

Anti-inflammatory Potential of some Eudesmanolide and Guaianolide Sesquiterpenes

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Abstract

Ten sesquiterpene lactones isolated from *Anvillea garcinii* (Burm.f.) DC ethanolic extract were assessed for their anti-inflammatory potential by myeloperoxidase (MPO) activity assignment, and mice paw swelling model. 3 α ,4 α -10 β -trihydroxy-8 α -acetyloxyguaian-12,6 α -olide (1), *epi*-vulgarin (3), 9 α -hydroxyparthenolide (4), garcinamine C (7), garcinamine D (8), garcinamine E (9), and 4, 9-dihydroxyguaian-10(14)-en-12-olide (10) showed explicit anti-inflammatory activity in rodent paw oedema and MPO assignment.

The findings of this study showed that the α -methylene γ -lactone moiety does not always guarantee an anti-inflammatory effect, but the presence of proline at the C₃ of the lactone ring improves the binding of sesquiterpene lactones with MPO isoenzymes, resulting in a more potent inhibition.

Introduction

Natural remedies and knowledge of their therapeutic potential have been used in nations for a long time, and these natural-based medications have been used to treat various diseases (Hamed et al.2017a,Hamed et al.2017b,Seri et al.2017). Based on evidence-based therapeutical findings in treating non-communicable diseases, interest in identifying natural bioactive metabolites and designing modern synthetic lead molecules based on them has grown in recent years. According to statistical data, more than 70% of the population in various countries currently uses natural remedies alone or in combination with official drugs (Gurib-Fakim.2006,Ríos et al.2015). Surveys of traditional Middle Eastern medicines revealed that a dozen of this region's medicinal plants are members of the Asteraceae family (Abu-Odeh;Talib.2021,Bahmani et al.2014,Michel et al.2020). *Anvillea* is a well-known *Asteraceae* genus that is widely distributed in Western Asia. Aerial parts of it are used by regional populations in various forms (infusions, decoctions, or tropical) to treat various ailments such as swelling, skin joint inflammation, arthritis, sore throats, chest colds, gastrointestinal disorders, and pulmonary disorders (Hammiche;Maiza.2006,Jamila;Mostafa.2014). Many studies have revealed the abundance of sesquiterpenes in these genera. For example, 9 α -hydroxyparthenolide and 8 α , 9 α -epoxyparthenolide were isolated from *A. radiata* aerial parts, and garcinamine E, 4 α ,9 α ,10 α -trihydroxyguaia11(13) en-12,6 α -olide, germacrene, and 9 β -hydroxyparthenolide-9-*O*- β -D-glucopyranoside were isolated from *A. garcinii* (Kandouli et al.2017,Perveen et al.2020). In addition to phytochemical studies, numerous studies have discovered that sesquiterpene lactones have anti-inflammatory activity via various mechanisms, including NO production and TNF- α inhibition. For instance, cynaropicrin, helenalin, tricarabrols A–C, budlein A, 8 α -hydroxyhirsutinolide, 8 α -hydroxyl-1-*O*-methylhirsutinolide, and many others (Cho et al.2000,Lyss et al.1997,Valério et al.2007,Youn et al.2012,Yuan et al.2020). The aim of this study is to evaluate the anti-inflammatory potential of ten sesquiterpene lactones isolated from, *A. garcinia*.

Materials And Methods

Plant Material

During the flowering stage of the plants, leaves of *A. garcinia* (Asteraceae) were collected in Riyadh (Saudi Arabia) in March 2020 and identified in the College of Pharmacy, King Saud University, with voucher number KSU-21599. This sample was placed in the King Saud University Herbarium (Department of Pharmacognosy), Riyadh, Saudi Arabia.

Extraction and purification of sesquiterpene lactones

The extraction, isolation, and structure elucidation methods have been the same as published earlier (Aati et al.2021,Perveen et al.2018a,Perveen et al.2020,Perveen et al.2019,Perveen et al.2018b). One kg of *A. garcinia* dried leaves was extracted three times with 15 L of 80 percent methanol, and the filtrate was concentrated by a rotary evaporator under reduced pressure. This crude extract (100 g) was suspended in 1 L H₂O and then subsequently fractionated by chloroform, *n*-butanol, and residual water. The *n*-butanol fraction was subjected to silica gel column chromatography and eluted with a gradient chloroform: methanol (9.5:0.5→1.0:9.0) as mobile phase. Nine sub-fractions (sub-fr1–9) were afforded for further purification, which was completed by using silica gel (with gradient mixtures of chloroform /methanol and dichloromethane/ methanol) and C-18 reverse phase column chromatography (with a gradient mixture of water/methanol). Silica gel F254 precoated plates (E. Merck, Darmstadt, Germany) were used for future purification. For compound detection, a ceric sulfate spray was applied at 254 nm.

