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MOLECULAR DOCKING, PASS PREDICTION AND ADME/T ANALYSIS OF SOME SELECTED ISOLATED COMPOUNDS FROM *ALPINIA CALCARATA* FOR ANALGESIC ACTIVITY

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ABSTRACT

Alpinia calcarata (Family - Zingiberaceae) is a medicinal plant grows in different parts of Bangladesh. It is commonly used in traditional medicinal system to treat cough, respiratory ailments, bronchitis, asthma, arthritis and diabetes. The aim of our study was to carry out molecular docking to investigate potential binding affinities of phytoconstituents from *Alpinia calcarata* namely 1,8-Cineole, Alpha Fenchyl Acetate, Calcaratarin-D, Herniarin, Methyl Cinnamate, Quercetin, Shyobunone and Syringic Acid towards COX-1 and COX-2 for analgesic activity. Server based *in silico* pass prediction of the compounds was performed. Selected phytochemicals were also analyzed for ADME/T properties using QikProp Module. Among a wide range of docking score quercetin and calcaratarin-D showed the best score against both cyclooxygenase enzymes which are -8.047 and -8.28 respectively. So quercetin and calcaratarin-D are the best compounds toward COX-1 and COX-2 as they posses highest docking scores. Pass prediction for analgesic activity of the selected constituents showed greater P_a than P_i for analgesic activity. Also the results from ADME/T properties ensured the compounds safe for human.

KEYWORDS: *Alpinia calcarata*, Molecular docking, PASS prediction, ADME/T properties, Analgesic.

INTRODUCTION

Plant-derived medicines have been part of traditional healthcare in most parts of the world for thousands of years as sources of active biological agents to fight diseases.[1] Traditional medical knowledge of medicinal plants and their use by indigenous cultures are not only useful for conservation of cultural traditions and biodiversity but also for community healthcare and drug development in the present and future.[2] The World Health Organization (WHO) encourages the use of plant based medicine due to its diversity, flexibility, easy accessibility, broad continuing acceptance, relative low cost, low levels of technological input, relative low side effects and growing economic importance.[3,4]

Scientists have now re-focused their interests on the traditional medicinal systems of many countries in their efforts to find out newer drugs for emerging diseases and better drugs for already existent diseases.[5] *Alpinia calcarata* Roscoe is such a medicinal plant belongs to the family Zingiberaceae commonly used in traditional medicinal systems which is cultivated in tropical countries including Sri Lanka, Malaysia and India.[6] It is also grown in different parts of Bangladesh.[7] Essential oil and extracts from this plant have been found to possess wide range of pharmacological and biological activities.[7] The most important part of *A. calcarata* is it's rhizome which is widely used to treat cough, respiratory ailments, bronchitis, asthma, arthritis and diabetes.[8,9] Research has shown antibacterial, anthelmintic, antifungal, antinociceptive, antioxidant, gastroprotective, aphrodisiac and antidiabetic effects of both the ethanolic and aqueous extracts of *A. calcarata* rhizomes.[6] Root, rhizome, stem, flower and leaves of *A. Calcarata* have been investigated and revealed the presence of protocatechinic acid, 1,8-cineole, quercetin, 4-O-methyl-syringic acid, methyl cinnamate, vanillic acid, camphene, α and β-pinene, α-fenchyl acetate, camphore, borneol and a number of diterpenes, alkaloids and flavonoids.[6,10]

Pain is a sensory and emotional experience based on actual and potential tissue damage or described in terms of such damage which in many cases represents the only symptom for the diagnosis of several diseases.[11,12] Pain is exerted by prostaglandins which are arachidonate metabolites and their production is mediated by two cyclooxygenase enzymes: cyclooxygenase-1 and cyclooxygenase-2.[13]

Throughout history man has used many different forms of therapy for the relief of pain. Among them, medicinal herbs are most commonly used medications worldwide to inhibit cyclooxygenase (COX-1 and COX-2) enzyme by inhibiting prostaglandins (PGEs)

synthesis.[12,14] *Alpinia calcarata* is such a plant identified with analgesic activity consists of the constituents showing the inhibition of selectively both cyclooxygenase-1 and cyclooxygenase-2.

