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Research article

In silico anti-inflammatory activity of lavender (*Lavandula officinalis*) essential oil bioactive compounds: Molecular docking analysis of COX-1 and COX-2, and ADMET prediction

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Abstract: Advanced investigations are in action worldwide to find medications with improved safety profiles. Natural resources are essential in the creation of innovative treatments and drugs that have fewer side effects. The essential oil (EO) of lavender (*Lavandula officinalis*) is well-known in alternative and complementary therapies for its use as wound-healing and antimicrobial ingredients. However, the exact pharmacological and anti-inflammatory aspects of naturally produced lavender essential oil (LEO) compounds are still unknown. As a consequence, it is essential to explain LEO drug molecular docking experiments with cyclo-oxygenase enzymes (COX-1 and COX-2). An attempt was developed in this study to discover the anti-inflammatory activity of LEO bioactive components. The online DockThor server was used for *in silico* molecule docking simulation. Interaction studies of LEO compound binding poses with COX were performed to get an understanding of the interacting amino acids and their inter-molecular bondings. Based on physicochemical attributes and toxicity, the docked compounds with the greatest binding affinities were also investigated for drug similarity utilizing the admetSAR tool and PASS platforms. Molecular docking studies exploring the bioactive principle targeted action revealed that electrostatic interactions and H-bonds make the main causative factor in inter-molecular connections associated with anti-inflammatory action. Seven top-ranked compounds were selected by virtual screening. Molecular docking revealed that limonene has the highest negative binding affinity (−8.536 kcal/mol) in complex with COX-1, followed by *α*-terpineol (−8.535 kcal/mol) and *p*-cymene (−8.515 kcal/mol), while two approved anti-inflammatory drugs (celecoxib and betamethasone) produced −8.191 and −8.041 kcal/mol respectively. Similarly, these terpenes can be documented as promising drug

candidates based on qualifying Lipinski's rule five. The selected terpenes showed excellent drug-like properties and a percentage of human oral absorption. Besides, it was found to be safe for the human body in toxicological risk assessment. This work gives insight into the anti-inflammatory mechanism of action of LEO terpenes. LEO drugs' pharmacokinetic data and molecular docking patterns may open the way for the development of new COX inhibitors with anti-inflammatory capability and improved pharmacokinetic and pharmacodynamic properties.

Keywords: anti-inflammatory drugs; cyclo-oxygenase enzymes; *Lavandula officinalis*; essential oil compounds; molecular docking; toxicity

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most frequently prescribed medicinal classes in old people and children [1,2]. These medications are typically used to treat inflammatory illnesses and to reduce pain associated with a variety of medical ailments or surgeries [3]. They are used to treat chronic inflammatory disorders such as arthritis, gout, and rheumatoid. NSAIDs work by inhibiting the cyclooxygenase (COX) enzymes, which decrease the production of prostaglandins (PGs), which are believed to be involved in the complicated process of inflammation [4].

Inflammatory responses caused by the production of histamine, bradykinin, and prostaglandins are part of the host's defense systems. COX are important enzymes in the biosynthesis of prostaglandins, which are the primary mediators of the inflammatory response, pain, and elevated body temperature (hyperpyrexia). The body generates two major isoforms of COX enzymes, namely cyclooxygenases-1 (COX-1) and cyclooxygenases-2 (COX-2). It has been reported that COX-1 is responsible for the production of important biological messengers such as prostaglandins and thromboxanes and is implicated in blood coagulation, pain-causing, and stomach protection, whereas COX-2 is implicated in pain triggered by inflammation and plays a key role in prostaglandin synthesis pathway in inflammatory cells and the nervous system [5,6]. When COX-1 is blocked, the inflammatory response is decreased, but gastrointestinal lining defense is also reduced. This might result in stomach distress, ulcers, and hemorrhage from the gastrointestinal tract. Whereas COX-2 is normally restricted to inflamed tissue, COX-2 inhibition causes significantly reduced stomach irritation as well as a lower risk of gastric hemorrhage [7]. As a result, selective COX-2 inhibitors such as rofecoxib (Vioxx®) and celecoxib drugs have been designed to alleviate COX-related inflammation [8]. However, Coxib medications have been removed due to an enhanced danger of long-term heart attacks and strokes [9].

Furthermore, NSAIDs are one of the most popular treatments in the world, however, they are not generally accepted by users, and hence their long-term usage in chronic medical conditions is accompanied with significant undesirable consequences. Long-term NSAIDS medication may cause stomach epithelial injury marked by localized necrosis, bleeding, and in some cases, severe ulceration [10,11]. The NSAID-induced gastropathy issues that limit the effectiveness of this class of medications are due mainly to the nonselective inhibitory activity of both constitutive (COX-1) and inducible (COX-2) homologs of cyclooxygenase, as well as the existence of corrosive carboxylic acid features and functions in their structure [12].

As a result, developing effective COX inhibitors from biological compounds is necessary. Medicinal plants, aromatic herbs, and their essential oils (EOs) have lately been recognized to have curative effects and also to have many health benefits. They have been shown to offer a wide range of medicinal benefits, including antibacterial, antifungal, antioxidant, anti-inflammatory, analgesic, and anticancer properties [13–15]. Lavender (*Lavandula officinalis* (Lamiaceae family)) is a popular aromatic plant in the Mediterranean region, including Algeria. Lavender has mostly been employed in medicinal and domestic culinary applications over the world. The EO extracted from lavender aerial parts is the primary contributor to its distinctive perfume and medicinal function [16,17]. In ethnomedicine, lavender is used as an anti-inflammatory medication [18,19]. As a result, it is important to describe the molecular docking study of lavender metabolites with COX-1 and COX-2.

The current study focuses on identifying potential treatment options that will be regarded as successful anti-inflammatory medication therapy. Molecular docking is a vital computational method in drug design and development projects, and it was used to match a small ligand as a guest with a variety of receptor molecules as hosts. This docking-based technology is often used to estimate a compound's attraction for a target protein. In this paper, molecular docking of various potential anti-inflammatory medicines and numerous terpenes discovered in LEO was done in this research to investigate the inhibition likelihood against COX-1 and COX-2 receptors using the DockThor server and BIOVIA Discovery Studio visualizer software. A total of 29 LEO terpene compounds were virtually screened on the COX-1 (PDB ID 3N8Y) and COX-2 (PDB ID 3LN1) enzymes. The binding affinities were compared to those of other anti-inflammatory medications. The docked compounds with the highest binding affinities were also screened for drug-likeness utilizing the SwissADME and PASS platforms, based on physicochemical, pharmacological, and toxicological features.

