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MOLECULAR DOCKING-GUIDED VIRTUAL SCREENING AND DE-NOVO DESIGN OF NOVEL COX-2 INHIBITORS FROM PHYTOCHEMICALS OF *PHYSALIS MINIMA*

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ABSTRACT

Background: Selective cyclooxygenase-2 (COX - 2) inhibitors reduce gastrointestinal side effects but carry severe complications, promoting the search for safer alternatives from natural sources.

Objectives: To identify protein COX - 2 inhibitor through molecular docking - guided virtual screening of phytoconstituents from Physalis minima and subsequent de-novo design of semisynthetic hybrids.

Methods: A total of 93 Physalis minima phytoconstituents from the IMPPAT database were screened against the human COX-2 enzyme (5IKR.pdb). Using the top natural lead scaffold, an in silico library of 200 NSAID - caffeic/quinic acid hybrids was designed. Lead candidates were evaluated using MM-GBSA binding energy calculation. SWISS ADME profiling, and a 100 ns molecular dynamic simulation via the Desmond module.

Results: Chlorogenic acid (IMPHY0011844) emerged as the top natural lead (binding affinity of -7.8 kcal/mol) from which a 200 in-house NSAID-caffeic acid and NSAID-quinic acid hybrids were designed. From the designed hybrids compound VR6 was evidenced strongest interactions with Arg120, Phe518, Gln192, and Ser530. ADME profiling predicted high gastrointestinal absorption, zero Lipinski violation, and lack of blood -brain barrier penetration. A 100ns molecular dynamics simulation verified that the VR6/5IKR complex exhibited highly stability, maintaining crucial interactions with Arg120 and Ser530 residues.

Conclusion: The hybrid molecule VR6 represented a promising, pharmacokinetically sound lead candidate that warrants chemical synthesis and further in vitro biological evaluation as a safer anti-inflammatory therapeutics.

KEYWORDS: COX-2 inhibitor, molecular docking, caffeic acid, quinic acid, NSAID's

INTRODUCTION

Inflammation is a protective physiological response initiated the body against harmful stimuli such as pathogens, tissue injury, toxins, and oxidative stress. Although acute inflammation plays a beneficial role in healing and defence mechanisms, chronic inflammation contributes significantly to the progression of several diseases including rheumatoid arthritis, osteoarthritis, cardiovascular diseases, diabetes, asthma, alzheimer's disease, and cancer. The inflammatory response is regulated by multiple biochemical mediators, among which prostaglandins are considered major contributors to pain, fever, redness, and swelling. These prostaglandins are synthesized from arachidonic acid through catalytic action of cyclooxygenase enzymes. Cyclooxygenase-2 (COX-2) [1].

Cyclooxygenase exists mainly in two isoforms, COX-1 and COX-2.COX-1 is constitutively expressed in most tissues and is involved in physiological functions such as gastric mucosal protection, and maintenance of renal blood flow. In contrast, COX-2 is an inducible isoform that is highly expressed during inflammatory conditions in response to cytokines, growth factors, and endotoxins. Elevated expression of COX-2 leads to excessive production of prostaglandins, thereby promoting inflammation and associated pathological conditions. Due to its selective involvement in inflammatory pathways, COX-2 has become an important molecular target in the discovery and development of anti-inflammatory agents [2, 3].

Non-steroidal anti-inflammatory drugs (NSAIDS) are among the most commonly prescribed medications for the treatment of inflammation and pain. Traditional NSAIDs such as aspirin, diclofenac, and ibuprofen act by inhibiting both COX-1 and COX-2 enzymes. However, non-selective inhibition often results in gastrointestinal irritation, ulceration, renal

toxicity, and bleeding complications because of COX-1 suppression. To overcome these limitations, selective COX-2 inhibitors were developed. Among them, celecoxib is widely used due to its potent anti-inflammatory and analgesic properties with comparatively reduced gastrointestinal side effects. Never the less, prolonged use of selective COX-2 inhibitors has been associated with cardiovascular complications, hepatotoxicity, and other adverse reaction. These safety concerns have encouraged researchers to explore natural bioactive compounds as safer alternatives for inflammation management [4].