The integration of computational and experimental strategies has been of great value in modern drug design and in the identification and development of novel promising compounds.[15] The discovery of new drugs has evolved from a random process of screening natural products to a suite of sophisticated procedures that include components from computational and structural chemistry.[16] Molecular docking can be a useful tool for *in silico* study that allows a faster and cheaper identification of the energetically most favorable ligand of the isolated compounds from plant which strongly binds to the protein target (receptor) with scoring functions.[17] Besides the development of computational models for the prediction of absorption, distribution, metabolism, and excretion (ADME) characteristics of drugs and druglike compounds at a very early stage of drug development is necessary to avoid costly late-stage failures, which are mainly due to toxicity or poor pharmacokinetics.[18]

The present study is based on the *in silico* molecular docking study of eight constituents isolated from *A. calcarata* plant namely 1,8-cineol, alpha fenchyl acetate, calcaratarin D, herniarin, methyl cinnamate, quercetin, shyobunone and syringic acid to investigate whether these compounds interact with the protein targets (COX 1 and COX 2). *In silico* PASS prediction of the compounds was measured with server and also the ADME/T properties were analyzed for drug-like activity of the selected components.

MATERIALS AND METHODS

Protein Preparation: Three-dimensional (3D) crystal structures of COX-1 (PDB id: 2OYE) and COX-2 (PDB id: 6COX) was taken from the Protein Data Bank in the pdb format.[19] By utilizing the Protein Preparation Wizard of Schrödinger-Maestro v11.1, both the structures were arranged and refined. Charges furthermore, bond orders were assigned, hydrogens were added to overwhelming atoms, selenomethionines were changed over to methionines and all waters were erased. Utilizing force field OPLS_2005, minimization was completed setting maximum overwhelming atoms RMSD (root-mean-square-deviation) to 0.30 Å.

Ligand Preparation: Compounds were reprocessed from PubChem databases in SDF format, i.e. 1,8-Cineole (CID: 2758), Alpha Fenchyl Acetate (CID: 6427102), Calcaratarin-D (CID: 102007111), Herniarin (CID: 10748), Methyl Cinnamate (CID: 637520), Quercetin

(CID: 5280343), Shyobunone (CID: 5321293) and Syringic Acid (CID: 10742). 3D structures for these compounds were made by using LigPrep with the force field OPLS_2005. Possible states for ionization were generated at target pH 7.0±2.0 using Epik. Stereoisomers were retained at most 32 per ligand.

Receptor grid generation

Receptor matrices were calculated for arranged proteins to such extend that various ligand poses bind inside the predicted active site during docking. In Glide, generation of grids were done keeping the default parameters of van der Waals scaling factor 1.00 and charges cutoff 0.25 with an OPLS_2005 force field. A cubic box of particular measurement centered on the centroid of the active site residue (Reference ligand active site) was created for receptor. For docking experiment, the bounding box was set to 16 Å × 16 Å × 16 Å.

Glide Standard Precision (SP) ligand docking

SP adaptable ligand docking was carried out in Glide of Schrödinger-Maestrov11.1,[20,21] inside which penalties were applied to non-cis/trans amide bonds. Van der Waals scaling component and partial charge cutoff was chosen to be 0.80 and 0.15, respectively for ligand atoms. Final scoring was carried out on energy minimized postures and displayed as glide score. The best pose with the least glide score value was recorded for every ligand.

***In silico* Prediction of activity spectra for substances (PASS)**

Prediction of phytochemicals namely 1,8-Cineole, Alpha Fenchyl Acetate, Calcaratarin-D, Herniarin, Methyl Cinnamate, Quercetin, Shyobunone and Syringic Acid for analgesic activity was done with the help of computer program PASS online server. It predicted activity spectrum of the compounds as probable activity (P_a) and probable inactivity (P_i). The ratio of P_a and P_i vary between 0.000 and 1.000. If $P_a > 0.7$, the probability of particular pharmacological action is high and if $0.5 < P_a < 0.7$, probability of particular pharmacological action is less. If $P_a < 0.5$, the compound is unlikely to exhibit pharmacological action but it may indicate the possibility of getting a new compound.[22, 23]

Ligand based ADME/Toxicity prediction

The QikProp module of Schrödinger-Maestro v.11.1 is an accurate prediction program for absorption, distribution, metabolism, and excretion (ADME) which produces certain descriptors related to ADME. On the basis of Lipinski's rule of five, ADME properties

determine drug-like activity of ligand molecules. ADME/T properties of the compounds were analyzed utilizing QikProp module and SwissADME.[24, 25]

RESULTS AND DISCUSSIONS

In silico studies on the compounds isolated from *Alpinia Calcarata* showed following results:

***In silico* PASS prediction:** Prediction of activity spectra for substances (PASS) of all the eight compounds was analyzed to find out their analgesic activity and results are shown in Table-1. Each compound showed P_a value higher than P_i value which implies the probability of higher analgesic activity of the compounds. Among them 1,8-Cineole and Alpha Fenchyl Acetate exhibited highest P_a for analgesic activity which are 0.768 and 0.642 respectively.