2. Materials and methods

2.1. Preparation of COX enzymes

From the protein data bank, the X-ray crystal structures of COX-1 and COX-2 (PDB codes 3N8Y and 3LN1, respectively) were retrieved (Table 1 and Figure 1). The deletion of ligands, water molecules, as well as other heteroatoms was done using the software BIOVIA Discovery Studio visualizer (Dassault Systèmes Corp., Version 2020). The protein's crystal structure was furthered by the addition of hydrogen after missing and incomplete residues were filled in. The PDB file of the improved receptor was then utilized to simulate docking.

Table 1. Protein target data.

PDB ID	COX 1 (PDB ID: 3N8Y)	COX-2 (PDB ID: 3LN1)
Title	Structure of aspirin acetylated COX-1 in complex with Diclofenac	Structure of celecoxib bound at the COX- 2 active site
DOI	10.2210/pdb3N8Y/pdb	10.2210/pdb3LN1/pdb
Author(s)	Sidhu RS, Lee J, Yuan C, et al.	Kiefer JR, Kurumbail RG, Stallings WC, et al.
Deposited	28-05-2010	01-02-2010
Resolution	2.60 Å	2.40 Å
Classification	Oxidoreductase	Oxidoreductase
Organism	*Ovis aries*	*Mus musculus*
Expression system	*Spodoptera frugiperda*	*Spodoptera frugiperda*
Method	X-ray diffraction	X-ray diffraction
Molecule	Prostaglandin G/H synthase 1	Prostaglandin G/H synthase 2
Chains	A	A, B, C, D
Sequence length	553 amino acids	587 amino acids
Total structure weight	134.2 kDa	278.19 kDa

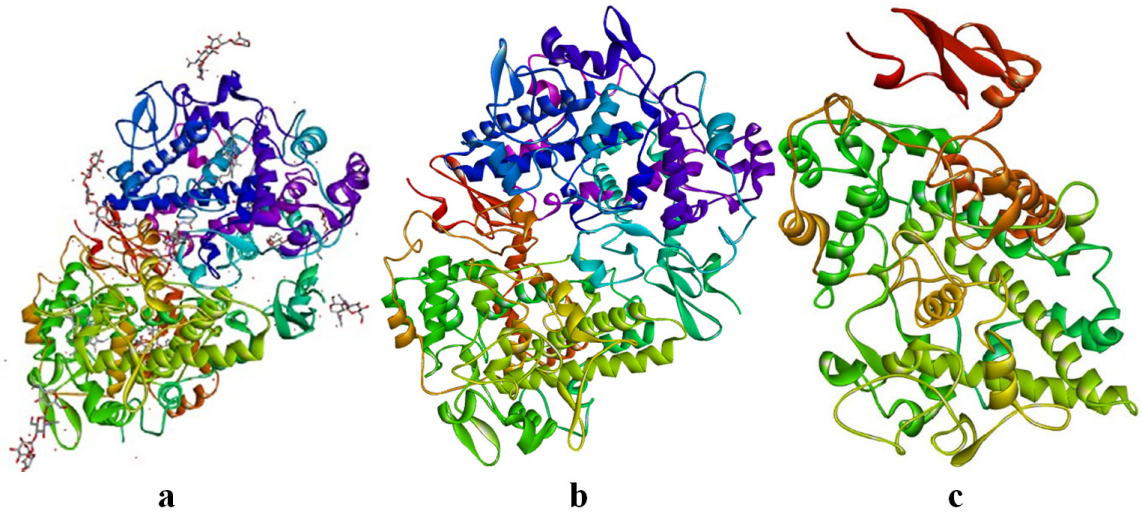


Figure 1. Three-dimensional crystal structure of the molecular target, COX-1 enzyme (3N8Y) was represented in (a) solid ribbon (b) without hetatoms (c) chaine A.

2.2. Literature survey and selection of ligands

LEO's total medicinal effect is provided by a diverse array of bioactive terpenes. Based on the percentage concentration in the LEO fraction, a study of the literature was conducted to identify the most important of these bioactive compounds. A literature search was carried out to obtain information about the LEO and its bioactive compounds from electronic databases such as Google scholar, PubMed, ScienceDirect, Wiley, MDPI, Springer, and other online journal publications and dissertations. There has been a lot of difference in the LEO chemical composition among different *Lavandula* species. We focused our chemical composition analysis on 29 terpenes that make up the bulk of lavender volatile oil. The compounds focused on in this study include limonene, α-terpineol,

p-cymene, *β*-phellandrene, *β*-ocimene, myrcene, *α*-bisabolol, geraniol, germacrene D, *β*-caryophyllene, linalyl acetate, caryophyllene oxide, lavandulol, lavandulyl acetate, bornyl acetate, neryl acetate, *cis*-linalool oxide, terpinen-4-ol, linalool, eucalyptol, *α*-pinene, *trans*-linalool oxide, geranyl acetate, fenchone, *β*-pinene, camphene, camphor, borneol, *β*-farnesene. From the PubChem (pubchem.ncbi.nlm.nih.gov) database, the small molecular structures of the significant bioactive LEO constituents were obtained in sdf format. The application BIOVIA Discovery Studio visualizer was used to compute bond lengths, display receptors, ligand structures, and hydrogen bonding connections. After a comprehensive study of the literature, 34 structures of ligand molecules (Figures 2 and 3) were found and obtained from the PubChem database.

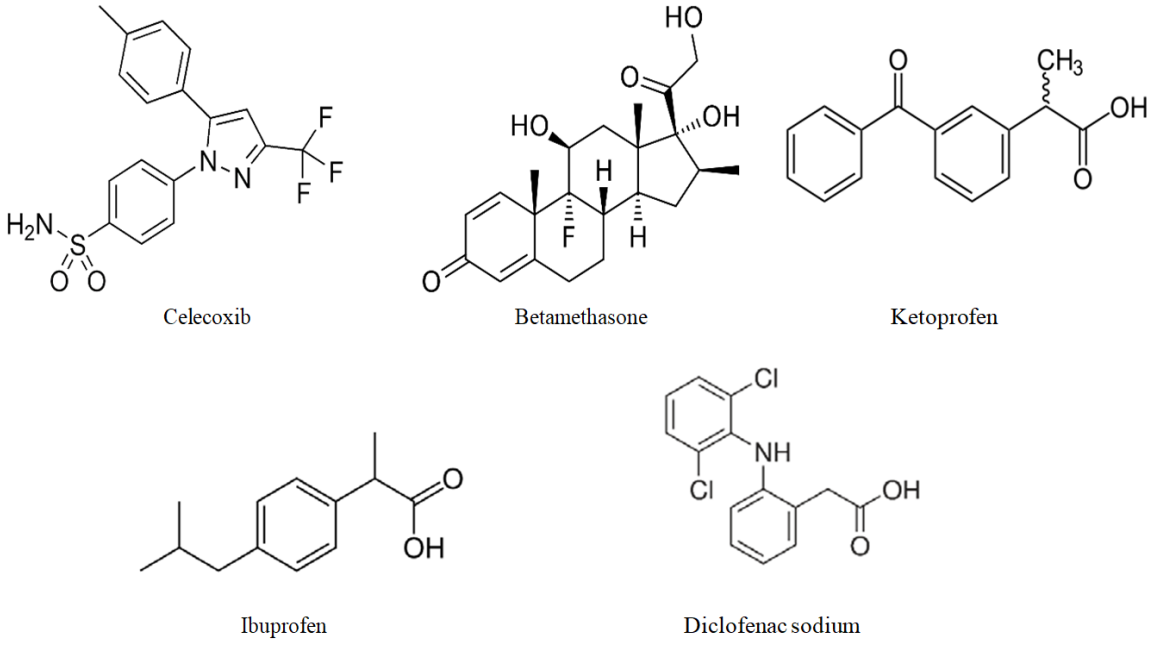


Figure 2. Chemical structure of selected anti-inflammatory drugs.

