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Original Research Article

Anti-Inflammatory Potentials of Elaeocarpus sphaericus Schum Fruit Compounds by Molecular Docking Approach

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ABSTRACT

Elaeocarpus sphaericus Schum fruit is a wild fruit and usually use as traditional herb medicine. In previous studies, *Elaeocarpus sphaericus* Schum promoted antifungal, antioxidant and anti-inflammatory activities through *in vitro* and *in vivo* observations. This study screened the *Elaeocarpus sphaericus* Schum fruit compounds as cyclooxygenase – 2 inhibitors through structure-activity relationship (SAR) and molecular docking approaches. The bioactivities of the compounds of the fruit were predicted through their structure by PASS two-way drug web server. Selected *Elaeocarpus sphaericus* Schum compounds with high anti-inflammatory activities were redocked with cyclooxygenase – 2 protein using Molegro virtual docker version 5.0, then visualized by Discovery Studio version 21.1.1. The 14 of 72 identified compounds showed high anti-inflammatory activity. Study results revealed that 14 compounds bound to COX – 2 protein, seven compounds of them blocked COX – 2 at inhibitor sites. The identified compounds were Malic acid, Xylose, Benzoic acid, Succinic acid, Fumaric acid, Rhamnose, and Ethyl Butyrate. In conclusion, the seven identified compounds actively inhibited COX – 2 protein and could be potential anti-inflammatory drug leads. Further *in vivo* investigation are required for future study.

***Keywords*:** Anti-inflammatory, Cyclooxygenase – 2, Docking, *Elaeocarpus sphaericus*, SAR

Introduction

Inflammation is a natural process in the immune system. It is a response to foreign substances by the body, such as chemical stimuli, parasites, bacteria, viruses, and antigens. The inflammatory responses could be normal because it activates many pro-inflammatory pathways and eliminates antigens in the body.[1, 2] However, the failure of antigen elimination could stimulate the pro-inflammatory cytokines and immune cells to be stressed, leading to hyperinflammation. Inflammation is triggered by several inflammatory mediators, such as interleukin, tumor necrosis factor-alpha (TNF-α), nitric oxide (NO), and Prostaglandin E2 (PGE2), which is activated by immune cells. The release of PGE2 is regulated by the expression of the cyclooxygenase 2 (COX-2) enzyme[3]. The activation of COX-2 stimulates cytokines, which further activate endothelial cells. Thus, to prevent hyperinflammation, the overactivity of COX-2 should be inhibited.[4, 5]
Herbs have been recognized for the richness of bioactive compounds and have been used for centuries to prevent and treat numerous diseases due to their safety, therapeutic properties, and accessibility [6–9]. Recently, the value of the therapeutic activity of herbs also showed promise in research. Some bioactive compounds in herbs have also been shown as anti-inflammatory agents.

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The Rudraksha (India) or genitri (Indonesia) has been known for its medicinal properties.[10] Phytochemical studies found that genitri is rich in triterpenes, tannins, alkaloids, and flavonoids that could exhibit antifungal, antimicrobial.

Materials and Methods

Ligand retrieval and bioactivity prediction
A total of 72 bioactive compounds were identified from *E. sphaericus* (genitri) fruit. The 3D structures were downloaded from PubChem NCBI database (Table 1). Those 72 bioactive compounds were screened for their bioactivity by using PASS online program. At last, 14 selected ligands were discovered to have high potential activity as anti-inflammtory agents and were chosen for docking simulation.

Protein retrieval
The 3D structure of the targeted protein, cyclooxygenase – 2, was used in this study. The COX-2 structure was downloaded from a protein data bank with ID 3MDL, and the native substrate, (2S)-2,3-dihydroxypropyl (5Z,8Z,11Z,14Z)-icosa-5,8,11,14-tetraenoate was used as a control[14].

Molecular Docking
Ligands and protein were re-docked with cyclooxygenase – 2 protein at specific grid, X= 21,07; Y = 15,67; Z = 66,26; radius 13. Docking was carried out by Molegro Virtual Docker version 5.0 with setting optimizer initial string; population size = 50; cavity = true; creation Energy Threshold = 100 (15–17). pose Generator = 10,10,30; recombine = true; max.simplex = 750; simplex steps = 300; simplex distance factor = 1; cluster threshold = 1.00; keep max.poses = 5.