Based on these procedures, ten known sesquiterpene lactone molecules (1–10) were yielded from *A. garcinia*, and their structures were identified based on various 1D and 2D-NMR spectroscopic methods. The proton and carbon 1D and 2D-NMR data were gathered with a Bruker AMX-500 spectrometer [1H NMR, TOCSY and ROESY, HSQC, COSY, NOESY, and Carbon-13 (125 MHz)]. Chemical shifts (δ ; in ppm, relative to tetramethyl silane (TMS) as standard) and coupling constants (J ; in Hertz scale (Hz)) are reported.

The purified sesquiterpene lactones were identified as 3 α ,4 α -10 β -trihydroxy-8 α -acetyloxyguaian-12,6 α -olide (**1**), 3 α ,4 α -10 β -trihydroxy-guaian-12,6 α -olide (**2**), epi-vulgarin (**3**), 9 α -hydroxyparthenolide (**4**), 9 β -hydroxyparthenolide (**5**), 9 α -hydroxyparthenolide-9-O- β -D-glucopyranoside (**6**), garcinamine C (**7**), garcinamine D (**8**), 4,9-dihydroxyguaian-10(14)-en-12-olide (**9**), and garcinamine E (**10**) (Fig. 1). The spectral data is attached as a supplementary file.

Experimental animals

Male BALB/c mice (weighing 25–30 g) were kept in a standard environmental condition with 12–12 hours of the light-dark cycle at 23 $\pm$ 1°C, 40% relative humidity, and a standard cereal-based diet. All experimental procedures were conducted based on Shiraz University of Medical Science guidelines about the use and care of laboratory animals under the institutional ethics committee (IR.SUMS.REC.1399.1352). Investigating paw inflammation in the current study also complies with the ARRIVE guidelines (Kilkenny et al.2010). The animals were divided into 13 groups (n = 5 per group). Acute carrageenan paw oedema was used as an inflammation model, with 200 μ L carrageenan solution (1% w/v) injected into the right plantar tissue of the hind paw. Indomethacin (5 mg/kg, i.p., as a standard anti-

inflammatory drug) and isolated compounds (10 mg/kg, i.p.) were injected one hour before the paw edema inflammation initiation. It should be noted that due to the small amount of purified molecules (approximately 10 mg), we could use one dose of this substance in animal studies. The anti-inflammatory potential of isolated compounds was then evaluated 3.5 hours after carrageenan-induced inflammation (Sharma et al.2004).

Assessment of paw edema

A volume displacement plethysmometer (Ugo Basile, Italy) was used to measure mice paw swelling 1 hour before oedema initiation and 3.5 hours after treatments. The anti-inflammatory potential of each compound was calculated based on the hind paw swelling inhibition according to the previously reported equation: % Inflammation = $(A-B/B) \times 100$. In this formula, A is carrageenan-induced hind paw thickness after 3.5 h, and B is early hind paw thickness before carrageenan injection (Sharma et al.2004).

Myeloperoxidase (MPO) activity assignment

Following deep anesthesia (thiopental, 80 mg/kg, i.p), 100 mg of each paw tissue was homogenized in a hexadecyl-trimethyl-ammonium bromide (HTAB) solution prepared by dissolving 0.5% w/v HTAB in 50 mM potassium phosphate buffer; pH = 6 at 4°C. Samples were centrifuged (3000 g, 20 min, 4°C), and 100 µL, the supernatants were added to 2.9 mL of potassium phosphate buffer (50 mM) containing O-dianisidine hydrochloride (16.7 mg/100 mL) and 0.0005% hydrogen peroxide. After 5 min incubation of samples at 25°C by adding 100 µL of 1.2 M hydrochloric acid, any possible reaction was stopped, and each sample absorbance was measured by an EPOCH® plate reader at 400 nm (Liu et al.1999).

