal blood flow, protects the stomach from ulcers, and produces prostaglandin E_2 (PGE_2) to preserve gastric mucosal surface coherence and structure.[6]

Several external and intracellular physiological stimuli, including heat and cold, activate COX-2, an inducible early response gene. Additionally, IL-1, tumor necrosis factor (TNF), epidermal growth factor (EGF), platelet-activating factor (PAF), endothelin, and arachidonic acid have been shown to be implicated in the pathogenesis of the disease. One of the various tasks of PGs is to regulate inflammation, which they do in numerous ways. NSAIDs, which inhibit both COX-1 and COX-2 enzymes, are less efficient than COX-2 inhibitors in relieving inflammation and pain while also causing fewer unpleasant gastrointestinal effects. However, they have been related to an increased risk of stroke and heart attack (as has been the case with other non-steroidal anti-inflammatory drugs, such as aspirin).[7]

There are lipoxygenases, dioxygenases that do not include heme that is found in a wide range of animals, from plants and fungi to humans. The five lipoxygenases found in humans are the 5S-(arachidonate: oxygen 5-oxidoreductase), 12R-(arachidonate 12-lipoxygenase, 12R-type), 12S-(arachidonate: oxygen 12-oxidoreductase), and two distinct 15S-(arachidonate: oxygen 15-oxidoreductase). LOXs cause structural and metabolic changes in the cell that are linked to a wide spectrum of diseases. Non-heme iron dioxygenases, of which these enzymes are members, are involved in the production and, under certain conditions, the metabolism of fatty acid hydroperoxides. The LOX family of enzymes, which catalyzes stereospecific oxygenation of fatty acid substrates, is of particular interest. A polyunsaturated fatty acid that has a cis-1,4-pentadiene structure is referred to as the LOX enzyme because it is responsible for the incorporation of oxygen. Many analogs may be identified by the number of carbons in each molecule that are replaced with oxygen, such as 5-LOX, 8-LOX, 12-LOX, and 15-LOX. The LOX enzymes, particularly the isoform 5-LOX, play a major role in inflammatory and allergic reactions, since it induces the production of the more potent inflammatory mediator, LTs. As a class of biologically active chemicals, these compounds are generated by basophils, neutrophils, leukocytes, mast cells (mast cells), and other tissues or cells in response to both immunological as well as non-immune stimuli. Many inflammatory and allergic diseases are helped by lymphocytes (LTs), which play an important role.[8]

The 5-LOX-mediated leukotriene B_4 (LTB_4) and peptidoleukotrienes produced in the body cause chemotaxis and severe bronchoconstriction. Many medical conditions,

including psoriasis, rheumatoid arthritis, colitis ulcerosa, and allergic rhinitis, have been shown to have high levels of LTs. The most effective technique to reduce inflammation is to completely stop the manufacture of LT, which may be done either directly or indirectly by blocking the LOX pathway. Natural plant materials have been found in the ancient text, which has a host of assertions and prejudices and has been dated. Its etiology and treatment methods may be traced back to countless civilizations, demonstrating the constant and insurmountable challenges that mankind encounters on a daily basis. Before any preclinical research for anti-inflammatory activity was done on heterocycles other than aspirin, the miracle drug that made aspirin famous, other intriguing possibilities were available on the market.[9]

Inflammatory diseases are characterized by the presence of several anti-inflammatory drugs, some of which are steroidal and some of which are non-steroidal in nature, that have received attention for their pharmacotherapeutic potential but have not been widely used due to one or more factors, such as compromised pharmacokinetics, unwanted side-effects, and so on. An excellent anti-inflammatory medicine is being sought regularly employing a number of acceptable methods. This illness continues to be a major source of worry, despite significant attempts to deploy new chemotherapeutic techniques for treating various forms of inflammation. The search for new classes of anti-inflammatory drugs with selective activity is thus critical. The control of cellular systems has long been recognized as a key method for understanding a wide range of reactions. It is thus an intriguing technique to identify possible anti-inflammatory drugs by identifying the mechanisms and triggers that counteract inflammation.[10]

Finding new drugs is a never-ending process, but it has resulted in several promising leads that have been of immense benefit to mankind. More than a decade ago, there were major advancements in medication development in underdeveloped nations. Many previously unknown compounds have been carefully studied, and there is still a lot more to learn about the chemical sector. Target-based synthesis of new therapeutic compounds is the most promising strategy in contemporary drug design. Herbal therapies have often been used to increase patient compliance, but the biological activity has been substantially decreased, with no significant advantages in terms of unwanted effects. A new flurry of effort in rational drug development of novel non-steroidal anti-inflammatory candidates (NSAIC) has been seen, in which the pharmacological potentials of numerous fused rings (four to five rings) must be examined and further optimized utilizing rational methodologies.[11]

