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Original Research Article

In Silico Investigation of the Anti-Inflammatory Activity of Some Diarylheptanoids

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Abstract

Purpose: The search for potentially non-toxic and efficacious anti-inflammatory agents has been of keen interest among researchers due to the side effects of existing anti-inflammatory agents, making their long-term use unsuitable. This study aimed to explore the mechanisms of the anti-inflammatory activity of some diarylheptanoids.
Methods: We performed molecular docking and MM/GBSA binding free energy calculations to assess the binding affinity of selected diarylheptanoids against nuclear factor-kB (PDB ID: 1NFK) and COX-2 (PDB ID: 3LN1). The stability of the lead complexes was evaluated using molecular dynamics simulations for 200ns. The SwissADME web tool and HyperChem 8.0 were used to predict the physicochemical and pharmacokinetic properties.
Results: The results revealed that platyphylloside and hirsutenone were potential NF-kB inhibitors with docking scores of -4.76 and -4.48 Kcal/mol; and binding free energies of -15.84 and -31.17 Kcal/mol. Furthermore, hirsutenone and yakuchinone were identified as potential inhibitors of cyclooxygenase 2 enzyme with docking scores of -11.81 and -10.63 Kcal/mol; and binding free energies of -54.72 and -45.95 Kcal/mol. The types of interactions between the diarylheptanoids' atoms and amino acid residues in the target protein active site were the same as those of the reference inhibitors; dexamethasone for NF-kB, and Celecoxib for COX-2, thus further confirming their potential as NF-kB and COX-2 inhibitors.
Conclusion: Inhibition of NF-kB remains a promising strategy in the treatment of inflammation, and hirsutenone has been identified as a potentially safe and effective anti-inflammatory agent for treating chronic inflammatory conditions, whose anti-inflammatory properties may include both NF-kB and cyclooxygenase 2 inhibition.

Keywords: Anti-inflammatory effect, diarylhepatanoids, molecular docking, molecular dynamics, cyclooxygenase-2 inhibition

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INTRODUCTION

Inflammation is a natural defense mechanism mediated by immune cells and cytokines in response to injury and disease to repair damaged tissues and eliminate harmful stimuli.[1] The inflammatory process begins with the rapid introduction phase where damaged cells activate multiple signal transduction cascades and transcription factors including the nuclear factor kappa-B (NF-κB), mitogen-activated protein kinase (MAPK), janus kinase (JAK), and signal transducers and activators of transcription (STAT). NF-κB signaling activates immune cells such as macrophages and circulating neutrophils close to the injury site to produce large amounts of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6), that recruit more immune cells to the inflamed site and facilitate the production of pro-inflammatory enzymes such as inducible nitric oxide synthase (iNOS) and cyclooxygenases (COX 1 and 2) resulting in NO and prostaglandin synthesis, respectively.[2] Chemokines produced by neutrophils undergoing apoptosis stimulate monocytes to release pro-inflammatory mediators such as reactive oxygen species (ROS) to enhance the inflammatory response further.[2]

The inflammatory response is beneficial promoting the recovery of injured tissues and clearance of the causative agent; however, inflammation may become dysregulated leading to redness, swelling, heat, pain, and loss of function,[3] thus requiring the use of anti-inflammatory drugs to abate the response. The existing anti-inflammatory drugs have been associated with side effects including immunosuppression and sepsis from steroid use; gastrointestinal complications and increased risk of cardiovascular events from the use of NSAIDs, thereby making their long-term use ill-suited, thus leading to the search for potentially non-toxic and effective therapeutic agents from natural sources as anti-inflammatory agents.[4,5,6] One such natural compounds are the diarylheptanoids (DAHs) which are a class of linear and macrocyclic secondary plant metabolites consisting of a 1,7-diphenylheptane skeleton having a wide range of biological activities including anti-inflammatory,[7] pro-apoptotic,[8] anti-influenza,[9] anti-emetic[10] and anti-cancer activities[11]. They are increasingly recognized as privileged structures in drug discovery and potential therapeutic agents.