Preparation of ligands and receptor

The myeloperoxidase crystal protein structures (7LAE, 7LAG, and 7LAN) were collected from the RCSB protein database. Chem3D 17.1 was used to perform 3D energy minimizations on all isolated sesquiterpenes using the MM2 method. For ligand docking, visualization, and any ligand-receptor binding interaction, iGEMDOCK Version 2.1 (<http://gemdock.life.nctu.edu.tw/dock/>) was used. Several parameters contribute to the iGEMDOCK function scoring, including hydrogen bonding, electrostatic bonding, Van der Waals, and steric energies (Vishvakarma et al.2019,Ya-Di et al.2011). This software automatically selects the receptor active box center and ligand binding site space before computing the ligand-receptor conformational binding interaction based on a generic evolutionary method. An accurate docking mode was run with the following parameters: binding site size of 8, Å, the population size of n = 800, generations n = 80, and the number of solutions n = 10. Co-crystallized ligands were used to ensure docking study validation (ligand orientation and position).

Control docking results showed a very good alignment between the original orientation of co-crystallized ligands and the experimental orientation of the docked compounds in active boxes (Yang;Chen.2004).

Based on the total minimum binding energy, the scores of all compounds were considered for further screening of myeloperoxidase activity inhibitory potential (kilocalories per mole). The ligands' geometries,

as well as cavities' box cavities and amino acid interactions, were analyzed using iGEMDOCK Version 2.1 and Discovery Studio visualizer Version 16. 1.0. 15350 (Sharma;Raghav.2021).

ADME properties

Studies on the absorption, distribution, metabolism, and elimination (ADME) of molecule properties are beneficial in new compound prediction for drug-likeness, membrane permeability, absorbance, metabolism, and other necessary parameters (Lipinski.2004, Veber et al.2002). In this study, various biological, chemical, and drug-likeness factors were calculated using an online server, <https://admetmesh.scbdd.com/>, and <http://swissadme.ch/> (Satpathy et al.2021, Wang et al.2022).

Statistical analysis

The mean $\pm$ standard deviation (SD) of at least 5 experiments was applied for all materials. The anti-inflammatory activity of the paw edema and MPO inhibitory results were calculated using GraphPad Prism version 7 (GraphPad Prism Software, San Diego, CA). A one-way analysis of variance (ANOVA) was used to compare all groups statistically. The significant level was set at $p \leq 0.05$.

Results And Discussion

An earlier study on the *n*-butanol fraction of an ethanolic extract of *A. garcinii* aerial parts revealed a high concentration of sesquiterpenoids in this plant. Various chromatographic approaches yielded ten known compounds (**1–10**) (Fig. 1) (Aati et al.2021, Perveen et al.2020). The compounds' structures were determined using one- and two-dimensional NMR spectroscopy and electrospray ionization mass spectrometry (ESI-MS). The following ten molecules were identified: 3 α ,4 α -10 β -trihydroxy-8 α -acetyloxyguaian-12,6 α -olide (**1**), 3 α ,4 α -10 β -trihydroxy-guaian-12,6 α -olide (**2**), epi-vulgarin (**3**), 9 α -hydroxyparthenolide (**4**), 9 β -hydroxyparthenolide (**5**), 9 α -hydroxyparthenolide-9-O- β -D-glucopyranoside (**6**), garcinamine C (**7**), 9-garcinamine-D (**8**), 4,9-dihydroxyguaian-10(14)-en-12-olide (**9**) and garcinamine E (**10**) (Fig. 1).

The paw edema anti-inflammatory assay on compounds (**1–10**; 10 mg/kg, i.p) revealed that the following five compounds (**1, 4, 7, 8**, and **10**) had the best effect, though there was only a very slight difference between these compounds and indomethacin as the standard. Similarly, compounds **1, 4, 7, 8**, and **10** exhibited significant anti-inflammatory effects in the MPO assay (Figs. 2 and 3). In this case, the aforementioned compounds outperformed their better potential.

In conclusion, based on our findings, garcinamine C-E had the best anti-inflammatory effect in this study. According to these findings and computational predictions, it appears that certain structural compartments play an essential role in the anti-inflammatory effects of these compounds (Fig. 1). Although it seems that the green highlighted part is a fundamental element for any anti-inflammatory effect, the proline or other substituents (highlighted in red) attached to this fundamental part play a booster role; some of the less effective parts in chemical structures are also determined by yellow color. Previous studies have confirmed our findings about these structural compartments of sesquiterpene