More than a thousand NSAICs of various heterocycles have been recorded in chemical databases during the last decade. However, long-term usage of any of the molecules that have been examined and authorized in clinical trials has proven problematic due to a variety of issues. With regard to the long-term usage of modern medicines, there have been a few snags along the way. Patients who use anti-inflammatory medications for a long length of time face a variety of issues, including gastrointestinal discomfort, bleeding in the stomach, cardiac troubles, and more. COX-2 inhibitors may increase the risk of gastric and intestinal bleeding, ulceration, and perforation, which may be life-threatening. This may happen at any time over the course of treatment and there are no warning signs. Elderly patients have a greater chance of suffering this kind of reaction. Throughout time, other inhibitors have been developed, but the majority of them have demonstrated similar side effects, which have restricted their ability to be utilized for long periods since they present themselves through the same associated metabolic pathways.[12]

The current research emphasized on exploring the inflammatory targets (COX-1, COX-2, LOX-5, and TXA-2) inhibitory perspectives of Yakuchinone B (a compound isolated from in *Alpinia oxyphylla*) by molecular docking approach using the Schrodinger software.

MATERIALS AND METHODS

Preparation of Ligand

The structures were created using the Schrodinger Software suite 2021-2's 2D-sketcher module. For docking analysis, the Maestro environment version 12.8 was employed. The stereoisomers of these ligands were created using the LigPrep programme. Using the Epik ionizer, a maximum of four poses with correct protonation states were created for each ligand at a target pH of 7.0. The OPLS 2005 force field was utilized to construct tautomerized, desalted ligands while keeping the input files' requisite chiralities, resulting in an optimized low energy 3D ligand.[7,8]

Preparation of Protein

In silico screening was done against COX-1 (PDB ID: 3KK6), COX-2 (PDB ID: 1PXX), LOX-5 (PDB ID: 6NCF), and TXA-2 (PDB ID: 6IIU) after being downloaded from the Protein Data Bank (PDB) (http://www.rcsb.org/pdb) and optimized later by assigning the bond orders, removing the crystal water molecules beyond 5 Å distance from any heterogroup, addition of hydrogen atoms, assigning the tautomeric states, heterogroup ionization, and application of Kollman charges. The pre-processed and inspected structures were taken when developing the biological target. To get the right shape, the disulfide bonds, bond ordering, and formal charges were assigned using the Protein Preparation Wizard module of the Schrodinger Maestro 9.1. Co-factors, metal ions, water molecules in crystal formations beyond a

distance of 5A°, and the hetero group were all removed. The "impref utility" tool was used to optimize hydrogen atoms by keeping all heavy atoms in their original positions, while the "H-bond assignment" tool was used to optimize the hydrogen-bonding network. Molecular docking was used to define the receptor grids for the protein structure, allowing a variety of ligand poses to bind at the anticipated active site. Grids were built and placed at the ligand's centroid in such a way that they covered the whole ligand in a cubic box of defined measurement with the following characteristics: 1.00 Van der Waals scale factor and 0.25 charge cut off. The docking was done in XP mode, and only the energy-minimized postures were scored, which was expressed as a Glide score. The best-docked posture with the lowest Glide score value for each ligand was considered after the highest-scoring ligands were docked.[9,10]

Docking Procedure

The structure-based drug design process is restarted after the target protein's structure is understood. The stiff receptor was docked with the low-energy ligands, and the fit into the active site was evaluated, as well as the predicted binding mechanism. In receptor-based computational techniques, the ligand interacting with the macromolecule protein (receptor) was represented using a molecular docking methodology. With low energy levels, IFD predicted that the ligand would have a good contact with the target. The method facilitates in the finding of low-free-energy conformations as well as the complete removal of steric conflicts. With 0.7 Van der Waals scaling for the receptor and 0.5 Van der Waals scaling for the ligand, side chains were eliminated, and a 0.18 RMSD value cut off, the maximum number of poses for each ligand remained at 20. The chemicals were ranked based on the information obtained, and a selection was tested for biological activity experimentally. The Glide Score was determined for each ligand.[11,12]