Natural products obtained from medicinal plants remain one of the most valuable sources for novel therapeutic agents. Plant-derived phytochemicals possess diverse biological activities and often exhibits fewer side effects compared to synthetic drugs. Among medicinal plants, the genus Physalis belongs to the family Solanaceae has gained considerable scientific attention because of its nutritional and pharmacological importance. Various Physalis species are rich in secondary metabolites such as Physalins, Withanolides, flavonoids, alkaloids, tannins, and phenolic compounds. These phytoconstituents have demonstrated significant antioxidants, anti-inflammatory, antimicrobial, immunomodulatory, hepatoprotective, antidiabetic, and anticancer activities in several experimental studies [5].

Among the different species, physalis minima is widely distributed in tropical and subtropical regions and has been traditionally used in Ayurvedic and folk medicine for the treatment of fever, inflammation, asthma, skin disorders, and pain-related conditions. Previous phytochemical investigations of physalis species have identified compounds capable of modulating inflammatory mediators and oxidative stress pathways. Several studies have suggested that physalins and withanolides isolated from physalis exhibit potent anti-inflammatory activity by suppressing cytokine production and inhibiting inflammatory enzymes including COX-2. However, detailed molecular interaction studies involving physalis-derived phytochemicals against COX-2 are still limited [6,7].

In recent years, computer-aided drug discovery approaches have become essential tools in pharmaceuticals and medicinal chemistry research. Molecular docking is a widely used in silico technique that predicts the preferred orientation, binding affinity, and intermolecular interactions between ligands and target proteins. Docking studies help in understanding the molecular basis of ligand-receptor interactions and accelerate the identification of potential lead molecules before experimental validation. This approach significantly reduces the time, cost, and labour involved in conventional drug discovery processes [8,9].

The 3D crystal structure reported in protein data bank (5IKR.pdb) provides detailed information regarding the amino acid residues present in the active binding pocket, hydrogen bonding interactions, hydrophobic contacts, and ligand orientation. These structural insights help researchers understand the mechanism of inhibition and design potent anti-inflammatory agents. In docking studies, phytochemicals obtained from medicinal plants such as Physalis minima are compared with standard drug like Celecoxib to evaluate their potential as safer and effective COX-2 inhibitors [10, 11].

MATERIAL AND METHODS

Molecular docking and binding free energy calculation studies

The 3D structure of human cyclooxygenase-2 enzyme co-crystallized with mefenamic acid (5IKR.pdb; 2.34 Å) was collected from Protein Data Bank (https://www.rcsb.org/structure/5IKR). The target protein was prepared by removing non-redundant chains, crystallographic ligands, metal ions, and water molecules. All the pre-processing steps were accomplished via Auto Dock Tools 1.5.6 program (ADT) [12]. ADT program was employed to assign Kollman charges and for merging the non-polar hydrogens into the bonded carbon atoms of the enzyme. Structures (Fig. 1) of chemical constituents from Physalis minima plant were obtained from IMPPAT database (https://cb.imsc.res.in/imppat/) and the file formats were converted from .sdf to .pdb formate [13]. For the ligands ADT program was used to assign Gasteiger charges, Non-polar hydrogens, and torsion degrees of freedom. A grid box was generated around centre of the active pocket with dimensions x = 37.326Å, y = 2.971Å, z = 58.774Å and the dimensions of the box size include x = 20.173Å, y = 22.652Å, z = 24.655Å. Molecular docking was performed as per the default protocol [14]. 3D and 2D interactions of the docked poses were extracted using Discovery Studio Visualizer-20.1 [15].