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Table 1: Ligands and accession number of genitri fruit's compounds

Compounds	Group	CID	Compounds	Group	CID
Fumaric acid	Dicarboxyclic acid	444972	epigallocatechin	Tannin	72277
Succinic acid	Dicarboxyclic acid	1110	Chlorogenic acid	Tannin	1794427
Benzoic acid	Aromatic acid	243	Syringin	Glycoside	5316860
Ethyl butyrate	Ester	7762	δ-tocopherol	Steroid	92094
Malic acid	Dicarboxyclic acid	525	γ-tocopherol	Steroid	92729
Cinnamic acid	Aromatic acid	444539	Campesterol	Terpenoid	173183
p-coumaric acid	Aromatic acid	637542	Isofucosterol	Terpenoid	5281326
Rhamnose	Glucose	25310	24-methylene pollinastanol	Steroid	118987255
Xylose	Glucose	135191	stigmasterol	Steroid	5280794
Vanillic acid	Aromatic acid	8468	β-sitosterol	Steroid	222284
esculetin	Coumarin	5281416	β-amyrin	Terpenoid	73145
caffeic acid	Aromatic acid	689043	Cycloeucalenol	Terpenoid	101690
scopoletin	Coumarin	5280460	obtusifoliol	Terpenoid	65252
Ferulic acid	Carboxyclic acid	445858	cycloartenol	Terpenoid	92110
Elaeokanine C	Alkaloid	442855	α-tocopherol	Steroid	14985
elaeocarpine	Alkaloid	280286	kaempferol-3-rhamnoside	Flavonoid	5316673
elaeocarpenine	Alkaloid	16747727	24-methylene cycloartanol	Terpenoid	94204
Isoelaeocarpine	Alkaloid	44423026	kaempferol-3-O-Dglucosid	Flavonoid	25203515
Grandisine B	Alkaloid	11402679	kaempferol-7-O-β-Dglucosid	Flavonoid	
isoelaeocarpiline	Alkaloid	280287	luteolin-7-glucoside	Flavonoid	5280637
Grandisine D	Alkaloid	16040172	phylloquinone	Quinone	5284607
elaeocarpidine	Alkaloid	355436	Elaeocarpucin E	Terpenoid	57379940
Naringenin	Flavonoid	932	Elaeocarpucin H	Terpenoid	57379943
isoelaeocarpicine	Alkaloid	44423024	Elaeocarpucin A	Terpenoid	57379694
Grandisine F	Alkaloid	16086543	Elaeocarpucin B	Terpenoid	57379695
Grandisine A	Alkaloid	11482807	Elaeocarpucin C	Terpenoid	57379696
Grandisine C	Alkaloid	16086540	Elaeocarpucin G	Terpenoid	57379942
Grandisine E	Alkaloid	16086541	Elaeocarpucin F	Terpenoid	57379941
Habbemine A	Alkaloid	44423032	Cucurbitacin E	Terpenoid	5281319
Habbemine B	Alkaloid	44423034	Cucurbitacin F	Terpenoid	5281320
Luteolin	Flavonoid	5280445	Rutin	Flavonoid	5280805
Kaempferol	Flavonoid	5280863	isorhamnetin-3-Orutinoside	Flavonoid	5481663
Catechin	Tannin	9064	rhamnazin-3-rutinoside	Flavonoid	15631731
Grandisine G	Alkaloid		isorhamnetin-3-rutinoside4'-rhamnoside	Flavonoid	73822546
Trifoliol	Coumestan	5487671	Geraniin	Tannin	3001497
Quercetin	Flavonoid	5280343	elaeocarpusin	Tannin	

Evaluator: Grid Resolution: 0.3. Torsion scheme: 1; Damp factor: 1; Include ligand electrostatics: No; Use Sp2Sp2 bond term: No; Skip torsion term: No; Use EPenal: Yes; Use EIntra: Yes; Use EInter: Yes; Max iteractions: 1500; Ignore structural waters: No; Ignore cofactors: No; Tabu Clustering: disabled, treshold: 2, penalty: 100, and RMSD calc: id. Soften Potential: false. Number of running 10x.

Complex visualization and data analysis
Ligands – protein complexes were visualized by using PyMol 2.2 and Discovery studio version 21.1.1. the data were analyzed by using Discovery studio version 21.1.1.