lactones. For example, saussureamines A and B (two prolinated sesquiterpene lactones isolated from *Saussurea lappa* Clarke roots) have significant inhibitory potential on NO production in lipopolysaccharide (LPS)-activated mouse peritoneal macrophages. Pulchellamin G, a powerful anti-inflammatory sesquiterpene lactone with anti-inflammatory effects on nitric oxide (NO), PGE2, TNF- α , and IL-1 β , is another example (Lee et al.2013,Matsuda et al.2000). Similar outcomes were also reported for helenalanprolines A and B, which inhibited NO production in LPS macrophages with IC₅₀ values of 15.8 and 13.5 μ M, respectively (Cai et al.2020). Matsumoto et al. have reported the anti-inflammatory potential of some amino acid-sesquiterpene lactones, including cynaropicrin, 11 β ,13-dihydrocynaropicrin, 3 β -hydroxy-8 α -[(S)-3-hydroxy-2-methylpropionyloxy] guaia-4(15),10(14),11(13)-trien-1 α , 5 α , 6 β -H-12,6-olide, and 3 β -hydroxy-8 α -[2-methoxymethyl-2-propenyloxy] guaia-4(15),10(14),11(13)-trien-1 α , 5 α , 6 β -H-12,6-olide from artichoke leaves (Matsumoto et al.2021). In other studies, the anti-inflammatory potential of other amino acid-sesquiterpene lactones such as tectoside, xanthatin-13-(pyrrolidine-2-carboxylic acid) was also reported: (Idres et al.2021,Kim et al.2013).

Different physicochemical parameters could affect the biological potential of molecules; additionally, an assessment of these factors may provide a valuable guide for any future drug development strategy. Lipophilicity, solubility, topological polar surface area, hydrogen-bond acceptor, and blood-brain barrier permeability are among the factors that have a significant impact on molecule activities. Molecule lipophilicity has been considered one of the most important factors in drug development, which is measured by the octanol/water partition coefficient, and in an ideal situation, it should be ≤ 5 . Other valuable parameters include the solubility of the molecule logS (should not be ≤ 6), the hydrogen-bond donor (HBD; should be ≤ 5), and the hydrogen-bond acceptor (HBA; should be ≤ 10). In addition to the previous items, we also used topological polar surface area (TPSA; should be $\leq 130 \text{ \AA}^2$) which is an essential item in ligand transport properties (Veber et al.2002,Vishvakarma et al.2019). Similar parameters were also included: gastrointestinal absorption (GI), blood-brain barrier permeability (BBB), permeability glycoprotein (P-gp), cytochrome P450 isoenzymes inhibition (CYP), molinspiration based Log P (miLog P; positive values are biologically active), and Lipinski's rule. The results showed that the TPSA, GI, and miLog P of the top compounds (compounds 1, 4, 7, 8, and 10) are within the range predicted by experimental and computational results. Docking binding energy and the active box amino acid cavity residue interactions (for the top molecules) showed promising results (**Table 1**, Fig. 4). Crystallographic studies of some MPO inhibitors' binding profiles in enzyme active sites revealed an important role for Hem 601 residue in ligand-protein interaction, as well as Arg 127, His 95, Glu 130, Phe 254, 295, and Pro 108 (Hu et al.2021). Different interactions, such as hydrogen bonding, π -stacking, and cation- π bounding were reported to be consistent with our computational findings based on the ligand structures (Forbes et al.2013,Shaw et al.2020). A molecular docking study between compounds (**1**, **4**, **7**, **8**, and **10**) with a grid activity site showed that Arg 127, Phe 99, His 95, Pro 108, and Hematin (Hem) 605 have significant roles in active box interactions. More computational analysis was showed proline and acetyl moieties in structures caused enhance ligand-active pocket interaction although presence of large more polar group such as glucose in compound 6 reduced active box amino acids interconnection with ligand through chemical space hindering. The presence of a small polar moiety at the C₃ of the lactone

ring improves the binding of sesquiterpene lactones with MPO isoenzymes, resulting in stronger inhibition.

Abbreviations

ADME: absorption, distribution, metabolism, and elimination; BBB: blood-brain barrier permeability; CYP: cytochrome P450 isoenzyme inhibition; ESI-MS: electrospray ionization mass spectrometry; GI: gastrointestinal absorption; HBA: hydrogen-bond acceptor; HBD: hydrogen-bond donor; HTAB: hexadecyltrimethyl-ammonium bromide; LPS: lipopolysaccharide; MPO: myeloperoxidase; NO: nitric oxide; TNF- α : tumor necrosis factor alpha; TPSA: topological polar surface area

Declarations

Acknowledgments

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Competing Interests

The remaining authors have no competing or conflicts of interest to declare.