The relative binding-free energy (ΔG bind) for the protein-ligand complexes was estimated using the PRIME Molecular Mechanics - Generalized Born Surface Area (MM-GB/SA) method with continuum solvent model embedded with OPLS4 force field [16]. In Prime MM-GB/SA, ΔG bind (binding free energy), was calculated with the equation: ΔG (bind) =E_complex (minimized) – E_ligand (minimized) + E receptor (minimized).

Molecular Dynamics

The binding pattern of ligand with protein with respect to time was evaluate by performing a 100ns MD simulation. Desmond module of Schrodinger Suite was utilized to assess the conformational stability of VR6 at the human cyclooxygenase-2 enzyme binding site. TIP4P water models are employed to solve complicated structures. The integration phases used a 2.0 fs time step. Using the Nose-Hoover thermostat and Martyna-Tobias Klein methods, the system's temperature and pressure were maintained at 300 K and 1.01325 bar, respectively. Before the production run, the system is minimized and calibrated. Then, 100-ns MD simulations were performed and the trajectory analysis was reported [17].

ADME Calculation

The ADME properties of the selected compounds VR1 and VR6 were predicted using the Swiss ADME online server (https://www.swissadme.ch/) to evaluate their drug-likeness and pharmacokinetics behaviour. Parameters such as molecular weight, hydrogen bond acceptor (HBA), hydrogen bond donor (HBD), Lipophylicity (Log P), Topological polar surface area (TPSA), gastrointestinal absorption, blood-brain barrier (BBB) permeability, skin permeation coefficient (Log Kp), and synthetic accessibility, and Lipinski's rule of five were analysed [18].