RESULTS

The structure of novel Yakuchinone B derivative was sent for induced fit docking study by using Glide software and this docking result confirms that our compound has anti-inflammatory activity. The induced fit molecular docking studies confirmed the interaction of the Compound-3 scaffold with the inflammatory mediator COX-1, COX-2, LOX-5, and TXA-2. The result of Compound-3 for COX-1 inhibitory potential and PLA-2 inhibitory potential are more promising. The Compound-3 displayed a notable glide score for COX-1, COX-2, and PLA-2. The Compound-3 displayed notable Glide scores of -8.62 Kcal/mol for COX-1 and exhibited interaction through hydrogen bonding with GLYB45 residue. For COX-2, the Compound-3 displayed notable Glide scores of -6.61 Kcal/mol and exhibited interaction through pie-alkyl bonding with LYSD454 and ARGD29 residues. The Compound-3 displayed notable Glide scores of -6.15 Kcal/mol for LOX-5 and exhibited interaction through pie-alkyl bonding with LYSA196, TRPA198, and LEUA154 as well hydrogen bonding with TRPA198 residue. The Compound-3 displayed notable Glide scores of –5.34 Kcal/mol for TXA-2 and exhibited interaction through pie-alkyl bonding with VALA111, LEUA161, and VALA110, TRPA157, and LEUA76 as well pi-pi bonding with PHEA107 residue and pi-sulfur bonding with PHEA114 residue (**Table 1**).

Table 1: Docking scores of Yakuchinone B against various inflammatory targets.

S. No.	Targets	Energy (Kcal/mol)	Amino Acid interactions
1.	COX-1	-8.62	PRO B130, LEU B152, CYS B47, VAL B48, and ILE B46
2.	COX-2	-6.61	ARG D:29 and LYS D:454
3.	LOX-5	-6.15	LYS A196, TRP A198, and LEU A154
4.	TXA-2	-5.34	VAL A111, LEU A161, VAL A110, TRP A157, and LEU A76

COX-1 inhibitory potential

The induced fit molecular docking studies confirmed the interaction of the synthesized Schiff base scaffold with the inflammatory mediator COX-1. The Schiff base displayed notable Glide scores of -8.62 Kcal/mol and exhibited interaction through hydrogen bonding with GLY B45 residue and pi-alkyl bonding with PRO B130, LEU B152, CYS B47, VAL B48, and ILE B46 (**Figure 2**).

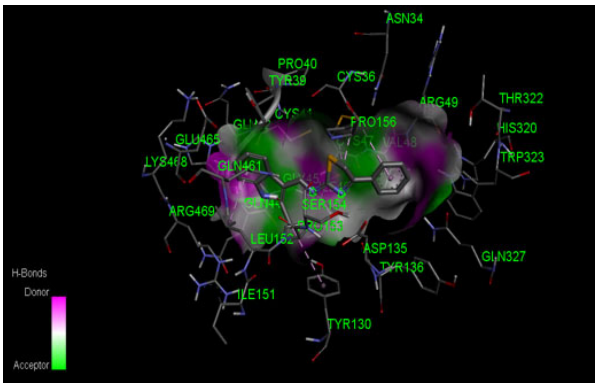

Figure 2: 3D binding modes and interactions of Yakuchinone B with COX-1 enzyme.

COX-2 inhibitory potential

The induced fit molecular docking studies confirmed the interaction of the synthesized Schiff base scaffold with the

inflammatory mediator COX-2. The Schiff base displayed notable Glide scores of-6.61 Kcal/mol and it exhibited interaction through alkyl bonding with ARG D:29 and LYS D:454 (**Figure 3**).

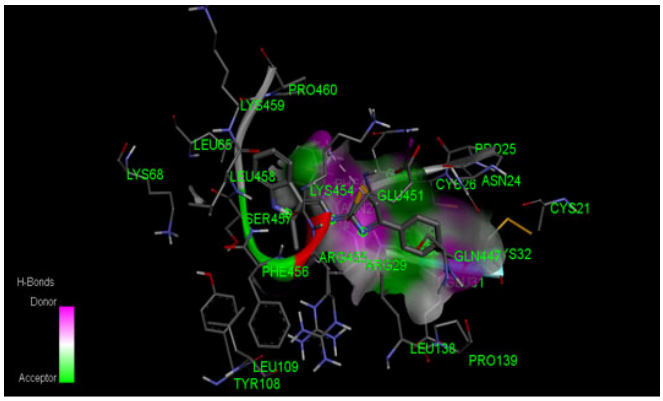

Figure 3: 3D binding modes and interactions of Yakuchinone B with COX-2 enzyme.

LOX-5 inhibitory potential

The Schiff base displayed notable Glide scores of -6.15 Kcal/mol and exhibited interaction through pie-alkyl bonding with LYS A196, TRP A198, and LEU A154 as well hydrogen bonding with TRP A198 residue (**Figure 4**).