As the anti-inflammatory activity of a compound is assessed by evaluating its ability to inhibit the production of pro-inflammatory mediators and the pro-inflammatory enzymes iNOS and COX-2, this study aimed at performing a computational assessment of the anti-inflammatory activity of 182 diarylheptanoids using molecular docking studies against NF-kB transcription factor and COX-2 enzyme, MMGBSA calculations, and molecular dynamics simulation.

MATERIALS AND METHODS

Ligand Preparation

A library of 182 diarylheptanoids with established anti-inflammatory activity were selected for structure-based virtual screening. Their 3D structures were downloaded in SDF format from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and prepared for docking using the LigPrep module in Maestro Schrodinger Suite. The OPLS4 force field was used to generate tautomeric forms and ionization states at pH 7.0 ± 1.0 using Epik.[12]

Protein Preparation and Receptor Grid Generation

The crystal structures of nuclear factor kappa B (NF-Kb; 1NFK) and cyclooxygenase-2 (COX-2; 3LN1) were downloaded from the rcsb Protein Data Bank (https://www. rcsb.org/pdb) in PDB format. Considering the receptor resolution and the ligand structure quality assessment, they were found to be good targets. Using the Protein Preparation Wizard module in Maestro Schrodinger Suite, water molecules were removed, hydrogen atoms added, and missing side chains were filled. The structure was optimized using PROPKA at a pH of 7.0 ± 1.0 and restrained minimization was performed using the OPLS4 force field. The receptor grid box was generated in each direction (x = 12Å, y = 12Å, and z = 12Å) around the centroid of the co-crystallized ligand.[13]

Structure-Based Virtual Screening

The docking simulations were performed using the ligand docking in the Glide package of Maestro Schrodinger Suite.[14] Initially, all 182 compounds were docked against 1NFK and COX-2 using high throughput virtual screening (HTVS), then the two top-scored diarylheptanoids per target protein were docked using the extra precision (XP) algorithm, and the binding modes of these compounds were analyzed using Maestro's pose viewer.

Binding Free Energy Calculation Using the Prime molecular mechanics with generalized born and surface area solvation (MMGBSA)

The binding free energy (ΔGbind) of the receptor-ligand complexes was calculated using the prime molecular mechanics with the generalized born surface area (MMGBSA) method. The binding free energy measures the strength of the interaction between a compound and its target and the stability of the complex formed; given by the equation:

ΔG (binding energy) = ΔG (complex) – [ΔG (protein) + ΔG (ligand)].[12]

MMGBSA calculations were performed using the OPLS4 force field. The more negative energy signified a stronger bond.[15]

Molecular Dynamics (MD) Simulation

To assess the stability of the receptor-ligand complexes, we performed molecular dynamics simulation on the lead complex for 1NFK and 3LN1, respectively. Molecular dynamics investigate the stability of protein-ligand complexes while mimicking physiological conditions including water molecules, lipid membranes, and sodium chloride.[16] Newton's equations were employed to assess the movement of water molecules, ions, micro- and macromolecules, while temperature and pressure were maintained at constant throughout the simulations.[17] The stability of simulations was evaluated by calculating the RMSD of the protein and ligand over time before analyzing the RMSF and protein-ligand contacts.

***In Silico* Prediction of Physicochemical and ADMET Properties**

The physicochemical properties of the selected compounds encompassing the drug-likeness (Lipinski's RoF), bioavailability score, leadlikeness, and synthetic accessibility were predicted using the SwissADME web tool. In addition, the pharmacokinetic properties including the blood-brain barrier (BBB) permeability, P-gp substrate, and LogKp were predicted using the same software.

RESULT AND DISCUSSION

Molecular Docking and Binding Free Energy Assessment

We performed HTVS of 182 DAHs with reported anti-inflammatory properties from previous studies.[7] The compounds were docked against 1NFK and 3LN1 after which the two top-scored DAHs per target protein were subjected to the extra precision (XP) algorithm and MMGBSA calculations. Platyphylloside (Compound 64) had a docking score of -4.76 Kcal/mol with an MMGBSA value of -15.84 Kcal/mol, and Hirsutenone (Compound 48) had a docking score of -4.48 Kcal/mol with an MMGBSA value of –31.17 Kcal/mol, when docked against 1NFK. Hirsutenone (Compound 48) had a docking score of -11.81 Kcal/mol with an MMGBSA value of -54.72, and Alnustone (Compound 20) had a docking score of -10.63 Kcal/mol with an MMGBSA value of -45.95 Kcal/mol when docked against 3LN1 (Table 1).