Results and Discussion

Anti-inflammatory potential activity prediction
The 72 genitri compounds were predicted for their anti-inflammatory activity with PASS online program. Result presented in heatmap chart showed that half of genitri compounds, 32 of the 72, were potential as anti-inflammatory agent (Figure 1). From 32 compounds found in heatmap, twelve of the compounds have high anti-inflammatory intestinal activity. Fumaric acid, Succinic acid, Benzoic acid, Ethyl butyrate, Cinnamic acid, p-coumaric acid, Rhamnose, Xylose, Vanillic acid, esculetin, caffeic acid, scopoletin, Ferulic acid, Grandisine D, Naringenin, Luteolin, Kaempferol, Catechin, Trifoliol, and Quercetin

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showed high anti-inflammatory activity. The twelve selected compounds also performed as low as cyclooxygenase inhibitors, lipoxygenase inhibitors and interleukin antagonists.

Molecular docking revealed cyclooxygenase – 2 inhibitor

The interaction of COX-2 with bioactive compounds in genitri is represented in Table 2. Superimposed ligands – COX-2 complex showed 14 genitri compounds posed at the same active sites of (2S)-2,3-dihydroxypropyl (5Z,8Z,11Z,14Z)-icosa-5,8,11,14-tetraenoate as control inhibitor (Figure 2). However, only 7 compounds were bound to the inhibitor sites of COX-2. The active sites of (2S)-2,3-dihydroxypropyl (5Z,8Z,11Z,14Z)-icosa-5,8,11,14-tetraenoate was PHE529, SER530, LEU117, and LEU531 with the binding energy of -385.4 kJ/mol. Ferulic acid bind to COX-2 with -252.4 kJ/mol through PHE518, GLN192, LEU352, and VAL523 amino acid residues (Figure 3). The bioactive compounds of genitri, p-Coumaric acid, Caffeic acid, Scopoletin, Cinnamic acid, Esculetin, and Vanillic acid, bound to COX-2 with high binding energy, however none of those compounds posed binding to COX-2 active sites. Benzoic acid, malic acid, ethyl butyrate, succinic acid, rhamnose, and xylose of genitri posed binding with SER530and PHE529 amino acid residues as cyclooxygenase active sites. Malic acid – cyclooxygenase – 2 produced binding energy -176.8 kJ/mol and interacted with ASN375 and SER530 residues. Xylose generated binding energy -175.4 kJ/mol, similar with malic acid. The active residues of xylose – COX-2 was SER530, MET522, TYR385, and GLY526. Benzoic acid was bound to COX-2 through PHE529, GLY533, PHE209, and LEU534 amino acid residues with binding energy -162.6 kJ/mol (Figure 2; Table 2). Interestingly, succinic acid bound to COX-2 through two amino acid residues, TYR385 and MET522, and performed higher binding energy than Fumaric acid, Rhamnose, and Ethyl butyrate.

The TYR385 and MET522 amino acid residues that were identified in Malic acid, Xylose, Benzoic acid, and Succinic acid were potential COX-2 inhibitors. The binding energy of ligands – COX-2 complex was determined by the types of interaction, number of hydrogen bonds, and ligands – protein complex. The high number of hydrogen bonds and hydrophobic interaction contributed to the low binding energy, with various ligands – protein interaction. The interaction types of ligands – protein complexes were hydrogen bonds, hydrophobic interactions, unfavorable bonds, and van der Waals forces (Table 2, Figure 3). Decreased binding energy correlated with tight ligands – protein interaction, varied interaction types, and number of hydrogen and hydrophobic interactions[18–21]. Though the binding energy of all bioactive compounds were not as high as others, the binding of ligands to protein active sites was more important to define ligands potency.