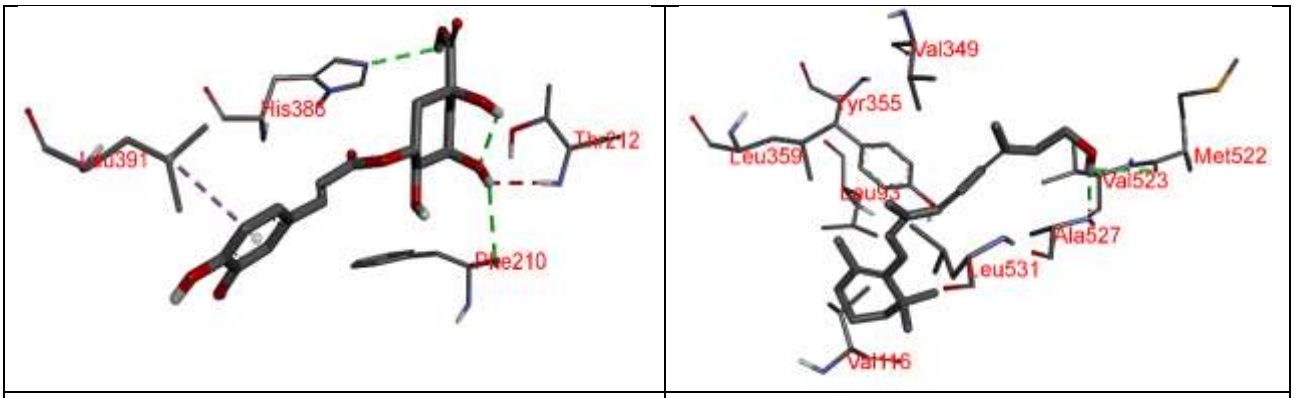
RESULTS AND DISCUSSION

Molecular docking and binding free energy calculation studies

From the molecular docking, the binding poses of a total IMPPAT 93 chemical constituents from Physalis minima were studied in the active pocket of human cyclooxygenase-2 enzyme (5IKR.pdb). It was disclosed that the binding affinity values were observed in the range of -7.8 to 25.1 kcal/mol. when compared with Mefenamic acid (-8.6 kcal/mol.) and Celecoxib (-9.5 kcal/mol.). All the molecules exhibited hydrogen bonding and hydrophobic interactions with the active pocket amino acids. The binding affinity values and their interacting amino acids for the top 10 scored IMPPAT compounds were mentioned in the Table 1. From the IMPPAT compounds, IMPHY0011844 (chlorogenic acid) (-7.8 kcal/mol) formed two hydrogen bonds with Phe210 and His386, the carboxylic acid and hydroxyl groups interacted with these amino acids. Another top scored compound, the terminal hydroxyl group of IMPHY001308 (Retinol) (-6.9 kcal/mol) interacted with Met522 and Val523 via hydrogen bonding interactions (Fig. 1).

Table 1. Binding energy values (kcal/mol) and interacting residues of top 10 scored IMPPAT compounds against 5IKR.pdb

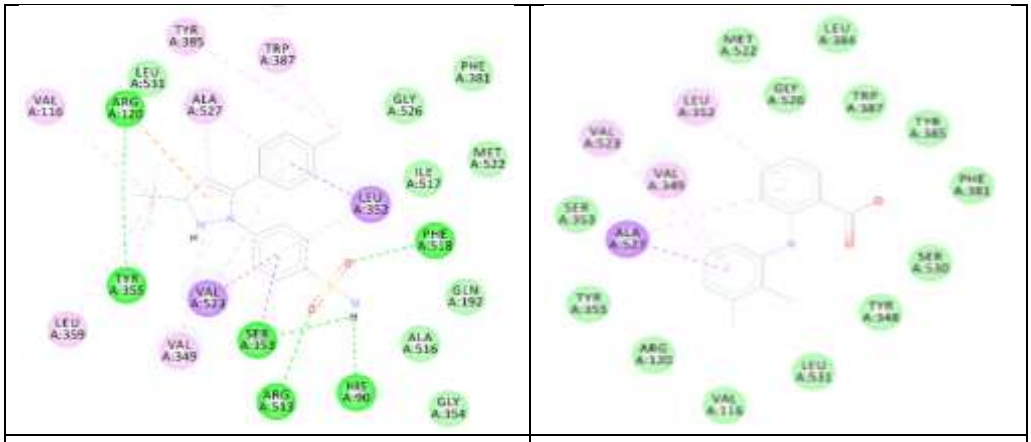
S.No.	IMPPAT Compound Code	Binding Affinity (Kcal/mol)	Interacting Amino acids
1	IMPHY011844	-7.8	Phe210, His386
2	IMPHY001308	-6.9	Met522, Val523
3	IMPHY012723	-6.8	Ser530
4	IMPHY001366	-6.7	Thr212, Asn382, Gln203
5	IMPHY011801	-6.7	--
6	IMPHY014990	-6.6	Ser530
7	IMPHY011797	-6.6	Arg120
8	IMPHY006485	-6.6	--
9	IMPHY011600	-6.5	--
10	IMPHY004631	-6.4	Arg120
11	Mefenamic acid	-8.6	--
12	Celecoxib	-9.5	Arg120, Tyr355, Ser353, Arg513, Phe518, His90



IMPHY0011844 | IMPHY001308

Fig. 1. 3D interaction diagram of IMPHY0011844 and IMPHY001308 in the catalytic pocket of 5IKR.pdb.

Comparing the standard molecules, Celecoxib (-9.5 Kcal/mol) and Mefanamic acid (-8.6 kcal/mol) in the active site of Human Cyclooxygenase-2 enzyme (5IKR.pdb), the IMPPAT compounds exhibited hydrogen bonding, hydrophobic Vander Waals, and pi-cationic interactions with Ser353, His90, Arg120, Tyr355, Phe518, and Arg513 (Fig. 2).



Celecoxib	Mefenamic acid

Fig. 2. 2D interaction diagram of Celecoxib and Mefenamic acid in the catalytic pocket of 5IKR.pdb.