Table. 1: Pass prediction of selected compounds for analgesic activity.

Compound Name	PASS prediction of analgesic activity	
	P_a	P_i
1,8-Cineole	0.768	0.005
Alpha Fenchyl Acetate	0.642	0.005
Calcaratarin D	0.391	0.116
Herniarin	0.392	0.116
Methyl Cinnamate	0.480	0.049
Quercetin	0.362	0.137
Shyobunone	0.538	0.019
Syringic Acid	0.528	0.023

ADME/Toxicity prediction: Molecular weight, H-bond donor, H-bond acceptor, Log P, Molar refractivity of the selected ligand molecules were analyzed for the prediction of pharmacokinetic properties and toxicities. All the chosen compounds were found to be satisfying Lipinski's rule of five for drug-likeness which are tabulated in Table-2.

Table. 2: ADME/T properties of selected compounds.

Compound Name	Molecular Weight[α] (g/mol)	HB Donor[β]	HB Acceptor[€]	Log P[¥]	Molar Refractivity[µ]
1,8-Cineole.	154.25	0	1	2.67	47.12
Alpha Fenchyl Acetate	196.29	0	2	2.89	56.33
Calcaratarin D	318.45	1	3	3.93	92.89
Herniarin	176.17	0	3	1.88	48.98
Methyl Cinnamate	162.19	0	2	2.22	47.43
Quercetin	302.24	5	7	1.23	78.03
Shyobunone	220.35	0	1	3.90	71.10
Syringic Acid	198.17	2	5	1.02	48.41

[α]Molecular weight (acceptable range: <500)

[β]Hydrogen bond donor (acceptable range: ≤5)

[€]Hydrogen bond acceptor (acceptable range: ≤10)

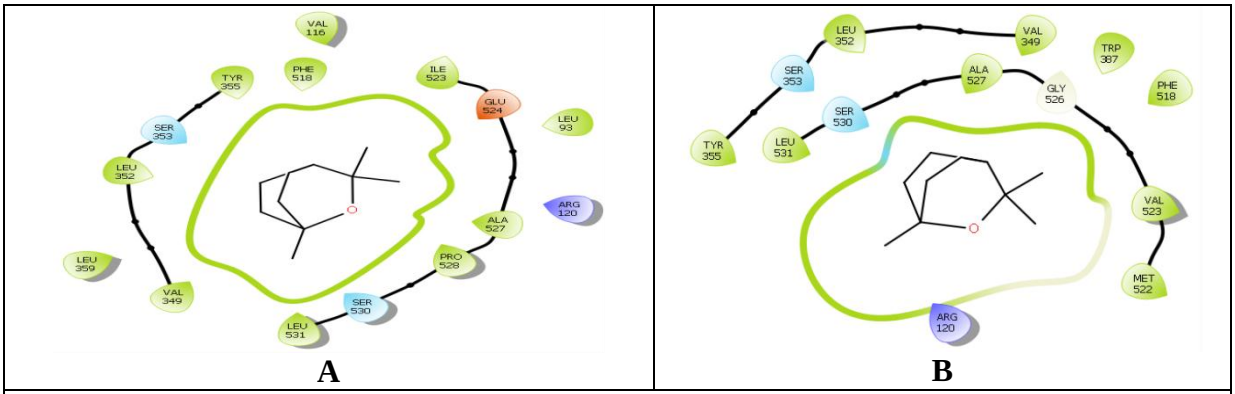
[¥]High lipophilicity (expressed as LogP, acceptable range: <5)

[μ]Molar refractivity (acceptable range: 40-130)

Molecular docking analysis: The aim of protein-ligand docking is to analyze the binding mode of a set of ligand molecules with specific protein. To mark out the potential lead molecule for analgesic activity, we performed molecular docking experiment of the selected compounds from *Alpinia Calcarata* with cyclooxygenase enzymes. The docking scores for each chosen compound with COX-1 and COX-2 enzyme using Schrödinger Maestro v11.1 are given in Table-3 and docking figures are showed in Figure: (1-8). Among all the selected compounds Quercetin exhibited highest docking score with COX-1 and Calcaratarin-D exhibited highest docking score with COX-2 which are -8.047 and -8.28 respectively.

