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Molecular docking and PASS prediction for antinociceptive activity of some isolated compounds from *Anisomeles indica* (L.) Kuntze. and ADME/T property analysis of the compounds

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ABSTRACT

Anisomeles Indica (L.) Kuntze (Family - Lamiaceae) is commonly known as Gobura, is found in fallow lands throughout Bangladesh. The plant has used for carminative, astringent, tonic properties and uterine infection by the tribal in Khagrachari, Bangladesh. The aim of present study to investigate *in silico* molecular docking study used for four phytoconstituents Acteoside, betonyoside A, campneoside II, β-Sitosterol, Isoacteoside, Ovatodiolide and stigmasterol which are isolated from *A. indica* to identify whether these compounds interact with the responsible protein (Cyclooxygenase 1 enzyme) and PASS prediction is done by sever. Also ADME/T properties of the phytoconstituents were analyzed using Qikprop 3.2 module. A wide range of docking score found during molecular docking by Schrodinger. Acteoside, betonyoside A, campneoside II, β-Sitosterol, Isoacteoside, Ovatodiolide and stigmasterol showed the docking score -5.362 , -2.468 , -4.711 , -2.575 , -6.771 , -1.806 and -2.397 respectively . Among all the compounds Isoacteoside showed highest docking score. So, Isoacteoside is the best compounds for selective Cyclooxygenase 1 (COX 1) enzyme inhibition, as it possessed best value in Molecular docking. In the PASS prediction for their analgesic activity of the isolated phytoconstituents, we found wide range of activity and all the compounds showed greater Pa than Pi value. From the ADME/T profiles of all the tested compounds, it cleared that they might safe for human. Further *in vivo* investigation need to identify Cyclooxygenase (COX 1) enzyme inhibitory activity of isolated compounds from *A. indica*.

Key words: *Anisomeles indica*, Cyclooxygenase enzyme, Molecular docking, PASS prediction, ADME/T properties.

INTRODUCTION

Anisomeles Indica is a camphor-scented perennial woody shrub which belongs to the family Lamiaceae. It is native to more or less throughout the country in fallow lands, is 1-1.5 m high. Leaves aromatic, 2.5-7.5 cm long, ovate, acute, crenate-serrate and softly pubescent. Flowers purple in dense whorls in axillary or terminal spickes. It is used in folk medicine in the treatment of diverse conditions such as inflammatory skin diseases, liver protection, intestinal infections, abdominal pain and immune system deficiencies. The plant has carminative, astringent and tonic properties; used for uterine infection by the tribal in Khagrachari [1].The Arial parts of the plant are valued as stimulant, expectorant, diaphoretic and insecticide.

Leaves are considered useful in chronic rheumatism, psoriasis and other chronic skin eruptions. Bruised leaves are applied locally in snake bites [2]. EtOH (50%) extract of the herb is hypothermic. Leaves extract is anti inflammatory and anti-arthritic in albino rats [3]. Leaves and flowers possess antibacterial properties against *Shigella dysenteriae* and *Staphylococcus aureus*, INABAET (vibrio) and *Salmonella typhi* [4]. *A. indica* has been shown to show anti-histaminerigic, anti-hyperalgesic and antinociceptive activities [5, 6].

Pain is the consequence of a intricate series of neuronal [7, 8], inflammatory [9], immunologic [10, 11], vascular [12, 13], and morphologic responses [13, 14] to tissue injury. It may be a specific enteroceptive sensation; it will be perceived as arising from a specific portion of the body, its temporal properties is elaborated, it can be differentiated qualitatively (for example, as stinging, pricking, burning, throbbing, dull or aching), and it involves dedicated subsets of peripheral and central neurons. Pain, which is in the peripheral nerves, the spinal cord and the brain is increasing, and we are becoming aware of the many neurochemicals involved and the critical interactions with other systems, such as the thermoregulatory, sympathetic and immune systems, that make pain an integrated physiological phenomenon [15].

In silico biology refers to computational models of biology, is an expression used to mean performed on a computer or via computer simulation. It is used in systems biology. Due to the vast amounts of data that is now generated by molecular and cell experimental biologists, computational biology is increasingly necessary to manage it. *In silico* biology draws from the vast amounts of biological information available, and applies sophisticated algorithms or simulations to advance scientific understanding. The results of these simulations can then be tested experimentally or serve as a guide for future physical experimentation.