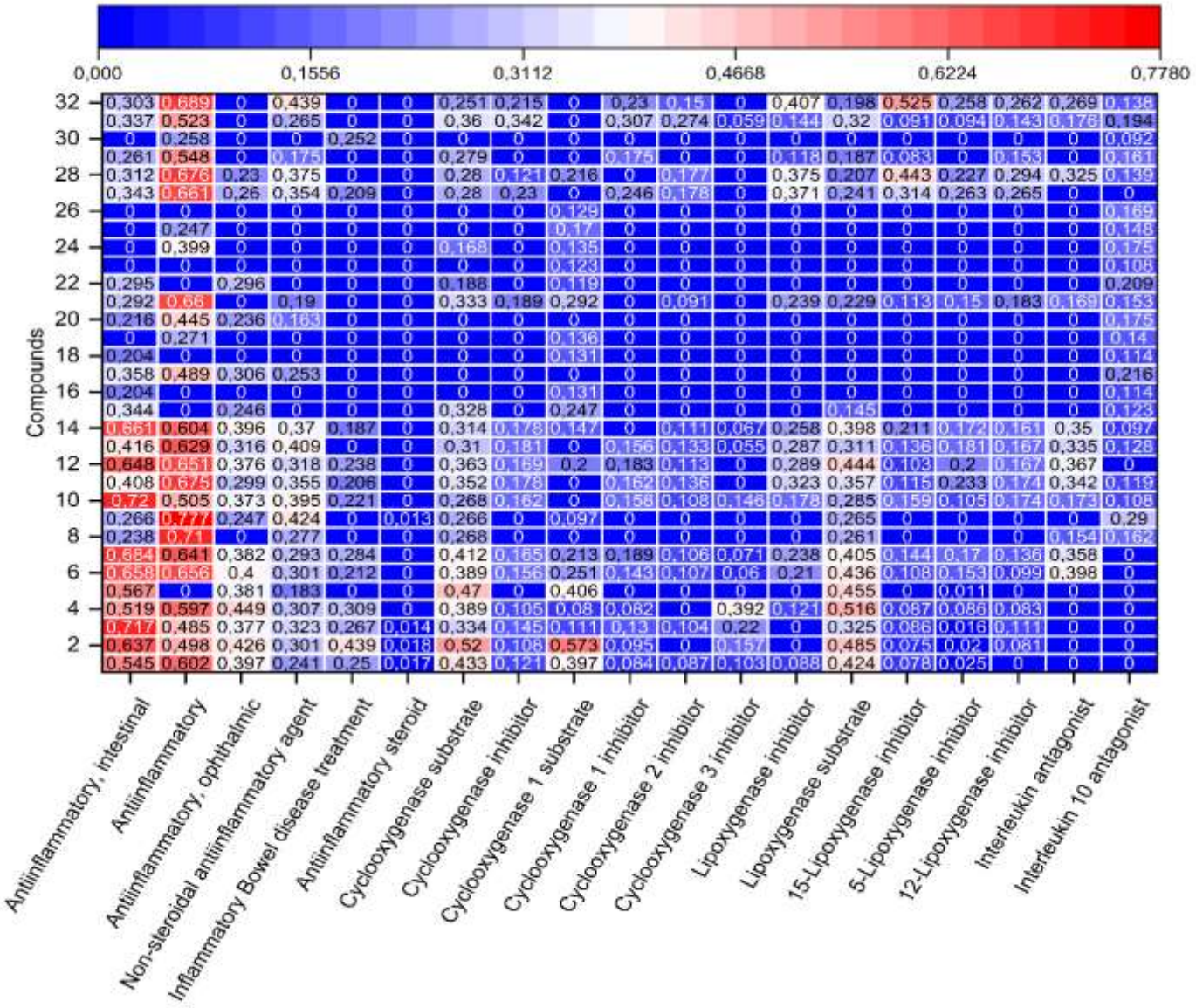

Figure 1: Heatmap chart of structure activity relationship of 32 compounds from genitri fruit extract. High anti-inflammatory activity is shown in red color, while low activity is show in blue color.

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Table 2: Interactions of COX-2 with bioactive compounds in genitri