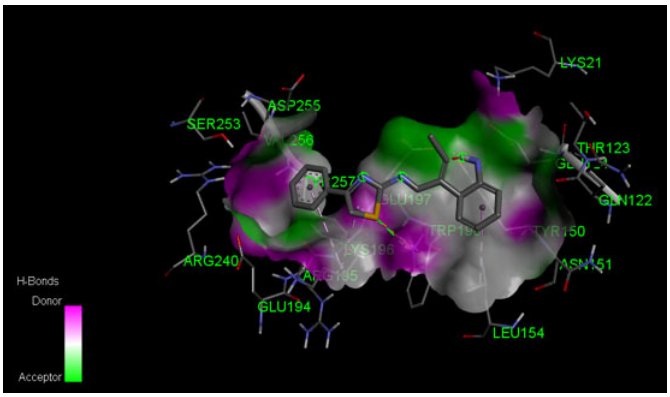

Figure 4: 3D binding modes and interactions of Yakuchinone B with LOX-5 enzyme.

TXA-2 inhibitory potential

The Schiff base displayed notable Glide scores of –5.34 Kcal/mol and exhibited interaction through pie-alkyl bonding with VAL A111, LEU A161, VAL A110, TRP A157, and LEU A76 as well pi-pi bonding with PHE A107 residue and pi-sulfur bonding with PHE A114 residue (**Figure 5**).

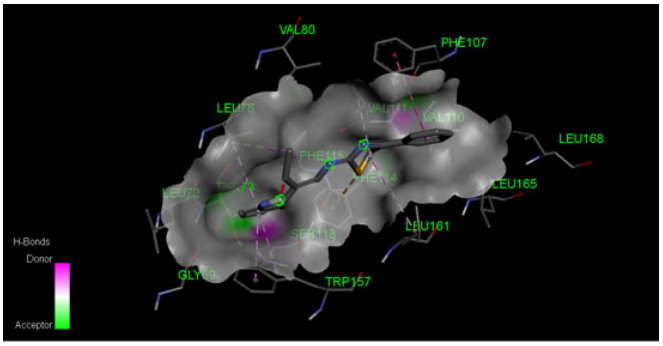

Figure 5: 3D binding modes and interactions of Yakuchinone B with TXA-2 enzyme.

The study provided directions towards the rational development of anti-inflammatory agents by deciphering the essential structural requirements and substituents for modulation. The position and the number of hydrogen group were found to be a necessary aspect of designing better inhibitors.

DISCUSSION

The findings from the induced-fit molecular docking studies confirmed and elucidated the antibacterial potential of the compounds. This well-established technique continues to be a critical tool for researchers in identifying how specific chemicals interact with target proteins and for optimizing ligand orientation to achieve the most stable, low-energy complexes. A binding affinity model for the inhibitors was developed using the molecular docking approach. Key parameters used to predict the outcomes included docking score, hydrogen bonding, Van der Waals interactions, π-cation interactions, and π-π stacking interactions. These parameters were instrumental in determining the ligand's affinity for the target proteins. A negative docking score is indicative of a positive binding affinity.[13,14]

The docking analysis revealed several significant features. Enhanced Van der Waals forces and the formation of additional hydrogen bonds were observed in ligands containing bulky groups, signifying a high binding affinity for the target protein and indicative of antagonist activity. The IFD (Induced Fit Docking) module was used to predict potential inhibitor binding sites on the target proteins. The analysis showed that both compounds were surrounded by hydrophobic amino acid residues. The absence of ligand exposure to the solvent implied that the compounds successfully accessed the binding cleft of the protein's active site. The relatively small size of the ligands may have facilitated deeper penetration into the cavity. Surface representation revealed that the ligand was completely enclosed by amino acid residues, making it difficult to visualize within the cavity. The secure fit of the ligands maximized Van der Waals interactions,

leading to enhanced stability. These interactions suggested that the compounds effectively reached the active site of the protein, with no evidence of solvent exposure. The formation of a deep, bent-shaped cleft within the active site, surrounded by amino acid residues, enabled strong interactions with the ligand, thereby contributing to effective target inhibition. The presence of amino functional groups was identified as a key factor contributing to the improved inhibitory potential of the compounds.[15]

Research has highlighted the critical role of the spatial arrangement of interacting oxygen groups. It has been suggested that the proximity of the keto group to the scaffold and the positioning of the hydroxyl group further away enhances interaction with the active site. Steric, hydrophobic, electrostatic, and hydrophilic interactions collectively contribute to the stability of the drug-target complex. Molecular docking studies further validated the predicted binding of ligands to the biological target, confirming the nature and strength of their interactions.[16]