Design on novel semisynthetic molecules

Based on the binding pose of top scored compound IMPHY0011844 (Chlorogenic acid) (-7.8 kcal/mol), which is an ester of caffeic acid and quinic acid, an NSAID-caffeic acid and NSAID-quinic acid hybrids were designed. Also considering the antioxidant, anti-inflammatory, and NF-Kb inhibitory properties of caffeic acid and quinic acid these novel semisynthetic hybrid molecules were designed. This was done by esterifying alcohol and carboxylic acid groups of NSAIDs with the carboxylic acid and alcohol groups of caffeic acid and quinic acid. An in house library of nearly 200 hybrids were designed and the binding poses were estimated in the active site of Human Cyclooxygenase-2 enzyme (5IKR.pdb).

The binding affinity values (Table 2) for the novel semisynthetic hybrid molecules ranged from -3.5 to -8.4 kcal/mol, indicating varying degrees of interaction between the ligands and the receptor. Among all the docked compounds, the top scored compound VR6 with a binding affinity of -8.4 kcal/mol exhibited the strongest interactions, forming four hydrogen bonds with the amino acid residues Arg120, Phe518, Gln192, and Ser530. This suggests a highly stable ligand–protein complex, indicating that VR6 has the highest binding potential among the tested molecules. Another compound VR1 showed binding affinity value of -7.8 kcal/mol formed two hydrogen bonds with Ser530, and Tyr355. All the designed novel semisynthetic hybrid molecules displayed hydrogen bonding and hydrophobic interactions with active site amino acids, Gln192, Ser530, Val523, Tyr355, Arg120, Tyr385, Phe518 and Met522. The most frequently involved amino acid residues were Ser530, Tyr355, Arg120, Tyr385, Gln192, Met522, Val523, and Phe518. Among these, Ser530 was the most commonly observed interacting residue, highlighting its critical role in ligand binding and stabilization. The compound VR6 with a binding affinity of -8.4 kcal/mol emerged as the most promising candidate with near value of Mefenamic acid (-8.6 kcal/mol) due to its highest binding affinity and multiple hydrogen-bond interactions, indicating strong potential for further biological evaluation.

Table 2. Binding energy values (kcal/mol) of top 10 scored novel semi-synthetic hybrid molecules against 5IKR.pdb

S.No.	Compound code	Binding Affinity (kcal/mol)	No. of Hydrogen Bonds	Interacting Amino Acid Residues
1	VR6	-8.4	4	Arg120, Phe518, Gln192, Ser530
2	VR1	-7.8	2	Ser530, Tyr355
3	VR2	-7.6	2	Ser530, Tyr355
4	VR3	-7.5	4	Ser530, Tyr355, Arg120, Tyr385, Phe518
5	VR8	-7.5	4	Ser530, Tyr355, Arg120, Tyr385, Phe518
6	VR15	-7.4	4	Arg120, Val523, Ser530
7	VR17	-7.4	2	Arg120, Ser530
8	VR7	-7.3	3	Tyr355, Arg120, Gln192
9	VR12	-7.1	1	Met522
10	VR5	-7.0	2	Ser530, Tyr385

The binding free energy (Table 3) of top two scored compounds from IMPPAT database (IMPHY001308 and IMPHY011844), designed novel hybrids (VR1 and VR6) along with standards Mefenamic acid and Celecoxib was estimated by MM-GBSA approach. Binding free energies for all the six complexes were calculated to analyse the major favorable energy contributors to ligand binding. Here, the designed novel semisynthetic hybrid molecules VR1 (-79.10 Kcal/mol.) and VR6 (-76.80 Kcal/mol.) exhibited good and lower Dg bind values when compared with standard compounds Mefenamic acid and Celecoxib which showed Dg bind values of -88.44 and -99.83 Kcal/mol. respectively.