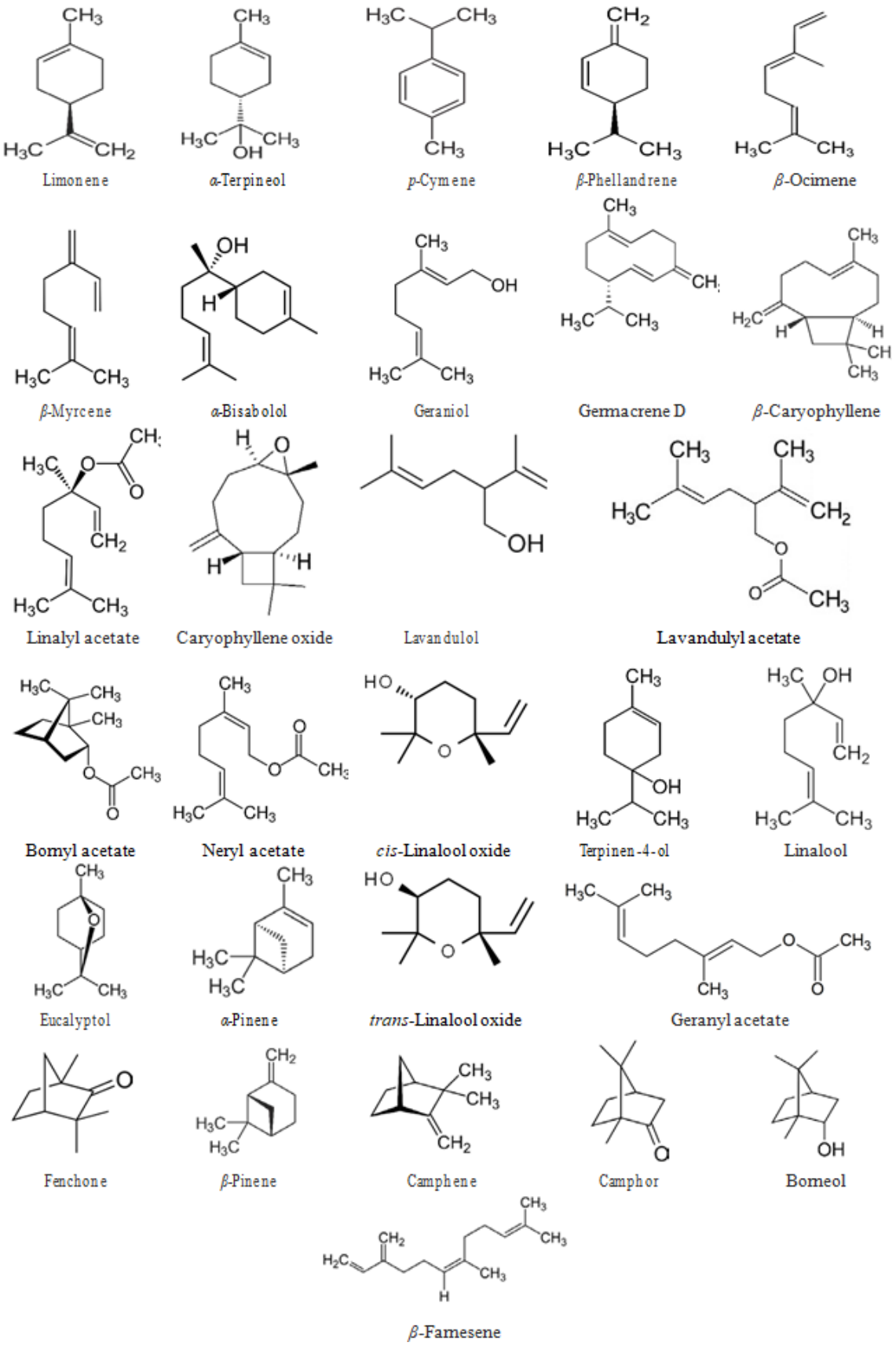


Figure 3. Chemical structure of all selected ligand terpenes in docking studies.

2.3. Molecular docking

In this research, we used the free DockThor Portal (www.dockthor.lncc.br) created by the Grupo de Modelagem Molecular de Sistemas Biológicos (GMMSB) (www.gmmsb.lncc.br) located at the Laboratório Nacional de Computaço Cientfica (LNCC) in Petrópolis, Brazil, for receptor-ligand dock. The DockThor Portal received the files of the retrieved ligands and receptors for docking simulation. The COX protein's active site with the biggest surface area was chosen for docking when all optimal ligands were applied. The following parameters were included in the docking process: Number of evaluations: 1000000; population size: 750; initial seed: −1985; number of runs: 24; docking: soft; spatial discretization of the energy grid: 0.25 Å; grid points: <1000000. All conformers with the best placements and dock scores for each ligand will be stored in the output folder. The technique additionally emphasizes the ideal conformer positioning for a certain ligand that has the best (minimum) score. The lowest interaction energy for each ligand and COX proteins for the ideal ligand position inside the binding site cavity was discovered once the docking procedure was complete. With the aid of the Discovery Studio visualizer, the interactions of intricate protein-ligand conformations were examined.

2.4. In silico ADME-toxicity prediction studies

Through examination of pharmacokinetic characteristics, a few molecules from the molecular docking analysis were assessed for their drug-like activity. The admetSAR program (http://lmmd.ecust.edu.cn) was used to estimate the pharmacokinetic profile (absorption, distribution, metabolism, excretion, and toxicity (ADMET)), of the LEO terpenes [20]. The topological polar surface area (TPSA), clog P, fragment-based drug-likeness, and drug score values were determined using the OSIRIS property explorer (www.organic-chemistry.org/prog/peo/). By using criteria such as molecular weight ≤ 500, logP ≤ 5, hydrogen bond donor ≤ 5, hydrogen bond acceptor ≤ 10, and TPSA ≤ 500, the ligands were further tested for the Lipinski rule of five. By inputting SMILES structures from PubChem notations or uploading SDF files, the molecules may be evaluated to determine their toxicological qualities. Toxicological modeling can then be used to generate a plethora of data regarding the effects associated with the structure.