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Table 1

Table.1. The biological and chemical properties of sesquiterpene lactones with better binding energy to MPO isoenzymes

Properties	The top selected compounds.					
	Comp. <i>1</i>	Comp. <i>4</i>	Comp. <i>7</i>	Comp. <i>8</i>	Comp. <i>10</i>	
Log <i>S</i>	-1.25	-2.25	-1.13	-1.13	-0.66	
Solubility	Very soluble	Soluble	Soluble	Soluble	Very soluble	
No. Heavy atoms	24	19	27	27	28	
No. of rotational bonds	2	0	3	3	3	
No. H-bond acceptors	7	4	7	7	8	
Num. H-bond donors	3	1	2	2	4	
Log <i>P</i> _{o/w}	1.98	2.50	2.14	2.51	1.96	
TPSA (Å ²)	113.29	59.06	99.60	99.60	127.53	
GI absorption	High	High	High	High	High	
BBB permeant	No	Yes	No	No	No	
miLog <i>P</i>	0.48	1.62	0.95	0.95	0.49	
CYP3A4 inhibitor	No	No	No	No	No	
<i>P-gp</i> substrate	Yes	No	Yes	Yes	Yes	
The binding energy of ligand to MPO isoenzymes (kcal/mol)						
MPO isoenzymes	Comp. <i>1</i>	Comp. <i>4</i>	Comp. <i>7</i>	Comp. <i>8</i>	Comp. <i>10</i>	Con *
7LAN	-103.33	-104.21	-112.18	-120.37	-108.14	-146.11
7LAE	-119.12	-105.78	-109.20	-128.91	-112.26	-129.73
7LAG	-115.11	-100.51	-124.15	-120.77	-121.88	-150.76

* Indomethacin was used as the control compound.