Table 1: Platyphylloside, Hirsutenone, and Dexamethasone (Reference Inhibitor) interactions with 1NFK active site

Compound	Docking Score (Kcal/mol)	MMGBSA (Kcal/mol)	Types of Interactions
Platyphylloside	-4.76	-15.84	H-bond: Tyr57(B), Ser246(B), Lys272(B), Arg305(A), Gln306(A) Charged (+): Lys241(B), Lys272(B), Arg305(A) Polar: His141(B), Ser240(B), Ser246(B), Gln306(A), Gln306(A) Hydrophobic: Tyr57(B), Ala242(B), Pro243(B), Phe307(A)
Hirsutenone	-4.48	-31.17	H-bond: Tyr57(B), Ser246(B), Lys272(B), Arg305(A), Gln306(A) Charged (+): Lys241(B), Lys272(B), Arg305(A) Polar: His141(B), Ser240(B), Ser246(B), Gln306(A), Gln306(A) Hydrophobic: Tyr57(B), Ala242(B), Pro243(B), Phe307(A)
Dexamethasone (Reference Inhibitor)	-2.401	-	H-bond: Tyr57(B), His141(B), Lys144(B), Thr143(A), Lys144(A)

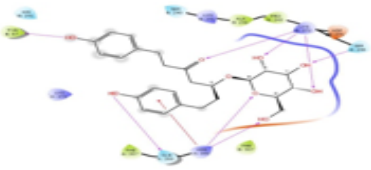
Thus, we identified Platyphylloside and Hirsutenone as potential NF-kB inhibitors; Hirsutenone and Alnustone as potential COX-2 inhibitors. The binding free energy further established the affinity of the DAHs for NF-kB and COX-2. Analysis of 1NFK-Hirsutenone complex using Maestro pose viewer revealed that Hirsutenone interacted with 1NFK active site through H-bond interactions with amino acid residues Tyr57(B), Thr143(B); polar interactions with His141(B), Thr143(B); charged (positive) interactions with Arg54(B), Lys241(B), Lys272(B); and hydrophobic interactions (Figure 1). Platyphylloside's atoms interaction with 1NFK active site revealed H-bonds with Tyr57(B), Ser246(B), Lys272(B), Arg305(A), Gln306(A); polar interactions with His141(B), Ser240(B), Ser246(B), Gln306(A); charged (positive) interactions with Lys241(B), Lys272(B), Arg305(A); and hydrophobic interactions (Figure 1). These binding interactions were consistent with the study by Srivastava *et al*.[18] They explored the structural and conformational dynamics of NF-kB inhibitors where the reference inhibitor, dexamethasone was docked against 1NFK, resulting in a docking score of -2.401Kcal/mol, and forming H-Bond interactions with Lys144(A), Tyr57(B), His141(B), Thr143(A) and Lys144(B) amino acid residues.[18] These findings suggest that Platyphylloside and Hirsutenone's anti-inflammatory activity may include NF-kB inhibition.

The nuclear factor-κB (NF-κB) is a family of transcription factors that control the expression of genes involved in many critical physiological responses such as inflammation, proliferation, differentiation, cell adhesion, and apoptosis. They exist as homo- and heterodimers consisting of the p50, p52, c-Rel, RelA (p65) and RelB subunits.[19] The NF-κB dimers are sequestered in the cytoplasm by a family of inhibitors called IκBs (Inhibitor of κB) in unstimulated cells where they remain inactive in the cytoplasm by ankyrin repeat domains.[20] In the canonical pathway, NF-κB is activated after degradation of IκBα by phosphorylation through the IκB kinase (IKK) resulting in nuclear translocation of various NF-κB complexes to induce the expression of several genes that have DNA-binding sites for NF-κB. The stimulation of these genes by activated NF-kB leads to the given physiological response; an inflammatory or immune response, a cell survival response, or cell proliferation.[21] The noncanonical NF-κB pathway involves different signaling molecules leading to the activation of the p52/RelB dimer.[22] The abnormal activation of NF-κB is a predominant feature of the inflammatory response, therefore targeting NF-κB signaling may represent a promising therapeutic approach for treating inflammatory diseases. Several natural products involved in anti-inflammatory activity have been shown to inhibit NF-κB.[23]