Ligand	Name	Distance	Types	Categories
(2S)-2,3-dihydroxypropyl (5Z,8Z,11Z,14Z)-icosa-5,8,11,14-tetraenoate (control)	:10:H6 - A:PHE529:O	1.67	Hydrogen Bond	Conventional Hydrogen Bond
	:10:H39 - A:SER530:OG	2.09	Hydrogen Bond	Conventional Hydrogen Bond
	:10:H2 - A:SER530:O	2.99	Hydrogen Bond	Carbon Hydrogen Bond
	:10:H4 - A:SER530:O	2.94	Hydrogen Bond	Carbon Hydrogen Bond
	:10:C23 - A:LEU117	5.43	Hydrophobic	Alkyl
	:10:C23 - A:LEU531	4.00	Hydrophobic	Alkyl
Ferulic acid	A:PHE518:N - :10:O4	3.14	Hydrogen Bond	Conventional Hydrogen Bond
	:10:H10 - A:GLN192:OE1	2.11	Hydrogen Bond	Conventional Hydrogen Bond
	:10 - A:LEU352	4.60	Hydrophobic	Pi-Alkyl
	:10 - A:VAL523	3.98	Hydrophobic	Pi-Alkyl
p-Coumari c acid	A:ALA378:N - :10:O3	2.69	Hydrogen Bond	Conventional Hydrogen Bond
	:10:H8 - A:ASN375:OD1	1.69	Hydrogen Bond	Conventional Hydrogen Bond
	A:GLY533:CA - :10	3.11	Hydrophobic	Pi-Sigma
	A:PHE209 - :10	4.03	Hydrophobic	Pi-Pi Stacked
Caffeic acid	A:PHE518:N - :10:O4	3.11	Hydrogen Bond	Conventional Hydrogen Bond
	:10:H6 - A:MET522:O	2.27	Hydrogen Bond	Conventional Hydrogen Bond
	:10:H8 - A:GLN192:OE1	2.12	Hydrogen Bond	Conventional Hydrogen Bond
	A:VAL523:CG1 - :10	3.92	Hydrophobic	Pi-Sigma
	:10 - A:LEU352	4.70	Hydrophobic	Pi-Alkyl
	:10 - A:ALA527	5.47	Hydrophobic	Pi-Alkyl
Scopoletin	:10:H5 - A:MET522:O	2.08	Hydrogen Bond	Conventional Hydrogen Bond
	A:SER353:CA - :10:O4	2.98	Hydrogen Bond	Carbon Hydrogen Bond
	:10:H7 - A:GLY526:O	2.39	Hydrogen Bond	Carbon Hydrogen Bond
	:10 - A:VAL349	5.34	Hydrophobic	Pi-Alkyl
	:10 - A:LEU352	4.23	Hydrophobic	Pi-Alkyl
	:10 - A:LEU352	4.83	Hydrophobic	Pi-Alkyl
	:10 - A:VAL523	4.55	Hydrophobic	Pi-Alkyl
	:10 - A:VAL523	5.34	Hydrophobic	Pi-Alkyl
Cinnamic acid	A:ALA378:N - :10:O2	3.01	Hydrogen Bond	Conventional Hydrogen Bond
	:10:H8 - A:ASN375:OD1	1.71	Hydrogen Bond	Conventional Hydrogen Bond
	A:GLY533:CA - :10	3.17	Hydrophobic	Pi-Sigma
	A:PHE209 - :10	3.98	Hydrophobic	Pi-Pi Stacked
	:10 - A:LEU534	5.15	Hydrophobic	Pi-Alkyl
Esculetin	:10:H6 - A:VAL349:O	2.36	Hydrogen Bond	Conventional Hydrogen Bond
	A:LEU352:CD1 - :10	3.88	Hydrophobic	Pi-Sigma
	A:MET522:SD - :10	5.50	Other	Pi-Sulfur
	A:TRP387 - :10	5.23	Hydrophobic	Pi-Pi T-shaped
	:10 - A:LEU352	5.25	Hydrophobic	Pi-Alkyl
	:10 - A:VAL523	4.65	Hydrophobic	Pi-Alkyl
Vanillic acid	:10:H7 - A:TYR355:OH	2.25	Hydrogen Bond	Conventional Hydrogen Bond
	:10:H8 - A:LEU352:O	1.68	Hydrogen Bond	Conventional Hydrogen Bond
	A:SER353:CA - :10	3.33	Hydrophobic	Pi-Sigma
	A:VAL523:CG1 - :10	3.49	Hydrophobic	Pi-Sigma
	A:VAL523:CG2 - :10	3.14	Hydrophobic	Pi-Sigma
Malic acid	A:ASN375:ND2 - :10:O4	2.83	Hydrogen Bond	Conventional Hydrogen Bond
	:10:H4 - A:SER530:O	2.19	Hydrogen Bond	Conventional Hydrogen Bond
	:10:H6 - A:SER530:OG	1.79	Hydrogen Bond	Conventional Hydrogen Bond
Xylose	:10:H8 - A:SER530:OG	2.92	Hydrogen Bond	Conventional Hydrogen Bond
	:10:H9 - A:MET522:O	2.03	Hydrogen Bond	Conventional Hydrogen Bond
	:10:H10 - A:TYR385:OH	2.23	Hydrogen Bond	Conventional Hydrogen Bond
	:10:H4 - A:GLY526:O	2.68	Hydrogen Bond	Carbon Hydrogen Bond
Benzoic acid	:10:H6 - A:PHE529:O	1.46	Hydrogen Bond	Conventional Hydrogen Bond
	A:GLY533:CA - :10	3.08	Hydrophobic	Pi-Sigma
	A:PHE209 - :10	3.98	Hydrophobic	Pi-Pi Stacked
	:10 - A:LEU534	5.37	Hydrophobic	Pi-Alkyl
Succinic acid	A:TYR385:OH - :10:O3	3.08	Hydrogen Bond	Conventional Hydrogen Bond