Figures

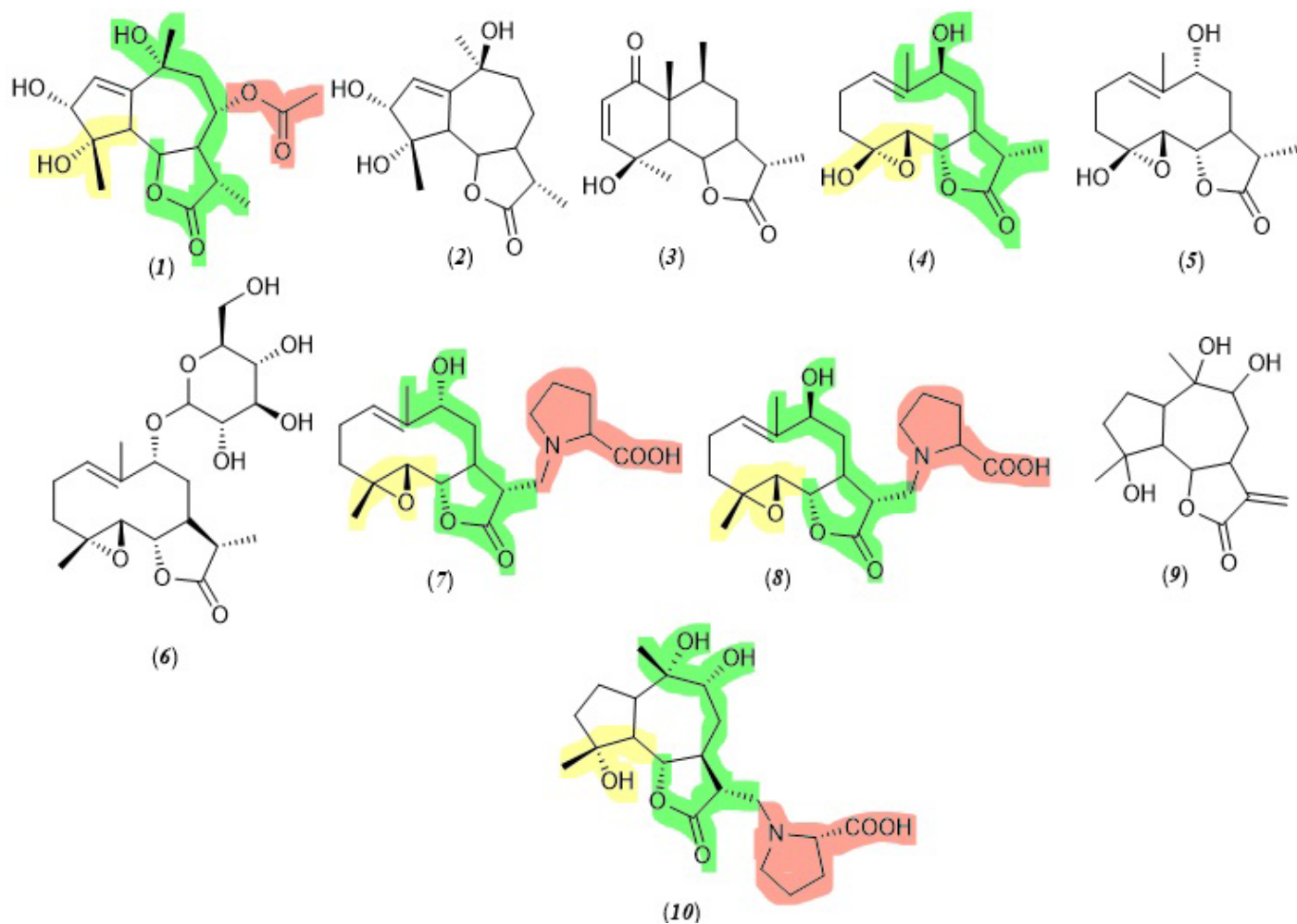


Figure 1

Chemical structure of Ten sesquiterpene lactones isolated from *A. garcinia*. The interactions of different molecular compartments with MPO isoenzymes are shown: the fundamental element (green highlighted), the booster element (red highlighted), and the less effective parts (yellow highlighted).

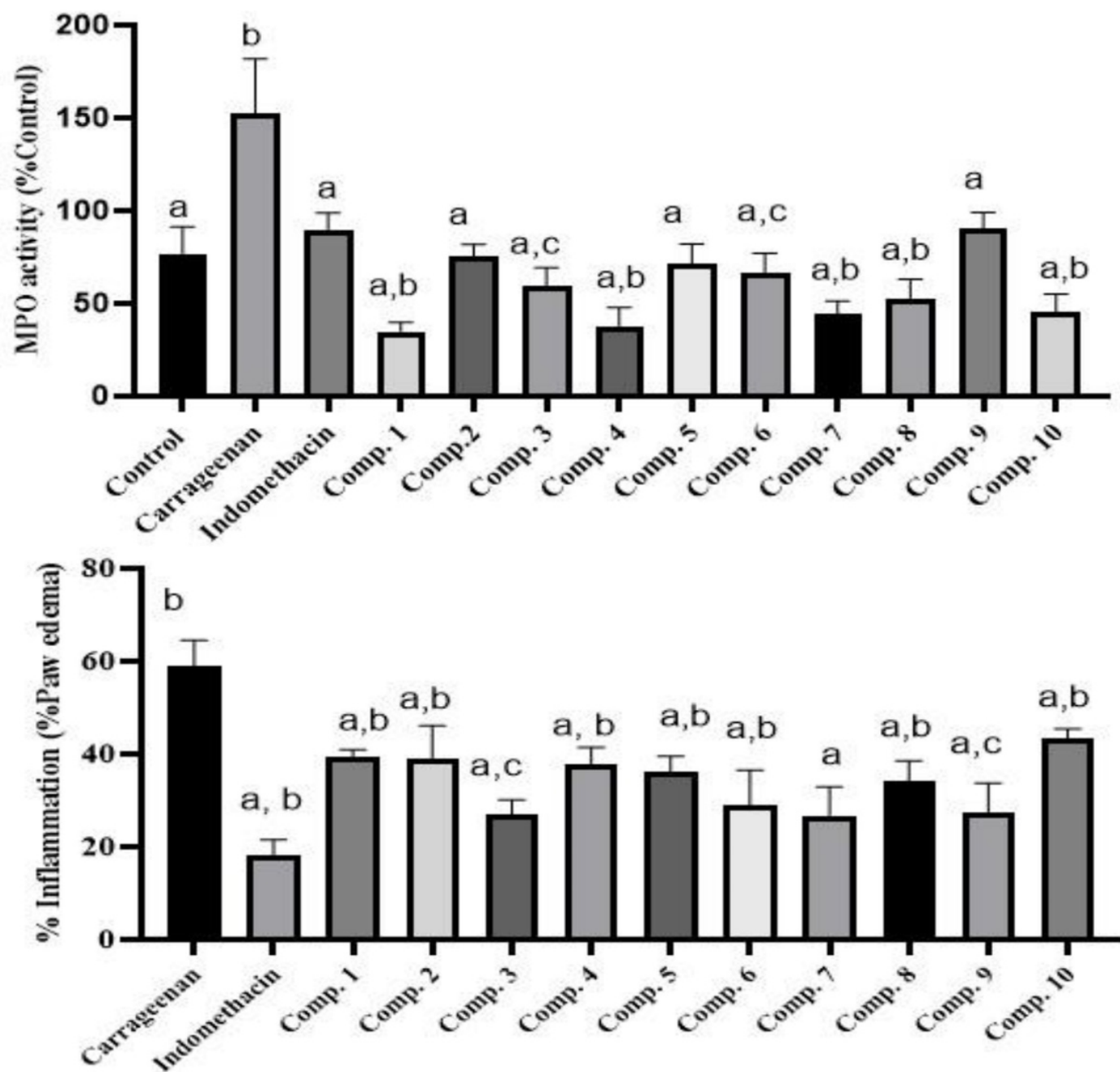


Figure 2

MPO inhibition potential and paw edema anti-inflammatory potential of compounds 1-10. ^a Significantly different with carrageenan $p \leq 0.0001$; ^b Significantly different with indomethacin $p \leq 0.0001$; ^c Significantly different with indomethacin $p \leq 0.05$ (n=5).