An antinociceptive or painkiller is any member of the group of drugs used to achieve analgesia, relief from pain. Antinociceptive drugs act in various ways on the peripheral and central nervous systems. They are distinct from anesthetics, which reversibly eliminate sensation. Antinociceptive substances interact with the transmitters and modulators of the pain system are helpful for many people with pain, but there is a great need for the development of better methods for the alleviation and control of both acute (immediate) and chronic (long-term, pathological) pain [15].

An *in vivo* evaluation was evaluated by antinociceptive assay. Furthermore, the mechanism of action of the isolated compounds from *Anisomeles indica* explored by molecular docking analysis, ADME/T property and PASS prediction studies.

MATERIALS AND METHODS

In silico Molecular Docking

Protein Preparation

Three dimensional crystal structure of COX 1 (PDB id:2OYE) was downloaded in pdb format from the protein data bank [16]. After that, structure was prepared and refined using the Protein Preparation Wizard of Schrödinger-Maestro v10.1. Charges and bond orders were assigned, hydrogens were added to the heavy atoms, selenomethionines were converted to methionines, and all waters were deleted. Using force field OPLS_2005, minimization was carried out setting maximum heavy atom RMSD (root-mean-square-deviation) to 0.30 Å.

Ligand Preparation

Compounds were retrieved from Pubchem databases, i.e. acteoside, betonyoside A, campneoside II, β-sitosterol, ovatodiolide, isoacteoside and stigmasterol. The 3D structures for these were built by using Ligprep2.5 in Schrödinger Suite 2015 with an OPLS_2005 force field. Their ionization states were generated at pH7.0±2.0 using Epik2.2 in Schrödinger Suite. Up to 32 possible stereoisomers per ligand were retained.

Receptor grid generation

Receptor grids were calculated for prepared proteins such that various ligand poses bind within the predicted active site during docking. In Glide, grids were generated keeping the default parameters of van der Waals scaling factor 1.00 and charge cutoff 0.25 subjected to OPLS 2005 force field. A cubic box of specific dimensions centred around the centroid of the active site residues (Reference ligand active site) was generated for receptor. The bounding box was set to 14 Å × 14 Å × 14 Å for docking experiments.

Glide Standard Precision (SP) ligand docking

SP flexible ligand docking was carried out in Glide of Schrödinger-Maestro v 10.1 [17, 18] within which penalties were applied to non-cis/trans amide bonds. Van der Waals scaling factor and partial charge cutoff was selected to be 0.80 and 0.15, respectively for ligand atoms. Final scoring was performed on energy-minimized poses and displayed as Glide score. The best docked pose with lowest Glide score value was recorded for each ligand.

In silico Prediction of activity spectra for substances (PASS)

Prediction of phytoconstituents namely acteoside, betonyoside A, campneoside II, β-sitosterol, ovatodiolide, isoacteoside, stigmasterol [19][20] for antinociceptive activity was done with the help of

computer program, PASS. Software estimates predicted activity spectrum of a compound as probable activity (P_a) and probable inactivity (P_i). The prediction of activity is based on structure-activity relationship analysis of the training set containing more than 205,000 compounds exhibiting more than 3750 kinds of biological activities. The values of P_a and P_i vary between 0.000 and 1.000. Only activities with $P_a > P_i$ are considered as possible for a particular compound. If $P_a > 0.7$, the probability of experimental pharmacological action is high and if $0.5 < P_a < 0.7$, probability of experimental pharmacological action is less. If the value of $P_a < 0.5$, the chance of finding the activity experimentally is less, but it may indicate a chance of finding a new compound [21-24].

ADME/T property analysis

Ligand based ADME/Toxicity prediction

The QikProp module of Schrodinger (Maestro, version 10.1) is a quick, accurate, easy-to-use absorption, distribution, metabolism, and excretion (ADME) prediction program design to produce certain descriptors related to ADME. It predicts both physicochemical significant descriptors and pharmacokinetically relevant properties. ADME properties determine drug-like activity of ligand molecules based on Lipinski's rule of five. ADME/T properties of the compound (DIM) was analyzed using Qikprop 3.2 module [25].