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Ligand	Name	Distance	Types	Categories
	:10:H6 - A:MET522:O	1.67	Hydrogen Bond	Conventional Hydrogen Bond
Fumaric acid	A:TYR385:OH - :10:O4	3.14	Hydrogen Bond	Conventional Hydrogen Bond
	:10:H3 - A:MET522:O	2.41	Hydrogen Bond	Conventional Hydrogen Bond
	:10:H3 - A:VAL523:O	2.60	Hydrogen Bond	Conventional Hydrogen Bond
	A:SER530:CB - :10:O2	3.43	Hydrogen Bond	Carbon Hydrogen Bond
Rhamnose	:10:H9 - A:MET522:O	2.39	Hydrogen Bond	Conventional Hydrogen Bond
	:10:H10 - A:TYR385:OH	2.80	Hydrogen Bond	Conventional Hydrogen Bond
	:10:H11 - A:MET522:O	1.62	Hydrogen Bond	Conventional Hydrogen Bond
	:10:C6 - A:VAL349	4.20	Hydrophobic	Alkyl
Ethyl Butyrate	A:SER530:OG - :10:O1	3.17	Hydrogen Bond	Conventional Hydrogen Bond
	:10:H4 - A:PHE209	2.79	Hydrophobic	Pi-Sigma
	:10:C3 - A:ILE377	4.52	Hydrophobic	Alkyl
	A:PHE205 - :10:C6	5.32	Hydrophobic	Pi-Alkyl
	A:PHE381 - :10:C3	4.25	Hydrophobic	Pi-Alkyl
	A:TYR385 - :10:C6	5.08	Hydrophobic	Pi-Alkyl