Table 3. PRIME MM-GBSA values (kcal/mol) of six complexes

Compound Code	MMGBSA Δ Binda	MMGBSA Δ Bind Coulombb	MMGBSA Δ Bind Hbondc	MMGBSA Δ Bind Lipod	MMGBSA Δ Bind vdWe
IMPHY001308	-42.65	-29.94	0.28	-28.51	-58.78
IMPHY011844	-41.51	25.97	-0.23	-5.13	-21.36
VR1	-75.10	-40.28	-4.32	-28.07	-46.63
VR6	-76.80	-116.69	-1.36	-30.18	-72.76
Mefenamic acid	-88.44	25.69	1.85	-31.10	-57.02
Celecoxib	-99.83	10.07	-1.23	-25.79	-45.31

[a]free energy of binding, [b]Coulomb energy, [c]hydrogen bonding, [d]hydrophobic energy, [e]van der Waals energy

ADME calculation

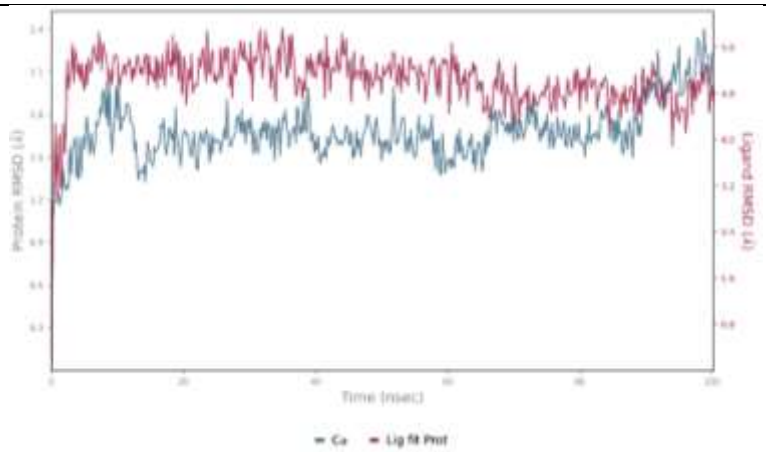
The ADME (Absorption, Distribution, Metabolism and Excretion) properties of the two selected compounds VR6 and VR1 (Table 4) were evaluated to assess their drug-likeness and pharmacokinetic behaviour. The lipophilicity (Log P) values were 3.35 for compound VR6 and 2.21 for compound VR1, suggesting moderate lipophilicity that favors membrane permeability without compromising aqueous solubility. The topological polar surface area (TPSA) for VR6 and VR1 were found to be 130.36 Å² and 104.06 Å², respectively indicating acceptable polarity for oral absorption. Both compounds demonstrated high gastrointestinal (GI) absorption, suggesting good oral bioavailability. However, neither compound was predicted to cross the blood-brain barrier (BBB), indicating a low probability of central nervous system penetration and potentially reduced CNS-related adverse effects. The predicted skin permeability (Log Kp) values were -6.04 cm/s for VR6 and -6.31 cm/s for VR1, indicating low skin permeability. The synthetic accessibility scores were 3.15 and 2.57, respectively, suggesting that both compounds are relatively easy to synthesize, with compound VR1 being slightly more synthetically accessible. Furthermore, both compounds complied with Lipinski's Rule of Five, showing zero violations, which supports their favourable drug-likeness and suitability as potential oral therapeutic candidates.