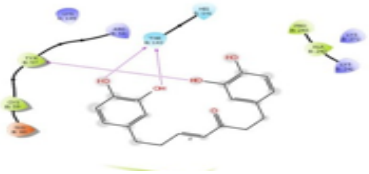
At the onset of the inflammatory response, NF-kB activates immune cells to secrete pro-inflammatory cytokines that activate pro-inflammatory enzymes, iNOS and COX-2 leading to nitric oxide and prostaglandin synthesis. Therefore, inhibition of COX-2 enzyme by NSAIDs has been a mainstay in anti-inflammatory therapy. The results from the Maestro pose viewer analysis of Hirsutenone-3LN1 complex interactions with 3LN1 active site revealed H-bond interactions with Leu338, Tyr341, Met508; charged (positive) interactions with Arg499; polar interactions with Gln178, Ser339, Ser516; and hydrophobic interactions (Figure 2). Alnustone interacted with the 3LN1 active site through H-bond interactions with Leu338, and Tyr341; charged (positive) interactions with Arg499; polar interactions with Ser339, and Ser516; and hydrophobic interactions (Figure 2). These findings were in agreement with studies of COX-2 inhibition by celecoxib, which reported that the inhibition is through H-bond, polar, charged positive, and hydrophobic interactions with amino acid residues, Arg106, Gln178, Val335, Leu338, Ser339, Tyr341, Tyr371, Trp373, Arg499, Phe504, Met508, and Leu517, in the receptor's binding pocket. [24,25,26] Thus, our results suggest that Hirsutenone and Alnustone's anti-inflammatory activity may include COX-2 inhibition.

COX-1 and COX-2 enzymes bear similar structures but differ in the dimensions and composition of their active sites with COX-2 active site being larger and more flexible, having the amino acid residue Val509 in place of Ile523 and Arg499 in place of His513 as seen in COX-1. This structural variation explains COX-2's selectivity for certain drugs.[27,28]

Selective COX-2 inhibitors have been associated with increased risks of cardiovascular events due to the inhibition of prostacyclin synthesis; a potent vasodilator. The DAHs as COX-2 inhibitors may retain vasoprotective effects as studies have shown that they can stimulate G-protein oestrogen receptors (GPERs; GPR30) to cause vasodilation through the NO-cGMP pathway.[29,30] Thus, DAHs may be suitable for long-term administration, rendering them promising therapeutic agents for managing chronic inflammatory conditions.

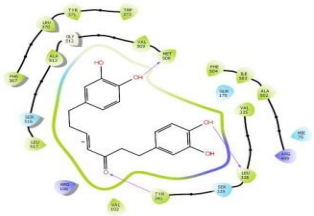


Platyphylloside

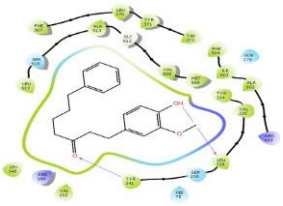


Hirsutenone

Figure 1: Binding Interactions of Platyphylloside and Hirsutenone with NF-kB: 1NFK active site

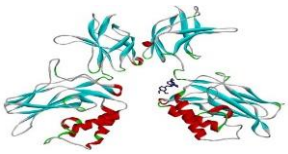


Hirsutenone

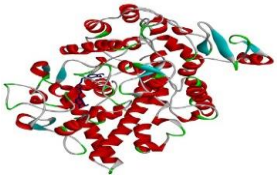


Alnustone

Figure 2: Binding Interactions of Hirsutenone and Alnustone with COX-2: 3LN1 active site