Table. 3: Docking results of selected compounds.

Constituents	Docking Scores	
	COX-1	COX-2
1,8-Cineole	-4.648	-6.447
Alpha Fenchyl Acetate	-5.239	-6.947
Calcaratarin-D	-7.059	-8.28
Herniarin	-7.511	-6.986
Methyl Cinnamate	-6.687	-6.019
Quercetin	-8.047	-7.747
Shyobunone	-6.652	-7.13
Syringic Acid	-6.349	-6.25



A **B**

Figure. 1: Docking of 1,8-Cineole with COX-1 (A) and COX-2 (B).

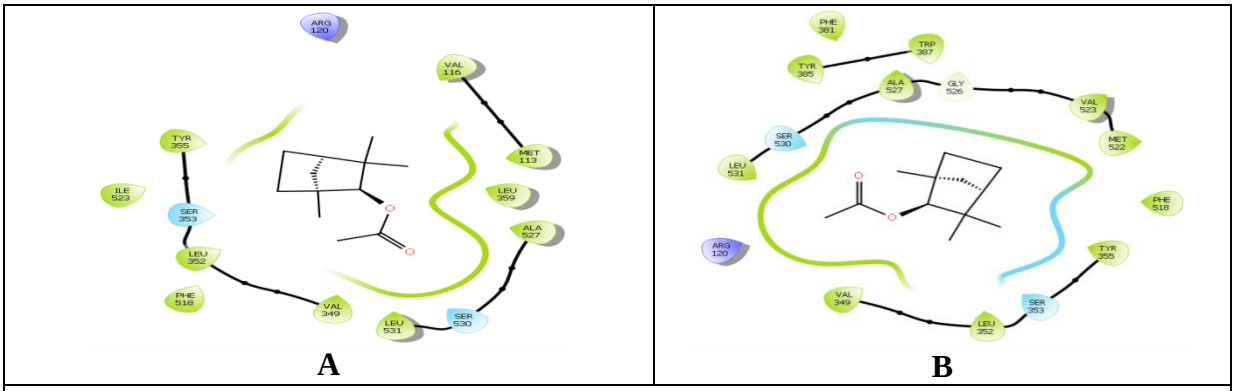
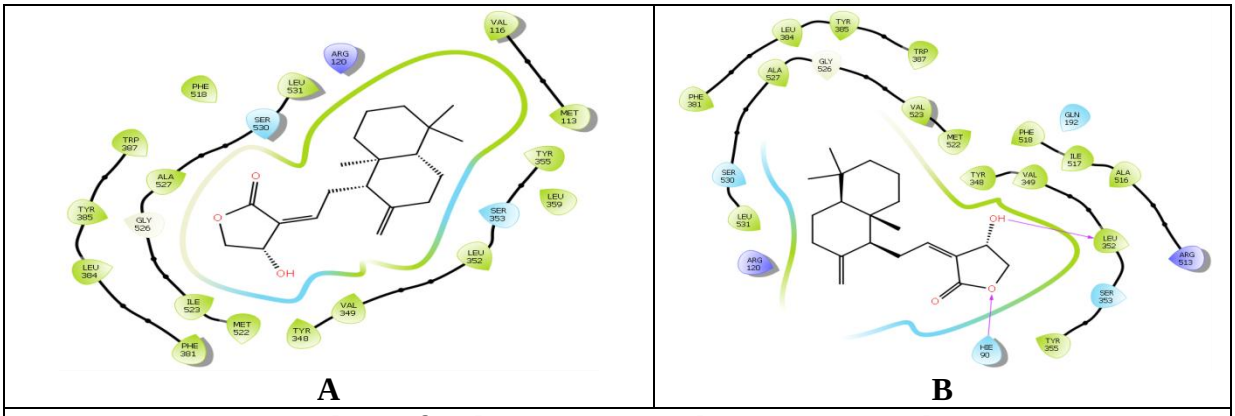
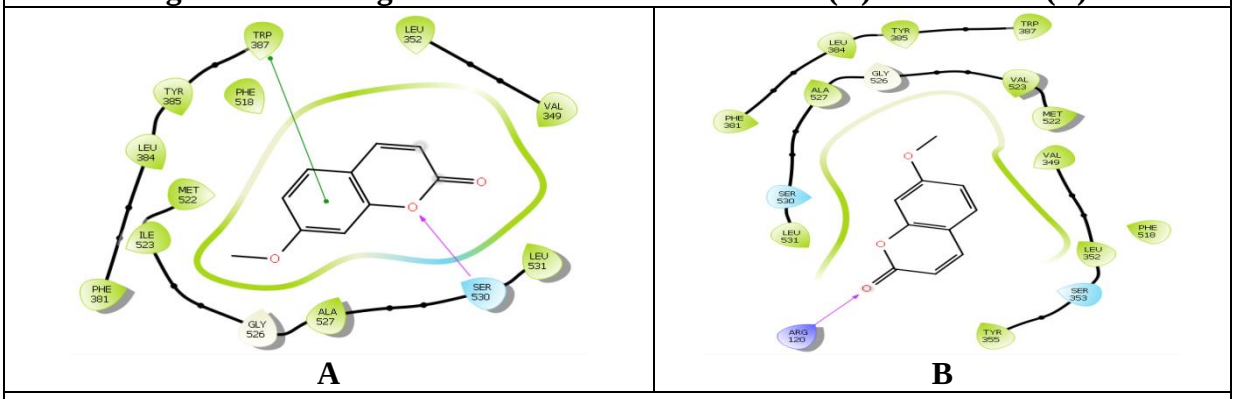