2.5. PASS computer program

PASS version, an online system that predicts possible pharmacological effects of a chemical based on its structural information, was used to obtain the biological activity spectra of previously reported LEO phytoconstituents. PASS is a computer-based tool used to predict several types of physiological responses for numerous substances including phytoconstituents. This program compares over 300 pharmacological effects and biochemical pathways of substances and provides probabilities of activity (Pa) and inactivity (Pi). The only constituents deemed to be viable for a certain medical activity are those with Pa greater than Pi [21].

3. Results and discussion

3.1. Molecular docking studies

The project that was submitted to the DockThor Portal makes use of the computing resources offered by the Brazilian SINAPAD (Sistema Nacional de Alto Desempenho) system, which has a high-performance platform. The top models were chosen after the DockThor Portal developed a variety of models for each docking operation between the COX receptor site and phytoconstituents. This computational process begins by docking each ligand molecule, followed by scoring. Using the DockThor server and the Discovery Studio software, docking experiments were conducted to examine the molecular interactions between the available active sites of target enzymes and LEO terpenes in order to determine the affinity of the compounds for COX-1 and COX-2. Based on their minimum binding energies associated with the complex formation at the catalytic activity, limonene, *α*-terpineol, *p*-cymene, *β*-phellandrene, *β*-ocimene, and terpinen-4-ol were rated in terms of their COX inhibitory activity. The docked chemicals' binding energies on COX-1 were determined to be between −8.536 and −8.438 kcal/mol (Table 2). Celecoxib and diclofenac sodium, two common anti-inflammatory medicines, had noticeably greater binding energies for the COX-2 target, showing that all of the chosen chemicals need less energy to block the protein.

Table 2. Docking data generated by DockThor server between various ligands molecules of the reference and LEO compounds with COX-1 & COX-2 enzymes.

Compound name	COX-1 binding affinity (kcal/mol)	Compound name	COX-2 binding affinity (kcal/mol)
Limonene	−8.536	Celecoxib	−8.673
α-Terpineol	−8.535	Myrcene	−8.495
p-Cymene	−8.515	*α*-Bisabolol	−8.458
β-Phellandrene	−8.486	*β*-Caryophyllene	−8.400
β-Ocimene	−8.463	*β*-Ocimene	−8.353
Terpinen-4-ol	−8.438	Diclofenac sodium	−8.313
Germacrene D	−8.413	Geraniol	−8.303
α-Pinene	−8.334	Germacrene D	−8.271
Myrcene	−8.332	*β*-Farnesene	−8.257
β-Pinene	−8.274	*β*-Phellandrene	−8.179
Camphene	−8.266	*p*-Cymene	−8.018
Fenchone	−8.265	Betamethasone	−7.990
Celecoxib	−8.191	Linalyl acetate	−7.979
Betamethasone	−8.041	Caryophyllene oxide	−7.893
β-Farnesene	−7.894	*α*-Terpineol	−7.868
Lavandulol	−7.888	Lavandulol	−7.731
Diclofenac sodium	−7.792	Lavandulyl acetate	−7.586
Caryophyllene oxide	−7.760	Bornyl acetate	−7.561
β-Caryophyllene	−7.696	Neryl acetate	−7.537

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Compound name	COX-1 binding affinity (kcal/mol)	Compound name	COX-2 binding affinity (kcal/mol)
Geranyl acetate	−7.661	*cis*-Linalool oxide	−7.522
Linalool	−7.591	Ketoprofen	−7.478
α-Bisabolol	−7.427	Terpinen-4-ol	−7.228
Ibuprofen	−7.385	Geranyl acetate	−7.211
Bornyl acetate	−7.349	Linalool	−7.073
Neryl acetate	−7.329	Eucalyptol	−6.999
Lavandulyl acetate	−7.224	*trans*-Linalool oxide	−6.992
Linalyl acetate	−7.208	*α*-Pinene	−6.980
trans-Linalool oxide	−7.133	Borneol	−6.945
cis-Linalool oxide	−7.018	*β*-Pinene	−6.929
Ketoprofen	−6.878	Ibuprofen	−6.929
Eucalyptol	−6.761	Fenchone	−6.917
Borneol	−6.727	Camphene	−6.913
Camphor	−6.690	Limonene	−6.904
Geraniol	−6.575	Camphor	−6.835

The best predicted binding energies for COX-1 and COX-2 were found to be for *β*-ocimene (Figure 4), with values of −8.463 and −8.353 kcal/mol, respectively, according to the molecular docking data shown in Table 3. Homnan et al. [22] looked at *β*-ocimene's ability to reduce inflammation. This hydrocarbon monoterpene strongly suppressed COX-2 activity and reduced prostaglandin E2 (PGE2) amounts in a dose-dependent way, with IC50 of 75.64 and much less than 20 g/mL, respectively. Kim et al. [23] studied the anti-inflammatory efficacy of EOs extracted from the Hallabong flower, which contained 11% β-ocimene. The hydro-distilled natural oils from the Hallabong flower (*Citrus medica* L. var. *sarcodactylis*) inhibited the lipopolysaccharide (LPS)-induced production of COX-2 enzyme on LPS-stimulated RAW 264.7 cells. Furthermore, it suppressed PGE2 production in a dose-dependent way, with an IC_{50} value of less than 0.01%. It is clear that the interaction energy of the limonene compound is lower in COX-2 (−6.904) than in COX-1 (−8.536), indicating that it is a selective COX-1 inhibitor. Nevertheless, only hydrophobic linkages between limonene and COX-1 could be seen, even though many amino acid residues are implicated in a specific binding mechanism.

Table 3. Summary of binding interactions and top-ranked LEO phytochemicals screened against COX-1 receptor (PDB ID: 3N8Y) binding site.