Table 4. ADME Properties of two compounds VR6 and VR1 calculated from SWISS ADME tool

ADME Parameters	VR6	VR1
Molecular weight	420.37 g/mol	300.26 g/mol
H-bond acceptors	8	6
H-bond donors	3	3
Log Po/w	3.35	2.21
TPSA	130.36 Å²	104.06 Å²
GI absorption	High	High
BBB permeant	No	No
Log Kp (skin permeation)	-6.04 cm/s	-6.31 cm/s
Synthetic accessibility	3.15	2.57
Lipinski Rule of Five	Yes; 0 violation	Yes; 0 violation

Molecular dynamics

A 100 ns molecular dynamic (MD) simulation was performed to evaluate the stability of the protein -ligand complex (VR6/5IKR.pdb) using the Desmond module of Schrodinger Suite. The simulation was conducted under NPT conditions at 300K with a system containing 58,193 atoms and 16,300 water molecules. The RMSD of protein Cα atoms (Fig. 3A) was observed in the range of 1.32 to 2.02Å with minimal fluctuations, and further reached 2.4Å at the end of the 100ns simulation. The ligand RMSD (Fig. 3A) was fluctuated between 5.12 to 5.61 Å which was finally stabilized reaching 4.82Å at the end of the trajectory simulation. From Fig. 3B, Protein RMSF analysis indicated that the ligand bound most amino acid residues exhibited low fluctuations ranging from 0.6 and 1.4Å. From the protein-ligand contact diagram (Fig. 3C), it was revealed that compound VR6 formed strong hydrogen bonds with Tyr115, Arg120, Tyr385, and Ser530 at 100-150% of 100 ns simulation trajectory. VR6 was embedded in the active pocket forming moderate hydrophobic interactions with amino acids Val89, Leu93, Val116, Arg120, Val349, Tyr355, and Ala527 with 50% of simulation trajectory. VR6 also formed ionic and water bridged interactions with highlighting the importance of Arg120 that formed multiple non-covalent interactions with the ligand. From 2D simulation interaction diagram (Fig. 3D), it was observed that the polar groups such as, -OH, -C=O and -COO- groups formed strong and multiple interactions with the active pocket residues.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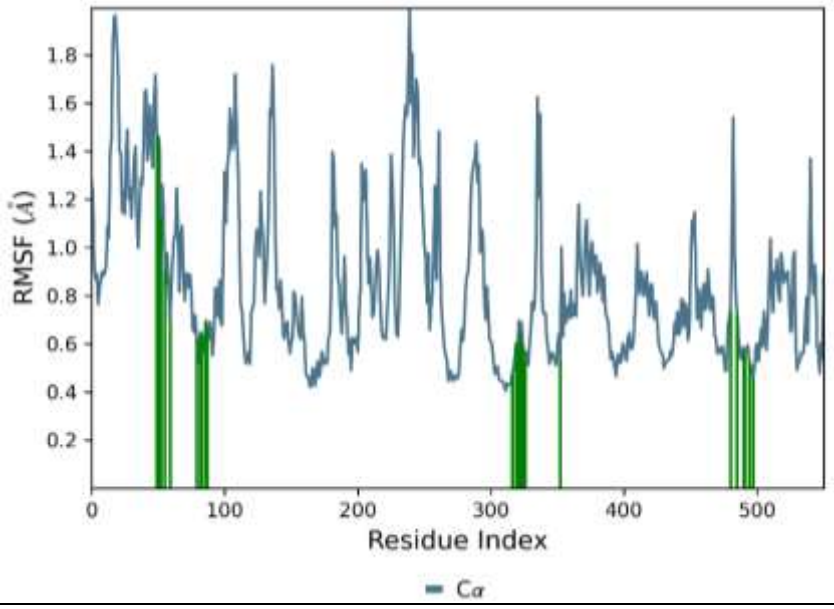