RESULTS AND DISCUSSION

***In silico* Molecular docking analysis**

Advances in computational techniques have enabled virtual screening to have a positive impact on the discovery process. Virtual screening utilizes docking and scoring of each compound from a dataset and the technique used is based on predicting the binding modes and binding affinities of each compound in the dataset by means of docking to an X-ray crystallographic structure [26]. Grid based docking study was used to analyze the binding modes of molecules with the amino acids present in the active pocket of the protein [27]. To identify the potential analgesic lead molecule, we have subjected the docking analysis of the active compounds of *A. indica* (L.) Kuntze to the active site cyclooxygenase enzymes viz. COX-1. In order to study the interaction of the compounds acteoside, betonyoside A, β-sitosterol, isoacteoside, stigmasterol with 2OYE. We performed Glide docking analysis by Schrodinger suite v10.1, where among of these compounds Isoacteoside shows highest docking score shown in Table 1. The negative and low value of free energy of binding demonstrates a strong favorable bond between 2OYE. Docking Score suggested that Isoacteoside had the highest affinity to the COX-1 enzymes corresponding to the other compounds. The results of docking analysis were described in Table 1 and the docking figure showed in Figure 1.

***In silico* PASS prediction**

Seven constituents namely acteoside, betonyoside A, campneoside II, β-sitosterol, ovatodiolide, isoacteoside, stigmasterol were analyzed by the PASS for their thrombolytic activity and results were used in a flexible manner. All the compounds showed greater Pa than Pi (Table-1). Stigmasterol showed highest Pa for thrombolytic activity (Pa=0.601).

ADME and Toxicity analysis

Ligand based ADME/Toxicity prediction

The drug-like activity of the ligand molecule was categorized using ADME properties by QikProp module of Schrodinger. The ADME properties of the acteoside, betonyoside A, campneoside II, β-sitosterol, ovatodiolide, isoacteoside, stigmasterol were evaluated with QikProp module of Schrodinger, shown in Table 3. The selected properties are known to influence metabolism, cell permeation, and bioavailability. Only predicted properties of the ovatodiolide was in the range for satisfying the Lipinski's rule of five to be considered as drug like potential. All other compounds were not satisfying the all five rules.

CONCLUSION

The present study revealed that *Anisomeles indica (L.) Kuntze* has the compound named Isoacteoside, which had the highest analgesic activity. Isolation of this compound will be imported to test the effectiveness of this compound and also its ADME profile for social benefit thus reducing the time and cost in drug discovery process.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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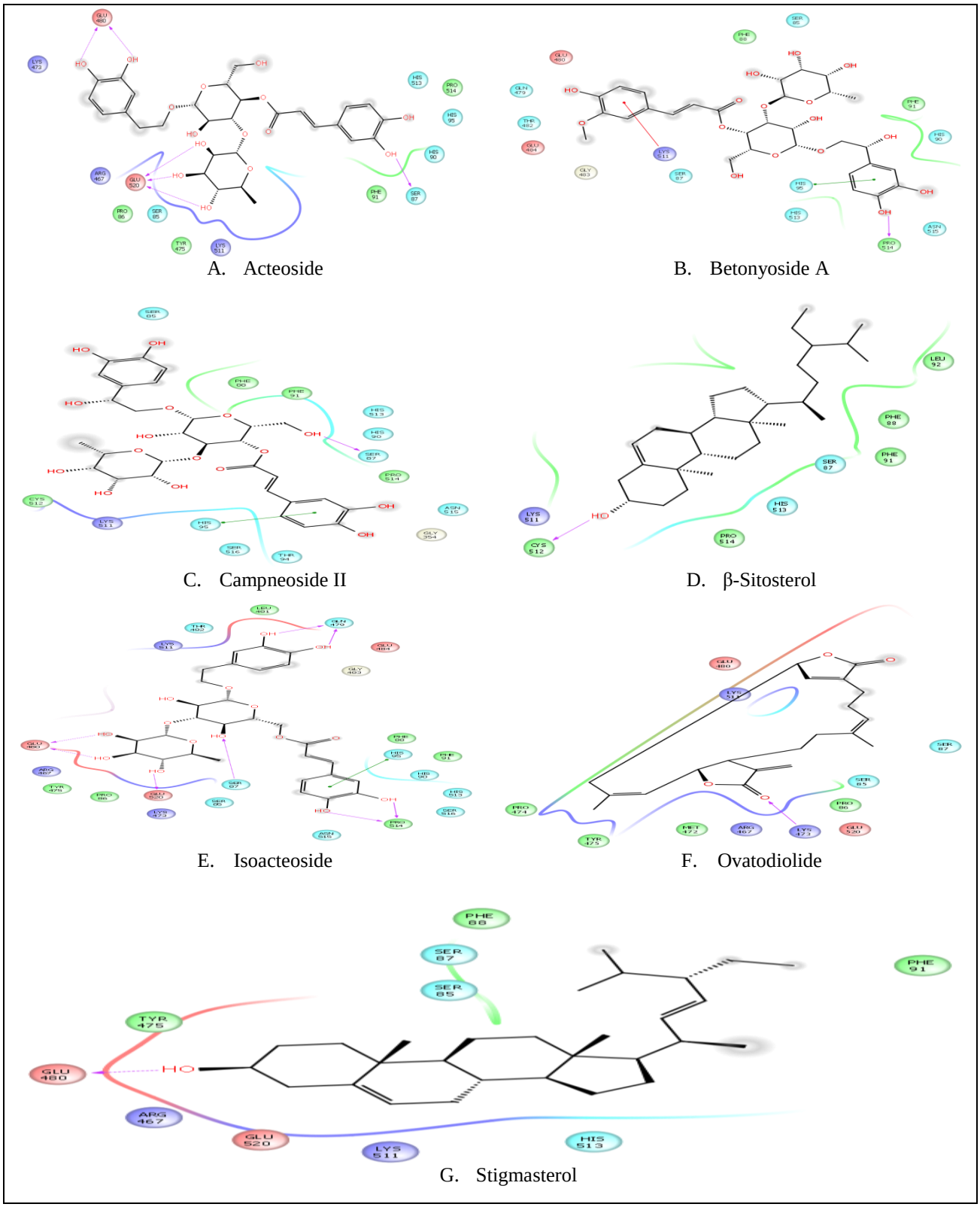