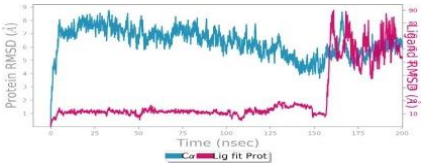


1NFK-Hirsutenone

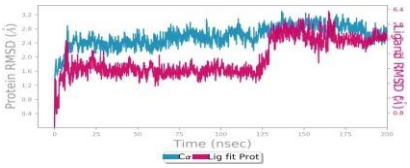


3LN1-Hirsutenone

Figure 3: 3-D Representation of Hirsutenone bound to the target protein's active site

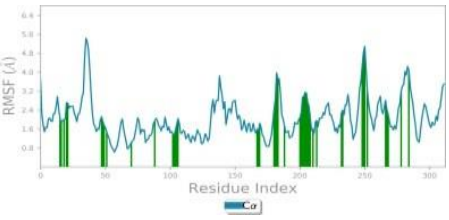


1NFK-Platyphylloside Complex

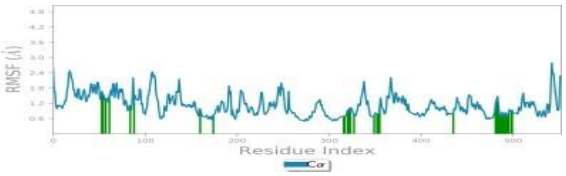


3LN1-Hirsutenone Complex

Figure 4: RMSD plot of 1NFK-Platyphylloside and 3LN1-Hirsutenone Complexes

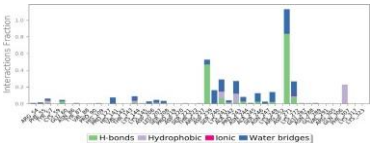


1NFK-Platyphylloside Complex

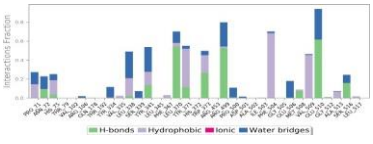


3LN1-Hirsutenone Complex

Figure 5: RMSF graph of 1NFK-Platyphylloside and 3LN1-Hirsutenone Complexes



1NFK-Platyphylloside Complex



3LN1-Hirsutenone Complex

Figure 6: Protein-ligands histogram of 1NFK-Platyphylloside and 3LN1-Hirsutenone Complexes

Table 2: Hirsutenone, Alunstone, and Celecoxib (Reference Inhibitor) Interactions with 3LN1 Active Site

Compound	Docking Score (Kcal/mol)	MMGBSA (Kcal/mol)	Types of Interactions
Hirsutenone	-11.81	-54.72	**H-bond:** Leu338, Tyr341, Met508 **Polar:** Gln178, Ser339, Ser516 **Charged (+):** Arg499 **Hydrophobic:** Val335, Leu338, Phe367, Leu370, Tyr371, Trp373, Ala502, Ile503, Phe504, Met508, Val509, Gly512, Ala513, Leu517
Alunstone	-10.63	-45.95	**H-bond:** Leu338, Tyr341 **Polar:** Ser339, Ser516 **Charged (+):** Arg499 **Hydrophobic:** Tyr334, Val335, Leu338, Tyr341, Phe367, Leu370, Tyr371, Trp373, Ala502, Ile503, Phe504, Met508, Gly512, Ala513, Leu517
Celecoxib (Reference Inhibitor)	-12.88	-79.21	**H-bond:** Leu338, Ser339, Arg499, Phe504 **Polar:** His75, Gln178, Ser339, Ser516 **Charged (+):** Arg106, Arg499 **Hydrophobic:** Val102, Val335, Leu338, Tyr341, Phe367, Leu370, Tyr371, Trp373, Ala502, Ile503, Phe504, Met508, Gly512, Ala513, Leu517 **Pi-Cation:** Arg106