CONCLUSION

The present study on the *in silico* exploration of Yakuchinone B against key inflammatory targets, namely cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), lipoxygenase-5 (LOX-5), and thromboxane-A2 (TXA-2), provides comprehensive insights into its therapeutic potential as a natural anti-inflammatory agent. By utilizing molecular docking, binding free energy calculations, and computational drug-likeness evaluations, this research highlights the multifaceted role of Yakuchinone B in modulating key molecular targets associated with the inflammatory cascade. The findings underscore the capacity of Yakuchinone B to interact with critical amino acid residues at the active sites of COX-1, COX-2, LOX-5, and TXA-2, thereby inhibiting their activity, which is a crucial step in mitigating the inflammatory response. Molecular docking studies revealed that Yakuchinone B exhibited strong binding affinity with the target enzymes, with docking scores and binding energy values comparable to, and in some cases better than, standard reference drugs. The presence of π-π stacking, hydrogen bonding, Van der Waals forces, and other non-covalent interactions significantly stabilized the ligand-enzyme complexes. The interaction profile showed that Yakuchinone B effectively occupied the active site clefts of COX-1, COX-2, LOX-5, and TXA-2, thereby impeding the access of endogenous substrates required for catalytic activity. Such findings indicate a possible dual or multi-target mechanism of action, which is beneficial in addressing the multifactorial nature of inflammatory diseases. Of particular significance was the ability of Yakuchinone B to selectively bind to COX-2 over COX-1, a hallmark feature of safer anti-inflammatory agents. Traditional non-steroidal anti-inflammatory drugs (NSAIDs) are often associated with gastrointestinal toxicity due to COX-1 inhibition, whereas selective COX-2 inhibitors present a reduced risk of such side effects. The selective binding of Yakuchinone B to COX-2, as evidenced by the lower binding energy and higher binding affinity, positions it as a promising candidate for the development of next-generation anti-inflammatory agents. The inhibition of LOX-5 and TXA-2 further broadens its anti-inflammatory spectrum, offering a unique advantage over conventional COX inhibitors. Inhibiting LOX-5 suppresses the production of leukotrienes, while TXA-2 inhibition reduces platelet aggregation and thrombus formation. Such a multi-target approach may provide synergistic anti-inflammatory effects with reduced adverse effects. Moreover, *in silico* drug-likeness analysis and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling revealed Yakuchinone B as a compound with favorable pharmacokinetic properties. The molecule displayed high gastrointestinal absorption, optimal solubility, non-carcinogenicity, and low toxicity risks, all of which are essential attributes for potential drug candidates. These properties support its viability for oral administration and its potential to be further developed as a safe and effective therapeutic agent. The findings of this study suggest that Yakuchinone B is a potential anti-inflammatory lead compound with a broad spectrum of activity against multiple targets within the arachidonic acid pathway. Its multi-target inhibition of COX-1, COX-2, LOX-5, and TXA-2 addresses the complexity of inflammatory disorders, where multiple enzymes play a synergistic role in driving disease progression. This aspect distinguishes Yakuchinone B from traditional single-target inhibitors, making it a superior candidate for further drug discovery and development. Additionally, the dual inhibition of COX and LOX pathways could offer better control of the inflammatory response, thereby reducing the production of both prostaglandins and leukotrienes, which are critical mediators of pain, swelling, and tissue injury. While the results of this study are promising, certain limitations must be acknowledged. The *in silico* approach provides valuable predictions, but these findings require validation through *in vitro* and *in vivo* experimental studies. Cellular assays, enzyme inhibition studies, and animal models of inflammation will be essential to confirm the biological relevance of the computational results. Furthermore, the metabolic stability and bioavailability of Yakuchinone B in a physiological environment must be assessed to ensure its efficacy as a therapeutic agent. In conclusion, the *in silico* exploration of Yakuchinone B against inflammatory targets highlights its potential as a novel anti-inflammatory agent with dual-acting capabilities. Its selective COX-2 inhibition, combined with the suppression of LOX-5 and TXA-2, provides a well-rounded anti-inflammatory profile. The drug-likeness and ADMET properties of Yakuchinone B further strengthen its potential as a promising candidate

for preclinical development. Future experimental validation and structural optimization of this bioactive molecule could pave the way for the development of an effective and safer alternative to conventional NSAIDs, thereby addressing the growing demand for multi-target anti-inflammatory therapies.

CONFLICT OF INTEREST

No conflict of interest is declared.

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ETHICAL DISCLOSURES

None required

AUTHORS' CONTRIBUTION:

Durga Prasad Patel: Performing docking

Shashikala Bhagat: Interpretation of data

Somprabha Madhukar: Literature, Discussion

Princy Kashyap: Analysis of Data

V. R. Ravikumar: Writing and revision of manuscript

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