PubChem ID	Compound name	Binding affinity (kcal/mol)	Active amino acids residues	Distance (Å)	Category	Type
22311	Limonene	−8.536	LEU353	5.20786	Hydrophobic	Alkyl
			VAL318	4.48233		
			LEU321	4.09047		
			ILE492	4.95029		
			VAL318	4.93115		
			ILE492	4.84844		
			ALA496	3.85553		
			LEU321	5.04185		
			ALA496	4.71957		
			PHE350	5.39045	Hydrophobic	Pi-alkyl
			TYR354	4.42773		
			TRP356	4.93007		
17100	*α*-Terpineol	−8.535	VAL318	4.16085	Hydrophobic	Alkyl
			LEU321	4.26425		
			ILE492	5.17717		
			VAL318	4.00893		
			ALA496	3.92114		
			LEU353	4.90529		
			LEU321	5.24608		
			ALA496	4.62466		
			PHE350	5.37118	Hydrophobic	Pi-alkyl
			TYR354	4.48363		
			TRP356	4.93781		
7463	*p*-Cymene	−8.515	GLY495	4.23719	Hydrophobic	Amide-Pi stacked
			VAL318	4.34579	Hydrophobic	Alkyl
			LEU353	4.55204		
			LEU321	5.16326	Hydrophobic	Pi-alkyl
			ALA496	4.90846		
			PHE350	5.35724		
			TYR354	4.5216		
			TRP356	4.93121		
11142	*β*-Phellandrene	−8.486	VAL318	5.09711	Hydrophobic	Alkyl
			ILE492	4.24168		
			ALA496	4.4928		
			LEU353	5.4746		
			LEU321	5.43761		
			ILE492	5.36154		
			ALA496	4.34849		
			TYR354	4.54422	Hydrophobic	Pi-alkyl
			TRP356	4.96094		

Continued on next page

PubChem ID	Compound name	Binding affinity (kcal/mol)	Active amino acids residues	Distance (Å)	Category	Type
5281553	*β*-Ocimene	−8.463	ALA171	4.33901	Hydrophobic	Alkyl
			LEU359	5.24116		
			HIS176	4.48699	Hydrophobic	Pi-alkyl
			HIS176	4.8897		
			HIS176	4.64473		
			PHE179	4.52532		
			TYR354	5.19321		
			HIS355	4.96911		
			HIS355	4.2718		
			HIS355	4.50183		
			HIS357	4.60123		
11230	Terpinen-4-ol	−8.438	VAL318	4.4207	Hydrophobic	Alkyl
			ALA496	3.96373		
			VAL318	4.88286		
			ILE492	5.48398		
			ALA496	3.53657		
2662	Celecoxib	−8.191	GLU316	1.52341	H bond	Conventional H bond
			PHE549	2.06864		
			SER548	3.10647	H bond	Carbon H bond
			GLN319	3.36899	Halogen	Halogen (fluorine)
			GLN327	3.53859		
			GLU316	4.45539	Electrostatic	Pi-Anion
			HIS550	5.08501	Hydrophobic	Pi-Pi stacked
			HIS550	4.31237	Hydrophobic	Pi-alkyl
9782	Betamethasone	−8.041	HIS355	1.8315	H bond	Conventional H bond
			GLU423	1.68056		
			HIS357	3.63158	Halogen	Halogen (fluorine)
			HIS355	5.48416	Hydrophobic	Pi-alkyl

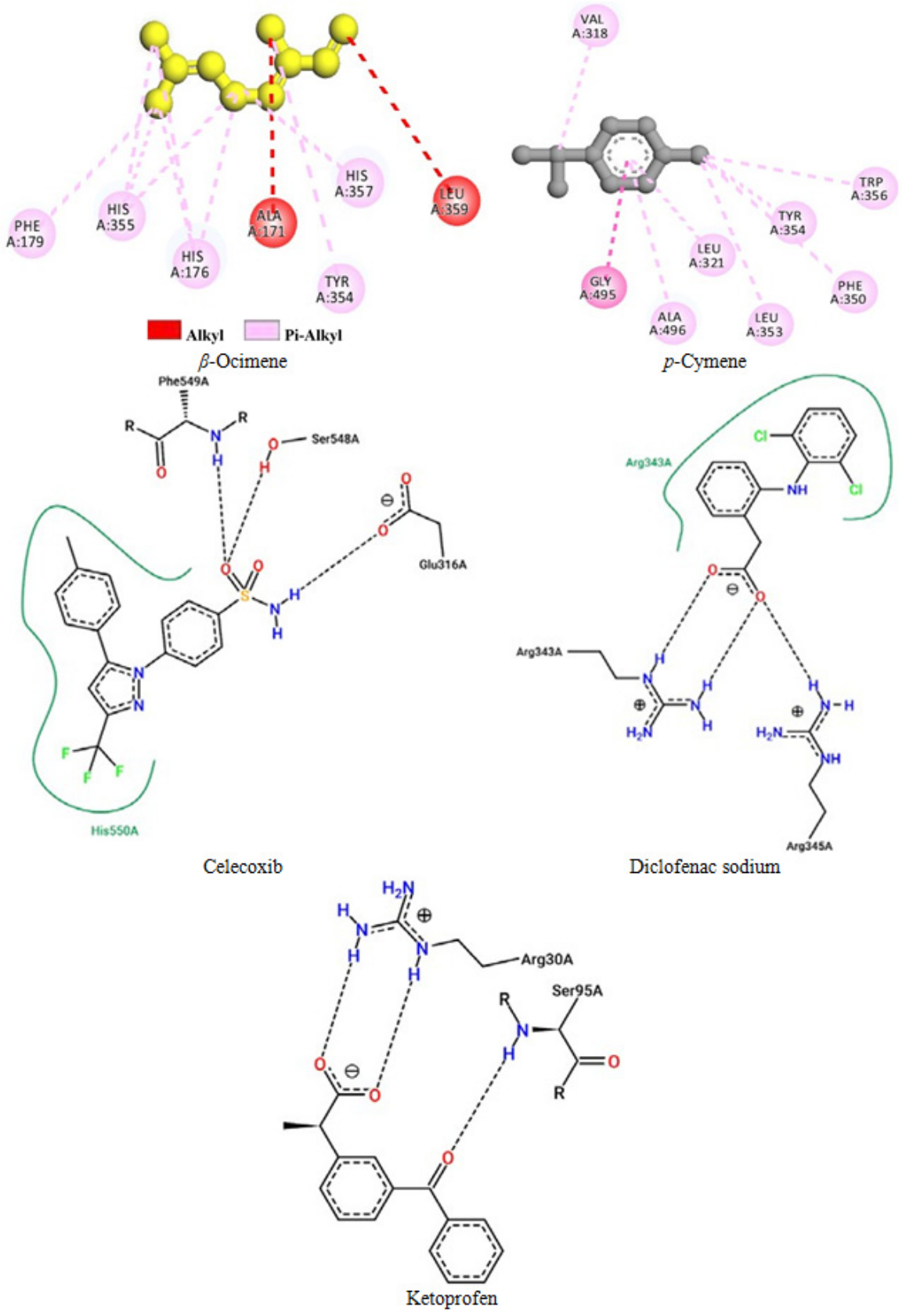


Figure 4. Snapshot represents the interaction between some selected ligands and COX-1.

By inhibiting the production of the inflammatory genes matrix metalloproteinase (MMP)-2 and -9, limonene significantly reduced clinical symptoms and intestinal mucosa destruction in rats with ulcerative colitis (UC). In addition, limonene treatment increased the expression of the proteins COX-2 and inducible nitric oxide synthase (iNOS) as well as antioxidants in UC rats [24]. In order to comprehend the biological and pharmacological effects of limonene on the production of pro-inflammatory mediators and cytokines in macrophage cells, Yoon et al. [25] performed an *in vitro* study and revealed that limonene prevents LPS from inducing PGE2 and nitric oxide (NO) production in RAW 264.7 cells. The synthesis of the iNOS and COX-2 enzymes was inhibited by limonene in a dose-dependent way. In addition, limonene dose-dependently reduced the production of TNF-α, IL-1β, and IL-6. These findings lead us to suggest that limonene could be a promising anti-inflammatory component.