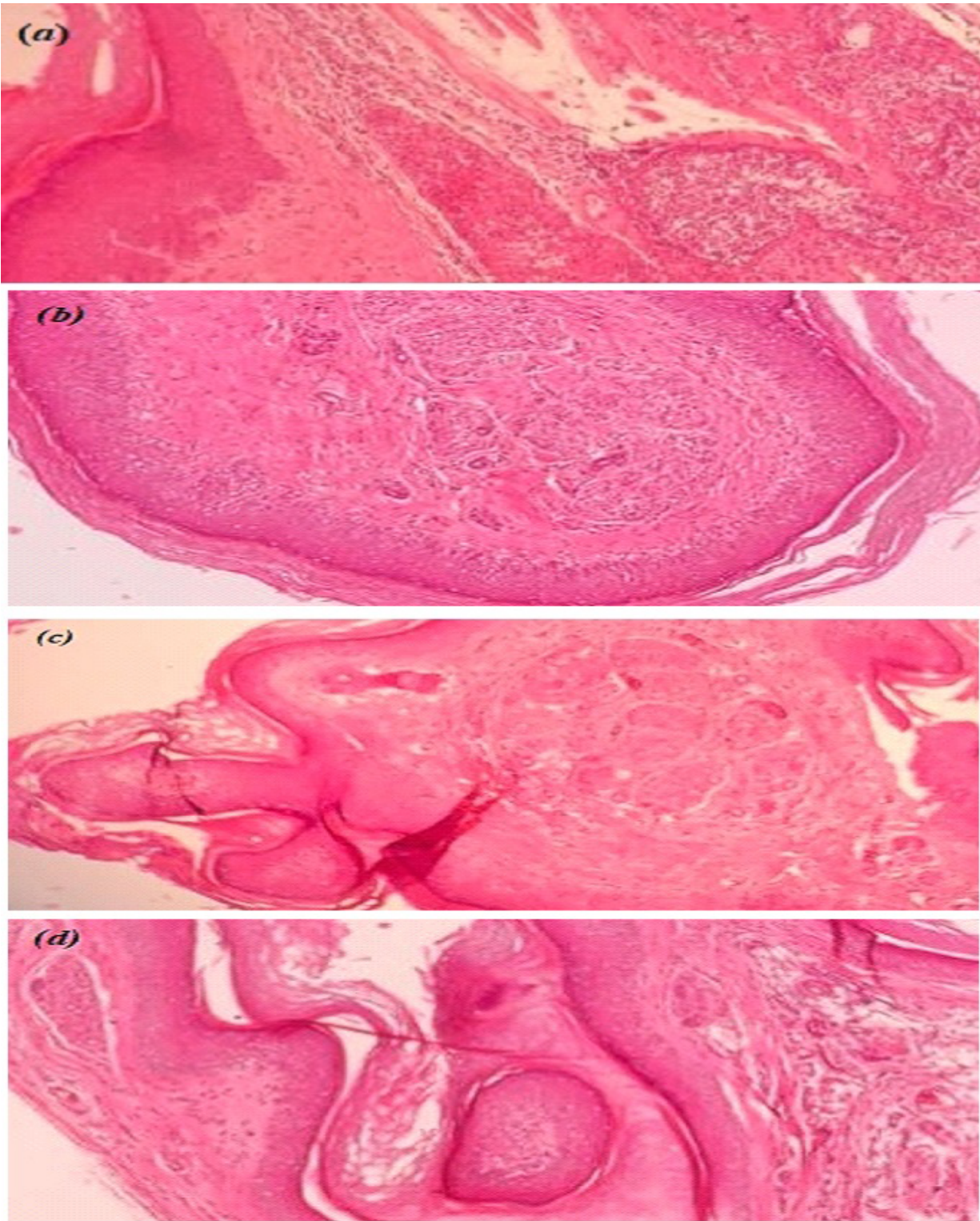


Figure 3

Microscopic evaluation of garcinamine C (7) and *epi*-vulgarin (3) anti-inflammatory effect in carrageenan-induced paw edema model. (a) paw tissue exposed to carrageenan after 3 hours. (b) post-treated paw tissues with garcinamine C. (c) post-treated paw tissues with *epi*-vulgarin. (d) post-treated paw tissues with indomethacin.