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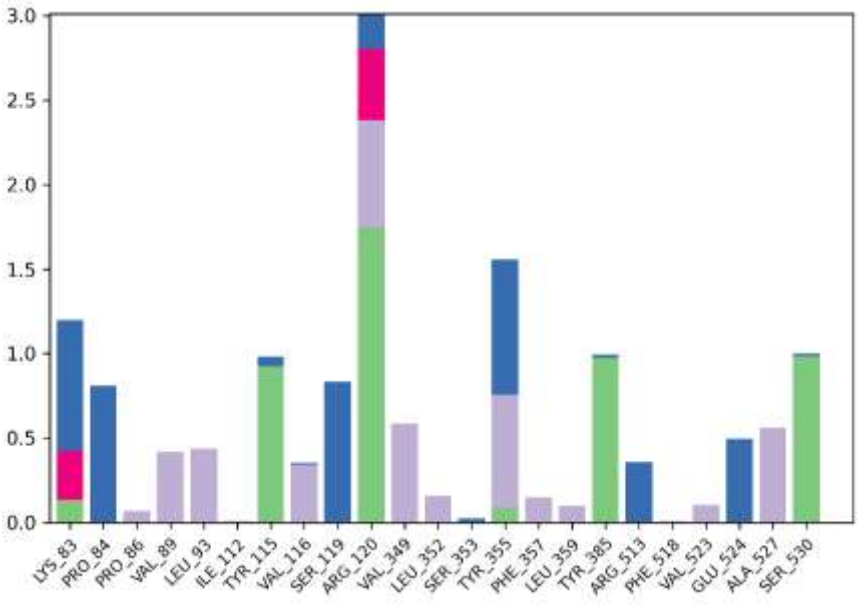
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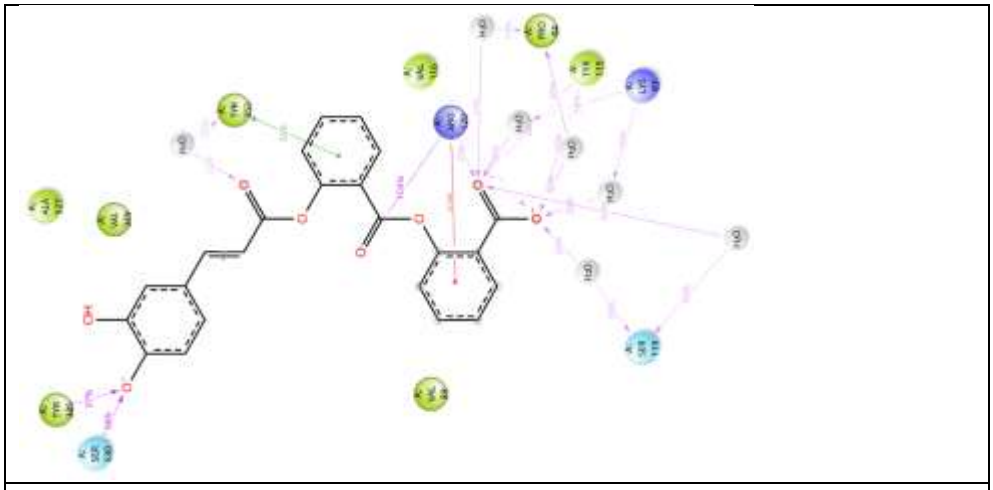

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Fig. 3. Plot represent (A) RMSD (Å) of the simulated positions of Cα atoms of VR6/5IKR.pdb complex protein. (B) RMSF profile of active site residues of complex during MD simulation (C) Protein-ligand interaction fraction of compound VR6 with active site residues during 100ns simulation trajectory. (D) 2D simulation trajectory diagram of VR6 with active site residues.

CONCLUSION

The study successfully integrated molecular docking-guided virtual screening and de novo drug design to identify novel, structurally optimized COX-2 inhibitors derived from Physalis minima phytochemicals. By utilizing the molecular architecture of the top-performing natural compound, Chlorogenic acid, we designed a unique library of semisynthetic hybrids aimed at maximizing anti-inflammatory efficacy while lowering conventional side effects. The primary finding of this research highlights is enhanced binding efficiency the designed hybrid VR6 achieved a highly competitive binding affinity (-8.4 kcal/mol), mirroring the potency of standard clinical NSAIDs. Ultimately, these computational insights provide a strong rational framework for the development of natural-synthetic hybrid therapeutics.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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