Molecular Dynamic (MD) Simulations

We performed molecular dynamic (MD) simulations to validate the stability of the diarylheptanoids docked against 1NFK and 3LN1. These simulations mimic the physiological environment while investigating the dynamic behavior and stability of the protein-ligand complexes over time.[16,17] We examined the protein-ligand root mean square deviation (RMSD), protein root means square fluctuation (RMSF), ligand RMSF, protein secondary structure, Protein-ligand contacts, and ligand torsion profile. The root means square deviation (RMSD) plots were generated to assess the stability of the complexes over the simulation period, while the root square fluctuation (RMSF) plots were generated to analyze the flexibility of 1NFK and 3LN1 amino acid residues in the presence of the hit ligands. MD simulations were performed on the lead complexes with the highest XP (extra precision) docking score against 1NFK and 3LN1, respectively. Platyphylloside-1NFK complex (lig-fit-prot) revealed that the system reached equilibrium after the first 10ns, and the equilibrium was maintained for 155ns with minimum and maximum values of 0.9 and 1.2 Å, and slight fluctuations at 30, 50, 110, and 149ns. At 155ns, the complex displayed a diffusion behaviour indicating a displacement of the ligand from 1NFK binding pocket, and the protein experienced a conformational change from 155ns to the end of the simulation. The Cα atoms reached a consistent fluctuation after 5ns which was maintained for 165ns, with a slight fluctuation, and equilibrium was maintained till the end of the evolution (Figure 4). The RMSF analysis of 1NFK showed the areas of highest fluctuations within the protein; that is, the N- and C-terminal characterized by the highest peaks. The green-coloured vertical bars represented the amino acid residues interacting with the ligand, and the results showed that some amino acid residues had stable interactions with Platyphylloside, as shown by the lower peaks which represent areas of fewer fluctuations within the protein (Figure 5).[17] This suggests that the interactions between Platyphylloside and 1NFK remained stable.

Platyphylloside's atoms interactions with 1NFK binding pocket were analysed using the protein-ligands contact histogram over the simulation period. The results showed hydrogen bond interactions with Tyr57, Glu60, Lys144, Arg227, Asp239, Lys241, Ser246, Asn247, Arg252, Asp

271, Lys241; hydrophobic bonds, ionic interactions, and water bridges (Figure 6). H-bonds play a significant role in ligand binding and drug design because of their strong influence on drug specificity, metabolization and adsorption. The number of H-bonds between a protein and a ligand depicts the strength and stability of binding interactions. The protein-ligands contact histogram for Platyphylloside-1NFK was consistent with the Mastro pose viewer analysis of the same complex.

Hirsutenone-3LN1 complex (lig-fit-prot) reached equilibrium after the first 15ns, and maintained equilibrium for 125ns with minimum and maximum oscillations at 1.2 and 1.6 Å. At 130ns, Hirsutenone-3LN1 complex displayed a diffusion behaviour indicating its displacement from 3LN1 binding pocket, however, equilibrium was achieved again at the same time, and maintained throughout the simulation. The Cα atoms achieved equilibrium at 15ns and maintained equilibrium throughout the simulation (Figure 4). The RMSF analysis of 3LN1 showed the N- and C- terminals which had the highest peaks and the most fluctuations. Hirsutenone's atoms interactions with 3LN1 occurred at residues with fewer fluctuations indicated by the green peaks (Figure 5). This implied that the interactions between the ligand atoms and the protein were stable. The protein-ligands contact histogram was used to analyze Hirsutenone interactions with 3LN1, and the results showed H-bonds at Asn 72, His75, Leu338, Ser339, Tyr341, Leu370, Tyr371, Trp373, Arg499, Pro500, Met508, Glu510, Gly512, Ser516; hydrophobic interactions, ionic, and water bridges (Figure 6). The protein-ligands contact histogram for Hirsutenone-3LN1 was consistent with the Mastro pose viewer analysis for the same complex.

Physicochemical and ADMET Properties Prediction

The physicochemical and ADMET properties of Alnustone and Hirsutenone were predicted using the SwissADME web tool. Assessment of their drug-likeness was performed based on Lipinski's rule of five; that is, it does not violate more than one of the following: ≤ 5 hydrogen bond donors; ≤ 10 hydrogen bond acceptors; a molecular mass < 500 daltons; and a Log P < 5 for octanol-water partition coefficient.[31] According to the aforementioned criteria, alnustone and hirsutenone emerged as potentially druggable with good bioavailability scores that affirm their drug-likeness (Table 3). The concept of Lead-likeness refers to a molecule's potential for optimization.[32]

Table 3: Physicochemical and Pharmacokinetic Predictions of Alunstone and Hirsutenone