Table 4. Summary of binding interactions and top-ranked LEO phytochemicals screened against COX-2 receptor (PDB ID: 3LN1) binding site.

PubChem ID	Compound name	Binding affinity (kcal/mol)	Active amino acids residues	Distance (Å)	Category	Type
2662	Celecoxib	−8.673	GLU257	2.19857	Hydrogen bond	Conventional H bond
			GLN256	2.02558		
			THR179	3.05721		
			ASN189	2.64444		
			HIS181	3.09038		Pi-donor H bond
			HIS181	4.93934	Hydrophobic	Pi-Pi T-shaped
			ILE241	4.7911		Alkyl
			LYS178	5.34418		Pi-alkyl
			VAL258	4.60764		
			VAL258	4.75717		
			HIS353	5.2587		
31253	Myrcene	−8.495	ALA169	4.05042	Hydrophobic	Alkyl
			LEU357	5.31713		
			LEU358	4.81577		
			HIS174	5.05216		Pi-alkyl
			HIS355	4.8889		
			HIS174	5.01		
			PHE177	4.71421		
			HIS353	4.63097		
			HIS174	4.97848		
			HIS353	4.03611		
			HIS355	4.48883		
			TRP354	4.65567		
			TRP354	4.85802		

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PubChem ID	Compound name	Binding affinity (kcal/mol)	Active amino acids residues	Distance (Å)	Category	Type
10586	*α*-Bisabolol	−8.458	THR179	2.30299	Hydrogen bond	Conventional H bond
			HIS181	2.22428		
			VAL258	5.14002	Hydrophobic	Alkyl
			LYS178	4.15079		
			VAL258	5.05092		
			VAL258	5.27629		
			HIS174	4.48034		Pi-alkyl
			HIS353	4.90952		
			HIS181	5.06576		
			HIS174	5.19112		
			HIS353	3.61505		
5281515	*β*-Caryophyllene	−8.400	VAL258	3.86278	Hydrophobic	Alkyl
			HIS174	5.46788		Pi-alkyl
			HIS174	4.71157		
			HIS181	4.93027		
			HIS174	5.2873		
			HIS174	4.58658		
			HIS353	4.28092		
5281553	*β*-Ocimene	−8.353	LEU358	4.86083	Hydrophobic	Alkyl
			ALA169	4.49891		
			LEU357	5.33171		
			HIS174	5.05417		Pi-alkyl
			HIS355	4.23129		
			HIS174	4.94839		
			PHE177	4.929		
			HIS353	4.4817		
			HIS174	4.89993		
			HIS353	4.2914		
5018304	Diclofenac Na	−8.313	GLN170	2.90417	Hydrogen bond	Conventional H bond
			HIS174	1.4732		
			HIS353	4.37635	Hydrophobic	Pi-Pi stacked
			HIS355	5.5618		Pi-Pi T-shaped
			HIS174	5.29974		Pi-alkyl
			HIS353	4.33105		
			HIS355	3.98766		
			VAL414	4.0637		
637566	Geraniol	−8.303	TRP354	1.82951	Hydrogen bond	Conventional H bond
			HIS355	2.93434	Hydrophobic	Pi-sigma
			ALA169	4.25559		Alkyl
			HIS174	4.49101		Pi-alkyl
			HIS174	4.86783		
			PHE177	4.76602		
			HIS353	4.24043		

Myrcene exhibits the greatest binding affinity for COX-2 (−8.495 kcal/mol) when compared to standard medications and other investigated substances (Table 3), despite binding to COX-2 residues ALA169, LEU357, LEU358, HIS174, HIS353, HIS355, PHE177, and TRP354 (Table 4 and Figure 5). Its lower binding affinity to COX-1 (−8.332 kcal/mol) than that of limonene, *α*-terpineol, and *p*-cymene, however, suggests that it is more competitive for the COX-2 enzyme. It interacts with hydrophobic residues of amino acids on COX-2 via associations with alkyl and pi-alkyl groups.