Figure 1: Docking results of A. acteoside, B. betonyoside A, C. campneoside II, D. β-sitosterol, E. isoacteoside, F. ovatodiolide, G. stigmasterol with 2OYE.

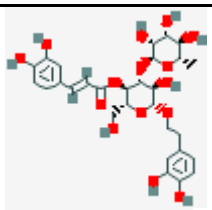
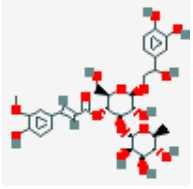
Table 1: Docking results of acteoside, betonyoside A, campneoside II, β-sitosterol, ovatodiolide, isoacteoside, stigmasterol with 2OYE (PDB: 2OYE).

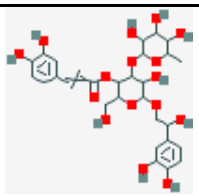
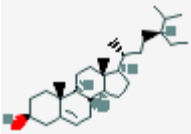
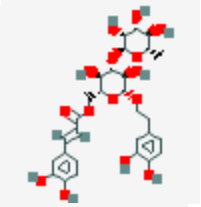
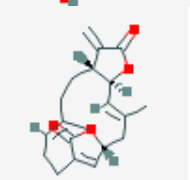
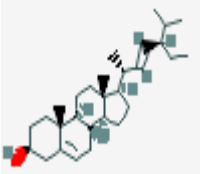
Compound Name	Docking Score	glide emodel	glide energy
Acteoside	-5.362	-55.907	-44.783
betonyoside A	-2.468	-27.687	-26.796
campneoside II	-4.711	-47.817	-40.214
β-Sitosterol	-2.575	-20.403	-19.348
Isoacteoside	-6.771	-77.437	-61.239
Ovatodiolide	-1.806	-12.137	-8.549
stigmasterol	-2.397	-19.423	-20.747

Table 2: PASS prediction of acteoside, betonyoside A, campneoside II, β-sitosterol, ovatodiolide, isoacteoside, stigmasterol for antinociceptive activity.

Phyto compound	PASS prediction of antinociceptive activity	
	Pa	Pi
Acteoside	0.466	0.058
betonyoside A	0.417	0.096
campneoside II	0.415	0.097
β-sitosterol	0.558	0.014
Isoacteoside	0.318	0.027
Ovatodiolide	0.798	0.007
stigmasterol	0.601	0.008

Table 3: ADME/T properties of acteoside, betonyoside A, campneoside II, β-sitosterol, ovatodiolide, isoacteoside, stigmasterol by QikProp.

Name of molecules	Pubchem ID	Structure	MW[α]	HB donor[β]	HB accepter[€]	Log P[¥]	Molar refractivity[µ]
acteoside	5281800		624	5	15	8.67	190.89
betonyoside A	102000760		654	9	16	-1.13	154.75

campneoside II	85091108		640	10	16	8.93	149.91
β-sitosterol	222284		414	1	1	8.62	129.21
isoacteoside	6476333		656	8	15	7.37	179.90
ovatodiolide	6451060		328	0	4	3.33	90.75
stigmasterol	5280794		412	1	1	7.87	129.12

[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 should be between 40-130.

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