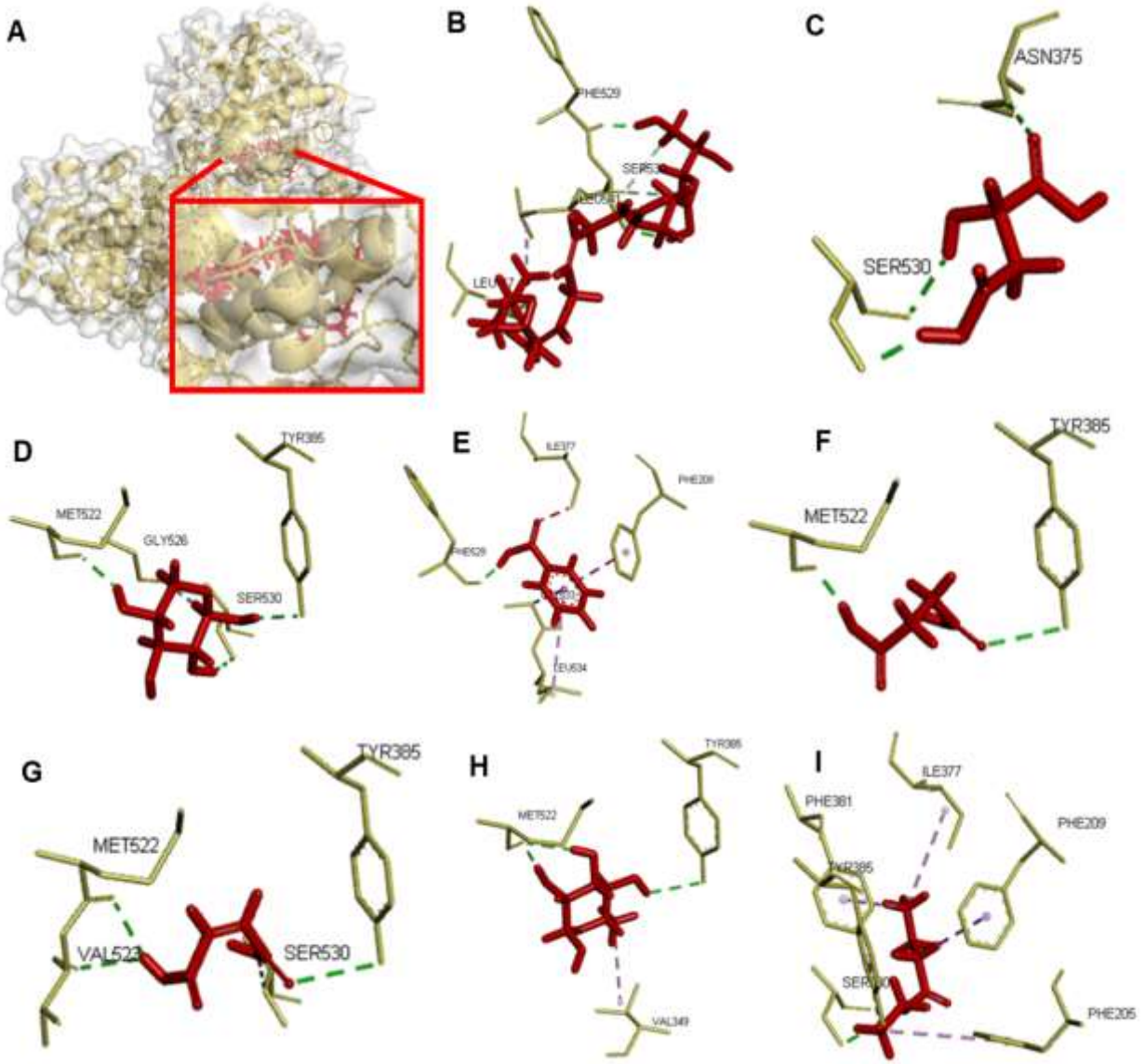

Figure 2: Binding poses of genitri compounds to cyclooxygenase – 2 protein, a. ligands – COX-2 superimpossed model, b. (2S)-2,3-dihydroxypropyl (5Z,8Z,11Z,14Z)-icosa-5,8,11,14-tetraenoate (control), c. Malic acid, d. Xylose, e. Benzoic acid, f. Succinic acid, g. Fumaric acid, h. Rhamnose, i. Ethyl Butyrate