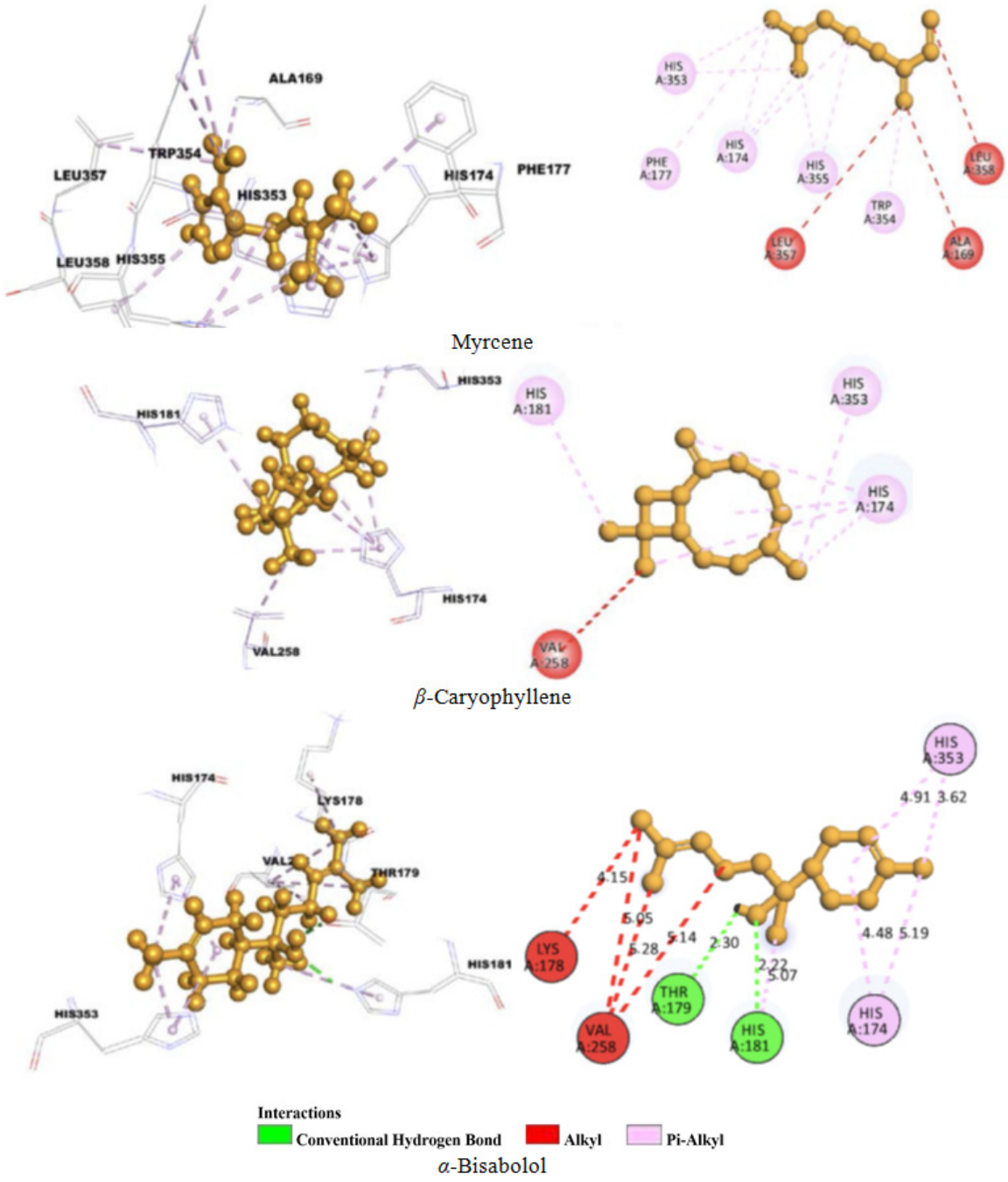


Figure 5. Snapshot represents the interaction between some selected ligands and COX-2.

Additionally, EOs extracted from aromatic herbs and medicinal plants that contain 10% or less of myrcene have been found to have anti-inflammatory benefits. There is evidence that the oil of *Eremanthus erythropappus* reduces edema and leukocyte extravasation in several organs, including the hind paw and lung [26,27]. Another myrcene-rich EO reduced the levels of pro-inflammatory cytokines and COX-2 within eight hours in a rat model of severe synovitis [28]. In arthritic human chondrocytes, pure myrcene reduced the expression of iNOS and interfered with the IL-1 signaling pathway [29]. These data demonstrate that myrcene and myrcene-containing EOs have potent anti-inflammatory and analgesic properties.

3.2. In silico pharmacokinetic prediction

Drug-likeness characteristics are important in determining the quality of emerging anti-inflammatory compounds. Based on their structure, early predictions of the pharmacokinetic behavior of prospective plant-derived EO compounds should aid in the identification of more safe and more efficient leads for further preclinical studies. In this research, we examined five of the most relevant pharmacokinetic and ADME indicators for LEO compounds to see if they may be used as drugs. These anticipated results would demonstrate the compounds' potential as drugs and point to the likelihood of them serving as an oral anti-inflammatory substitute.

Table 5 shows the outcomes of using Osiris Property Explorer to estimate the drug-likeness of compounds based on several chemical descriptors. The majority of substances have partition coefficients (clog *P*) values less than 5, although others (such as *β*-caryophyllene) defy the Lipinski rule of five for lipophilicity and may have low oral bioavailability and penetration. The Lipinski rule of five is clearly broken by the most powerful molecule (*β*-caryophyllene), which has a log *P* value of 5.49. In contrast, the other five compounds are predicted to be orally active and have log *P* values ranging from 4.47 to 1.81. Additionally, compounds are attractive drug candidates for additional study and development because of their lower TPSA score (zero), which indicates favorable drug-like properties, and their high drug-likeness score. The ADME properties and toxicological profile of the LEO molecules were also investigated using an online admetSAR cheminformatic system to detect prospective and secure drug candidate(s) and to screen out substances that are most likely to fail in successive stages of the development process due to unfavorable ADMET properties.

Table 5. Drug-likeness prediction through OSIRIS property explorer.

	Mutagenic	Tumorigenic	Irritant	Reproductive effect	clog *P*	TPSA	Solubility	Drug likeness	Drug score
Celecoxib	-	-	-	-	2.59	86.36	−4.17	−8.11	0.37
Myrcene	-	+	+	+	4.29	0	−2.5	−7.82	0.09
α-Bisabolol	-	-	+	-	4.47	20.23	−3.16	−1.47	0.27
β-Caryophyllene	-	-	-	-	5.49	0	−3.66	−6.48	0.31
β-Ocimene	-	-	+	-	4.23	0	−2.33	−5.46	0.24
Diclofenac Na	-	-	-	-	1.81	52.16	−4.64	2.3	0.71
Geraniol	-	-	+	-	3.49	20.23	−1.89	−3.57	0.27

Drugs' destiny *in vivo*, or ADME, has a complete or partial impact on how they behave pharmacologically. The blood/brain partition coefficient (Plog BB), Caco-2 cell permeability (PCaco), human intestinal absorption (log HIA), P glycoprotein nonsubstrate and non-inhibitor (log

pGI), and probability of Caco-2 cell permeability (log Papp) are among the *in silico* projected pharmacokinetic (ADME) attributes of all studied ligands and are shown in Table 6.

According to the findings in Table 6, the chemical *β*-caryophyllene is not carcinogenic, whereas myrcene and *β*-ocimene failed the AMES toxicity test and were therefore found to be carcinogenic. The calculated LD50 dosage (1.4040–1.6722 mol/kg) for the selected terpenes in a rat acute toxicity model appears to be secure enough for research on *in vivo* anti-inflammatory efficacy. A molecule's degree of intestinal absorption after oral delivery is measured by the HIA score. If the score is below one, the absorption can be quite high. All terpenes in the current investigation had HIA scores that range from 0.9538 to 0.9926, indicating that they will be well assimilated from the gastrointestinal tract [30]. The estimated cell permeability (PCaco-2) of selected terpenes, which ranges from 0.7228 to 0.6327, is also reported to be within the acceptable range (−1 to +1), aiding in the transit of the bioactive compounds to the gut and, thus, improving absorption. It may be deduced from the anticipated log BB score (0.9536–0.9312) that these terpenes have the highest likelihood of crossing the blood-brain barrier and having an effect on the function of the central nervous system.

Table 6. ADME prediction for the top-ranked compounds using the admetSAR toolbox.