Figure. 2: Docking of Alpha Fenchyl Acetate with COX-1 (A) and COX-2 (B).



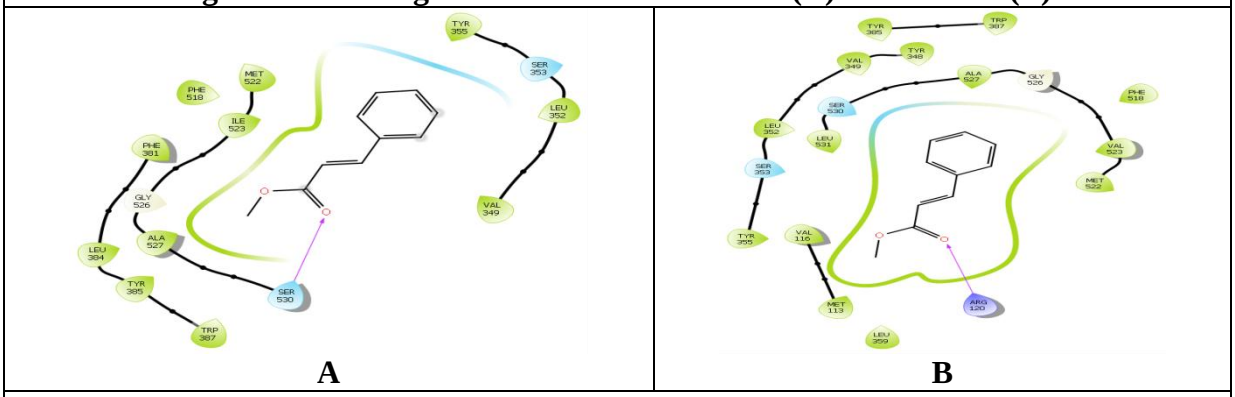
A B

Figure. 3: Docking of Calcaratarin-D with COX-1 (A) and COX-2 (B).



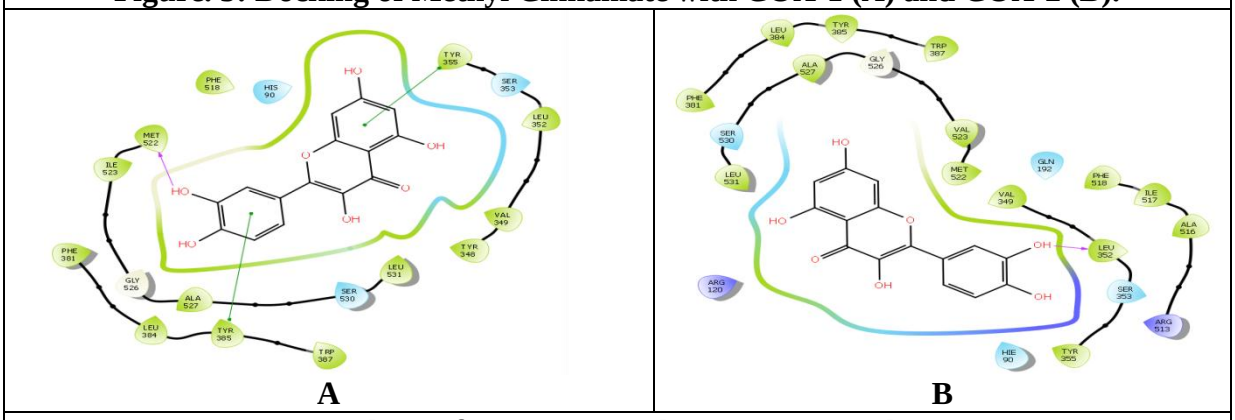
A B

Figure. 4: Docking of Herniarin with COX-1 (A) and COX-2 (B).