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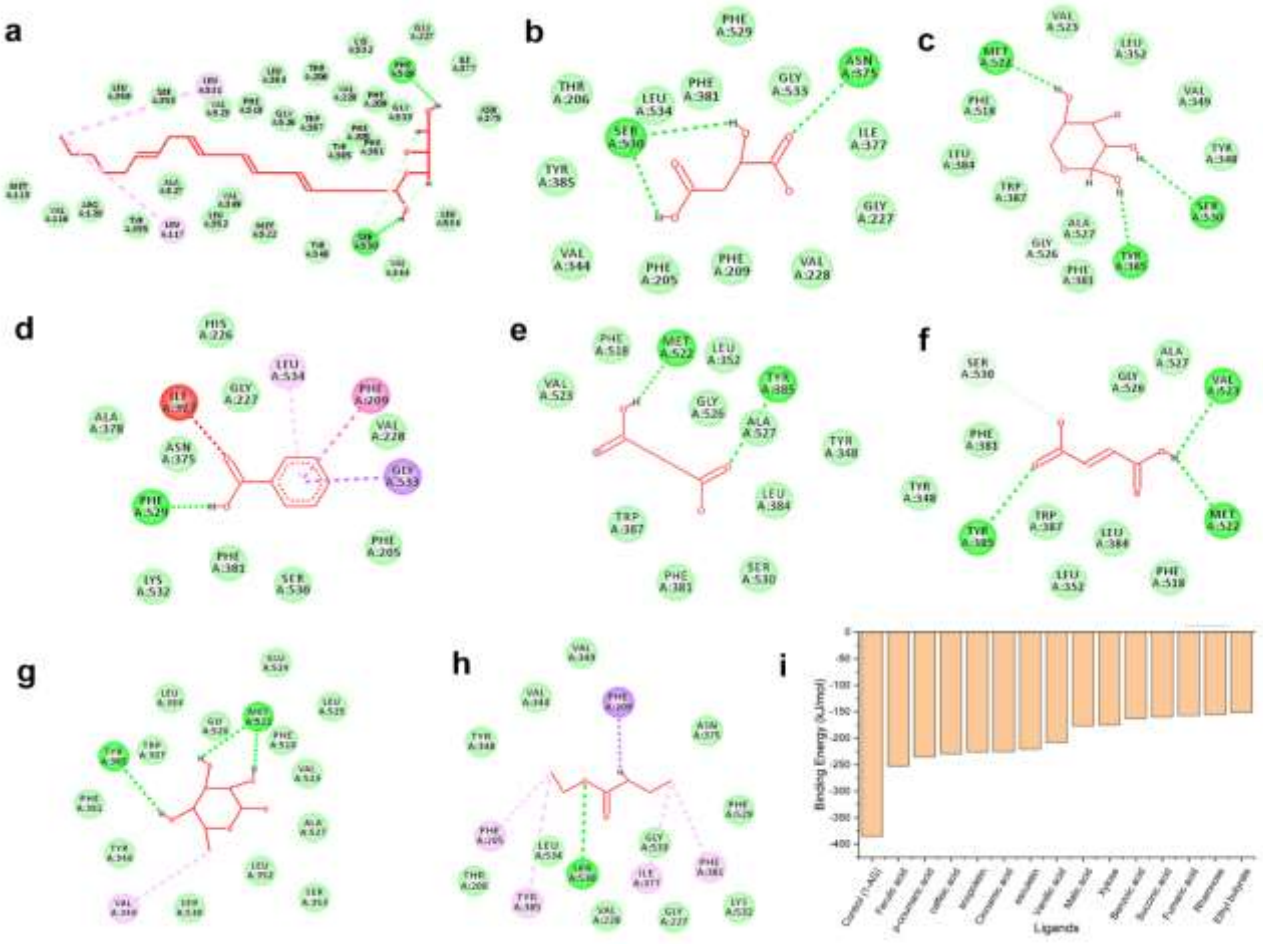

Figure 3: two-dimensional structures and binding energy plot of genitri compounds – COX-2 complexes, a. (2S)-2,3-dihydroxypropyl (5Z,8Z,11Z,14Z)-icosa-5,8,11,14-tetraenoate (control), b. Malic acid, c. Xylose, d. Benzoic acid, e. Succinic acid, f. Fumaric acid, g. Rhamnose, h. Ethyl Butyrate, i. Binding energy of ligands – COX-2.

Cyclooxygenase inhibitors were mostly non-steroidal anti-inflammatory agents and functionally repressed inflammation. Several inhibitors, synthesize and natural compounds were reported as anti-inflammatory agents. Three of the twelve Schiff base derivatives, PS18, PS19 and PS33, significantly inhibited COX-1 or COX-2 proteins[22]. Several studies identified over 800 phytochemical compounds from plant herbs that reduce inflammation[23–29]. Ginger bioactive compounds, including gingerol, shogaol, and paradol, inhibited cyclooxygenase – 2[30–37]. Essential oil compounds from *Cymbopogon citratus* also revealed antiinflammatory activity[38–40]. Furthermore, the black rice anthocyanins, delphinidin – 3- O-glucoside and peonidin – 3- O-glucoside are shown to be anti-inflammatory agents[41].

Conclusion

This study found that Malic acid, Xylose, Benzoic acid, Succinic acid, Fumaric acid, Rhamnose, Ethyl Butyrate were potentially cyclooxygenase -2 protein inhibitors. The proposed mechanism of Malic acid, Xylose, Benzoic acid, Succinic acid, Fumaric acid, Rhamnose, Ethyl Butyrate was blocking cyclooxygenase – 2 protein at the inhibitor region of COX-2 protein. These compounds might be used to reduce inflammatory progression. However, further in-vivo study is required.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

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

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