	Blood-brain barrier	Human intestinal absorption	Caco-2 permeability	P-glyco protein substrate	P-glyco protein inhibitor	Renal organic cation transporter	AMES toxicity	Carcin ogens	Caco-2 permeability (LogPapp, cm/s)	Rat acute toxicity (LD50, mol/kg)
Celecoxib	BBB+	HIA+	Caco2+	-	-	-	-	-	1.0149	2.3719
	0.9713	1	0.8866	0.9287	0.8619	0.8582	0.7185	0.7905		
Myrcene	BBB+	HIA+	Caco2+	-	-	-	-	+	1.5571	1.404
	0.9478	0.9538	0.7228	0.6521	0.701	0.8183	0.9227	0.5684		
β-Caryophyllene	BBB+	HIA+	Caco2+	+	-	-	-	-	1.5225	1.4345
	0.9536	0.9926	0.6327	0.5779	0.5989	0.8269	0.9167	0.6863		
β-Ocimene	BBB+	HIA+	Caco2+	-	-	-	-	+	1.5641	1.6722
	0.9312	0.9764	0.6913	0.6792	0.7425	0.8829	0.8917	0.7261		
Diclofenac Na	BBB+	HIA+	Caco2+	-	-	-	-	-	1.8481	2.855
	0.9827	0.8998	0.8196	0.8827	0.8557	0.8776	0.8443	0.6747		
Geraniol	BBB+	HIA+	Caco2+	-	-	-	-	-	1.2481	1.6146
	0.9375	0.9846	0.6445	0.5851	0.8865	0.8179	0.9132	0.5055		

3.3. PASS predictions biological activity

The biological activity spectra of previously known phytochemical compounds were obtained using the online PASS version. These predictions were assessed and made available in Table 7 for flexible usage. The range of biological activities that a chemical substance exhibits when it interacts with different types of biological entities is known as its biological activity spectrum. It allows us to combine information from several sources in the same training set, which is required since no one publication covers all of the diverse aspects of a compound's biological action.

Table 7. The PASS prediction findings reveal the biological activity spectrum and toxicity of the top-ranked LEO terpenes.

Compound name	Pa	Pi	Biological activity spectrum predicted by PASS	Pa	Pi	Possible adverse & toxic effects
Celecoxib	0.955	0.002	Cyclooxygenase 1 inhibitor	0.671	0.016	Pseudoporphyria
	0.859	0.003	Non-steroidal anti-inflammatory agent	0.569	0.013	Ulcer, peptic
	0.809	0.007	Antiarthritic	0.571	0.02	Methemoglobinemia
Myrcene	0.941	0.004	Mucomembranous protector	0.829	0.004	Skin irritation, high
	0.896	0.005	Antineoplastic	0.786	0.01	Hyperglycemic
	0.836	0.012	Antieczematic	0.791	0.026	Toxic, respiration
α-Bisabolol	0.847	0.005	Apoptosis agonist	0.862	0.016	Behavioral disturbance
	0.83	0.013	Antieczematic	0.843	0.003	Skin irritation, moderate
	0.727	0.006	Antithrombotic	0.822	0.02	Conjunctivitis
β-Caryophyllene	0.915	0.005	Antineoplastic	0.836	0.004	Sensitization
	0.897	0.005	Antieczematic	0.788	0.005	Irritation
	0.745	0.011	Antiinflammatory	0.545	0.062	Nephrotoxic
β-Ocimene	0.928	0.004	Antieczematic	0.82	0.004	Skin irritative effect
	0.806	0.004	Carminative	0.777	0.004	Lacrimal secretion stimulant
	0.91	0.004	Mucomembranous protector	0.816	0.004	Skin irritation, high
Geraniol	0.953	0.003	Mucomembranous protector	0.951	0.002	Skin irritation, moderate
	0.77	0.004	Antiulcerative	0.925	0.005	Anemia
	0.766	0.001	Antiviral (rhinovirus)	0.878	0.004	Hyperglycemic
Limonene	0.961	0.001	Carminative	0.856	0.005	Gastrointestinal disturbance
	0.896	0.005	Antieczematic	0.811	0.015	Respiratory failure
	0.812	0.01	Antineoplastic	0.675	0.005	Sedative
α-Terpineol	0.862	0.005	Respiratory analeptic	0.887	0.011	Euphoria
	0.837	0.003	Carminative	0.839	0.015	Ocular toxicity
	0.825	0.014	Antieczematic	0.838	0.019	Behavioral disturbance
p-Cymene	0.919	0.004	Mucomembranous protector	0.961	0.009	Toxic, respiration
	0.881	0.002	Carminative	0.928	0.003	Hematemesis
	0.884	0.006	Antieczematic	0.878	0.004	Gastrointestinal hemorrhage
β-Phellandrene	0.916	0.004	Antieczematic	0.827	0.012	Ulcer, aphthous
	0.883	0.002	Carminative	0.799	0.005	Irritation
	0.83	0.009	Antineoplastic	0.725	0.032	Conjunctivitis
β-Ocimene	0.928	0.004	Antieczematic	0.82	0.004	Skin irritative effect
	0.91	0.004	Mucomembranous protector	0.777	0.004	Lacrimal secretion stimulant
	0.858	0.005	Apoptosis agonist	0.754	0.01	Hypomagnesemia
Terpinen-4-ol	0.838	0.011	Antieczematic	0.852	0.007	Hematemesis
	0.829	0.003	Carminative	0.779	0.023	Ulcer, aphthous
	0.796	0.02	Antiseborrheic	0.702	0.015	Optic neuritis

Pa (probability "to be active") estimates the chance that the studied compound is belonging to the sub-class of active compounds. Pi (probability "to be inactive") estimates the chance that the studied compound is belonging to the sub-class of inactive compounds.

The probable activity (Pa) values were higher than Pa > 0.5, and the probable inactivity (Pi) scores were extremely near to 0, demonstrating that the compound is highly expected to demonstrate these activities. It is also notable that the selected terpenes have very suitable molecular properties and predictable pharmacological activities against COX-1 and COX-2 enzymes.

A literature survey corroborates the docking finding, revealing that LEO compounds have antibacterial properties [31] and function as antioxidants by reducing lipid peroxidation [32,33]. As a result, we believe that the chosen phytoconstituents will boost immunity while inhibiting COX enzymes [34]. Anti-inflammatory phytochemical constituents with stronger docking scores, higher binding energies, and better interaction with conserved catalytic residues that may induce inhibition/blockade of the COX protein pathways might be viable preventive and curative options [35,36].

4. Conclusions

There is a pressing need to create new substances with therapeutic action in order to develop drugs with fewer negative effects. The current work assesses the potential for binding interactions between phytocompounds from LEO and COX enzymes by molecular docking. Molecular docking revealed that limonene has the highest negative binding affinity in complex with COX-1, followed by α-terpineol and *p*-cymene. Myrcene exhibits the greatest binding affinity for COX-2 when compared to standard medications, followed by α-bisabolol and β-caryophyllene. The LEO's chosen phytochemicals were found to be highly selective, have substantial binding potential, and react strongly with COX-1 and COX-2 receptors by computational screening. Best docking scores, ligand placement at the region of inhibition, interaction profiles with catalytic residues, and appropriate ADMET values all point to the likelihood that myrcene and β-ocimene may be effective COX inhibitors. Based on satisfying Lipinski's rule five, these terpenes can also be identified as prospective therapeutic candidates.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

B.S.B.: original draft preparation; A.B.: review and editing. All authors have read and agreed to the published version of the manuscript.

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