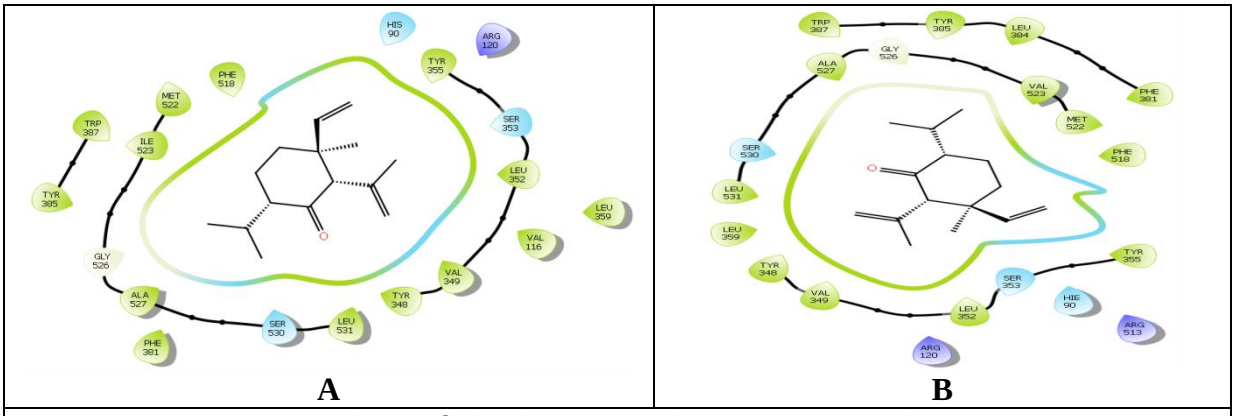
A B

Figure. 5: Docking of Methyl Cinnamate with COX-1 (A) and COX-2 (B).



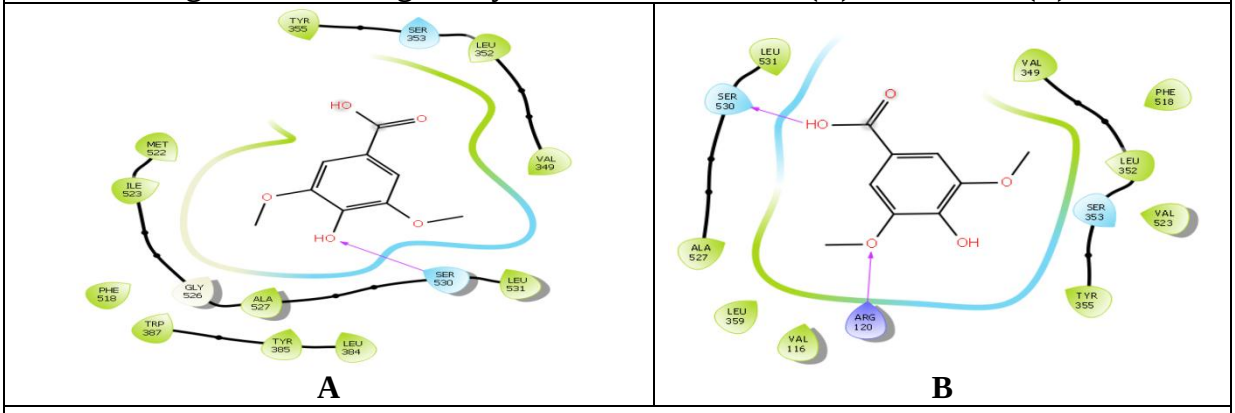
A B

Figure. 6: Docking of Quercetin with COX-1 (A) and COX-2 (B).



A **B**

Figure. 7: Docking of Shyobunone with COX-1 (A) and COX-2 (B).



A **B**

Figure. 8: Docking of Syringic Acid with COX-1 (A) and COX-2 (B).

CONCLUSION

The present study showed that all the selected constituents of *Alpinia calcarata* significantly interact with cyclooxygenase enzymes. Two compounds namely Quercetin and Calcaratarin-D are the best compounds for selective COX-1 and COX-2 inhibition respectively as they exhibit higher binding affinities.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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