Physicochemical Property	Alunstone	Hirsutenone
Molecular weight	312.40 g/mol	328.36 g/mol
Num. of Rotatable Bonds	9	7
Consensus Log Po/W	4.09	2.77
Drug Likeness (Lipinski)	Yes; 0 violation	Yes; 0 violation
Bioavailability Score	**0.55**	**0.55**
Medicinal Chemistry Leadlikeness	No; 2 violations	Yes
Synthetic Accessibility	2.31	2.48
BBB Permeant	Yes	No
P-gp Substrate	No	No
LogKp	-5.44	-6.11

Thus, lead optimization studies such as quantitative structure activity relationship (QSAR) analysis could be performed on Hirsutenone to synthesie pharmacologically active derivatives.[33] Based on the predicted physicochemical properties, Hirsutenone met the requirements for lead-likeness while Alnustone did not, having 2 violations. A synthetic accessibility score of less than 6 indicates that a molecule can be synthesized.[34] Alnustone and Hirsutenone had synthetic accessibility scores 2.31 and 2.48 respectively, indicating their potential for successful synthesis (Table 3). The number of rotatable bonds is an important physicochemical parameter influencing a molecule's conformation and oral bioavailability. Generally, compounds with less than 10 rotatable bonds are likely to display stable conformations and enhanced oral bioavailability.[35] The results showed that Alnustone and Hirsutenone had 7 and 9 rotatable

bonds, indicating stable conformations and potential for good oral bioavailability (Table 3).

Log P, a measure of the lipophilicity, is a parameter that determines a molecule's solubility, absorption, and distribution properties. For a good balance between solubility and passive diffusion permeability, the Log P value should be less than 5.[36] Based on this study, Alnustone had a Log P value of 4.09, while hirsutenone Log P value was 2.77 suggesting good solubility, oral absorption, and distribution (Table 3).

The pharmacokinetic properties prediction indicated that Alnustone and Hirsutenone were not substrates for P-glycoprotein (P-gp) which suggests that they may exhibit high oral bioavailablity and intestinal absorption. Substances that cross the BBB may pose a health risk based on their potential to release toxic metabolites in the brain and bloodstream.[37] From our study, Alnustone emerged BBB permeant, while Hirsutenone did not, which suggests that Hirsutenone poses less risk of toxicity. LogKp measures a molecule's skin permeability where more negative values signify reduced skin permeability.[37] Alnustone's LogKp value was -5.44 while Hirsutenone LogKp value was -6.11, suggesting that both compounds were unlikely to penetrate the skin effectively (Table 3).

HyperChem 8.0 was employed to predict the pharmacokinetic properties of Platyphylloside as the compound's size was too large for the SwissADME online server. Platyphylloside had a Log P value of 4.33 suggesting good solubility, oral absorption and distribution, and a MW of 476.52 which indicates its potential to cross biological membranes to get to its target receptor (Table 4).[31]

Table 4: Molecular Descriptors of Platyphylloside

Partial Charge (e)	SAG (Sq.Å)	VOL (CuÅ)	HE (Kcal/mol)	Log P	MR (CuÅ)	POL (CuÅ)	MW (g/mol)
0.00	753.35	1333.04	-34.53	4.33	75.60	48.36	476.52

ADMET properties predictions of Platyphylloside using HyperChem 8.0. Surface Area Grid (SAG), Volume (VOL), Hydration Energy (HE), Octanol/Water partition coefficient (Log P), Molar Refractivity (MR), Polarizability (POL), Molecular Weight (MW).

The physicochemical and pharmacokinetic predictions of Alnustone, Hirsutenone, and Platyphylloside revealed that they were potentially druggable, with good solubility, high bioavailability, and were easily distributed.

CONCLUSION

This study has provided more understanding of the anti-inflammatory activity of diarylheptanoids, Alnustone, Hirsutenone, and Platyphylloside. Also, it has been identified that the anti-inflammatory activity of Hirsutenone may include NF-kB and COX-2 inhibition. Future perspectives following this study include lead optimization of Hirsutenone to synthesize pharmacologically active derivatives that could be promising agents for treating chronic inflammatory conditions.

Conflict of interest

The authors declare no conflict of interest.

Authors Declaration

The authors hereby declare that the works presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

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