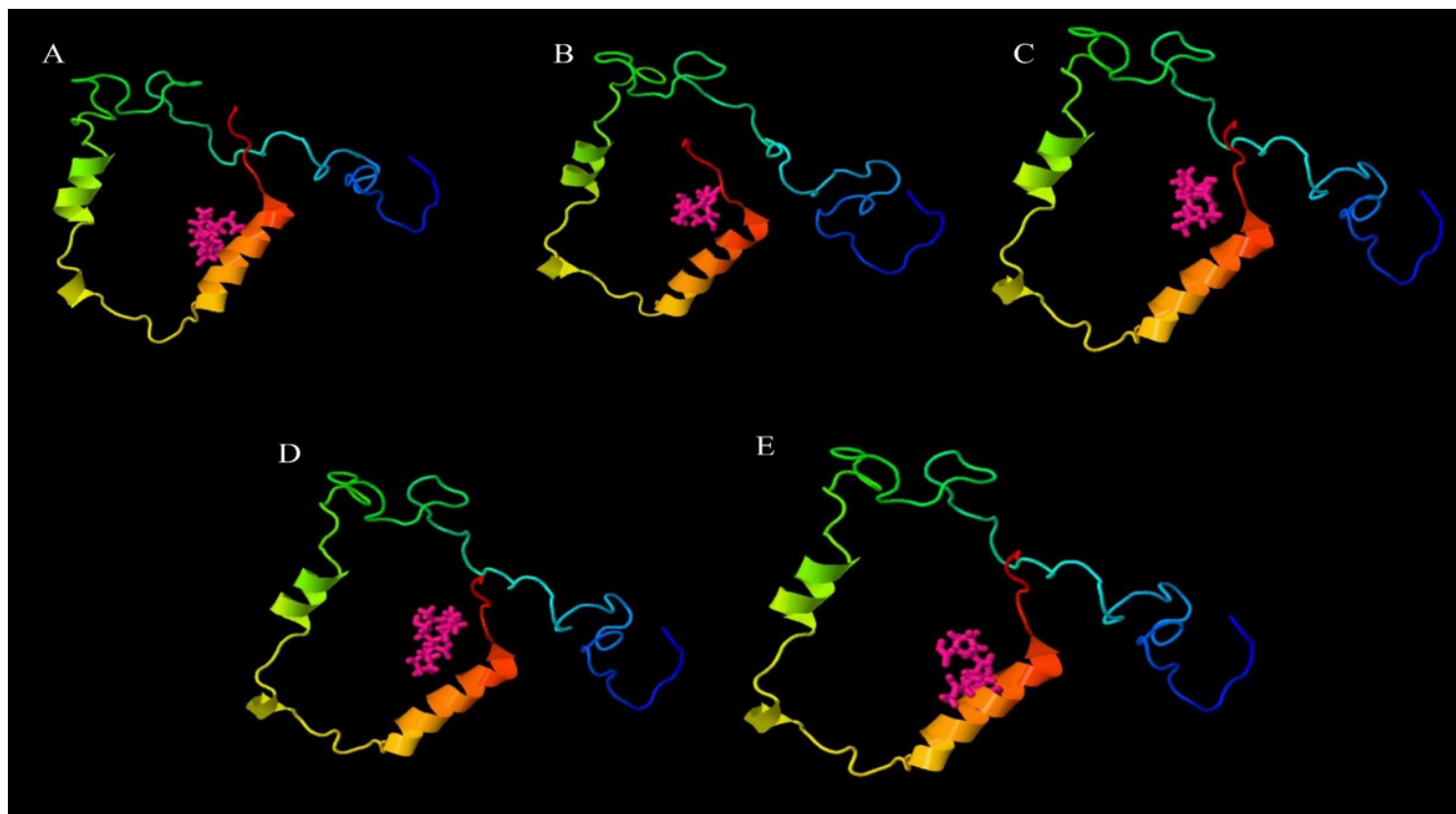


Figure 4

The top selected compounds [*1* (A), *4* (B), *7* (C), *8* (D), *10* (E)] in the center of the binding pocket of 7LAG; docked compounds (violet part) showed in the binding site.

Supplementary Files

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