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Molecular docking and ADME/T analysis for identification of novel potential COX inhibitors of some isolated compounds from *Clausena lansium* for analgesic treatment

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Abstract
Developing a new agent in the analgesic field, plants secondary metabolites can be a good source for the Non-Steroidal Anti-inflammatory Drugs (NSAID) drug development. For this purpose we subjected the active compounds *Clausena lansium* of to reveal its potentiality by molecular docking analysis to find out its potent compound against COX-1 and COX-2 which was done by Maestro v 10.1 (Schrodinger) docking analysis. Docking studies by Maestro v 10.1 (Schrodinger) showed that Murrayanine and Clausenaline E of *Clausena lansium* had the lowest docking score respectively against the COX-1 and COX2 which are -6.471 and -8.325. Murrayanine and Clausenaline E from *Clausena lansium* detected with significant docking score which may be a potent analgesic compound because the less docking score, the compound will be more potent.

Keywords: *Clausena lansium*, COX inhibitors, molecular docking, ADME/T analysis

Introduction
Plants have been considered as a rich supply of conventional medication for many years because they produced a wide variety of bioactive molecules, maximum of that have been advanced as pills for the remedy of numerous diseases. In lots of developing countries, conventional medication is one of the number one fitness concern systems [1-3]. Many ancient civilizations like Chinese medicine, Ayurbed medicine and Unani medicine have a confirm belief on treatment of plant medicine [4]. Large-scale evaluation is an essential primary step for systemic isolation and identity of the lively principles of the nearby flora exploited in medicine with the intention of new drug discovery [3].
Pain is associate unwanted and emotional experience because of the injury of tissue [5]. medication that are used presently for the managing of pain are either steroidal like corticosteroids or non-steroidal like aspirin. All of these medication possess more or less toxic result like nephropathy, kidney failure, hypersensitive reaction, etc. [6, 7]. The extract of plant that contains effective analgesic compound helps to get a new drug without any toxic effects [8].
In silico is an expression used to mean "performed on computer or via computer simulation". In silico methods can help in identifying drug targets via bioinformatics tools. They can also be used to analyze the target structures for potential binding/active sites, generate candidate molecules, check for their drug likeness, dock these molecules with the target, rank them according to their binding affinities, further optimize the molecules to improve binding characteristics The utilization of computers and computational methods permeates all aspects of drug discovery nowadays and forms the core of structure-based drug design [9].
Traditionally healthful plants have served to be efficient thrombolytic agents for ages because of their wealthy diversity of phytochemicals. *Clausena lansium* (Family- Rutaceae) is also known as wampee which is an evergreen tree 3–8 m tall. Its leaves are smooth and dark green. White flowers in late March are white, with four or five petals, about 3–4 mm in diameter. The fruit is oval, about 3 cm long and 2 cm in diameter, and contains two to five seeds that occupy ~40-50% of the fruit volume. The tree reaches a maximum height of 20 meters. It grows well in tropical or subtropical conditions and is susceptible to cold.

Wampee trees grow well in a wide range of soil, but will grow best in rich loam [10].

The aim of the study to find the mechanism of action of the isolated compounds from *Clausena lansium* was explored the COX 1 and COX 2 inhibitory activity by molecular docking analysis used to measure the compounds as drug.

Materials and Methods

In silico analysis

Molecular docking analysis of isolated compounds

Protein Preparation

Three dimensional crystal structure of COX 1 (PDB id: 2OYE) [11] and COX 2 (PDB id: 6COX) [12] was downloaded in pdb format from the protein data bank [13]. 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. claulamines E, clausemarin B, Clausenaline C, Clausenaline E, Murrayanine, vanillic acid and Xanthotoxol.

Glide Standard Precision (SP) ligand docking

SP flexible ligand docking was carried out in Glide of Schrödinger-Maestro v10.1 [14, 15] within which penalties were applied to non-cis/trans amidebonds. 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.

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 [15].

This analysis is done by following server,

- http://www.scfbioiitd.res.in/software/drugdesign/lipinski.jsp#anchortag
- https://ilab.acdlabs.com/iLab2/index.php
- http://www.molinspiration.com/cgi-bin/properties

Results and Discussions

In silico analysis

Molecular docking analysis

In this study, the binding mode of α-amylase enzyme was investigated by doing computational analysis, glide docking. Both glide standard (SP) and extra precision (XP) mode had been introduced, where extra precision mode used for cross validation purpose. The results of docking analysis were described in Table 1 and the docking figure showed in Figure 1. Among all the compounds, Murrayanine and Clausenaline E showed well docking score againt COX 1 and COX 2 repectively.

Table 1: Docking score of different compounds with the receptors.

Compounds	Docking Score with COX 1	Docking Score with COX 2
Claulamines E	-5.252	-6.93
Clausemarin B	-5.958	-6.479
Clausenaline C	-5.477	-
Clausenaline E	-6.412	-8.325
Murrayanine	-6.471	-7.828
Vanillic Acid	-4.702	-6.592
Xanthotoxol	-6.336	-7.458

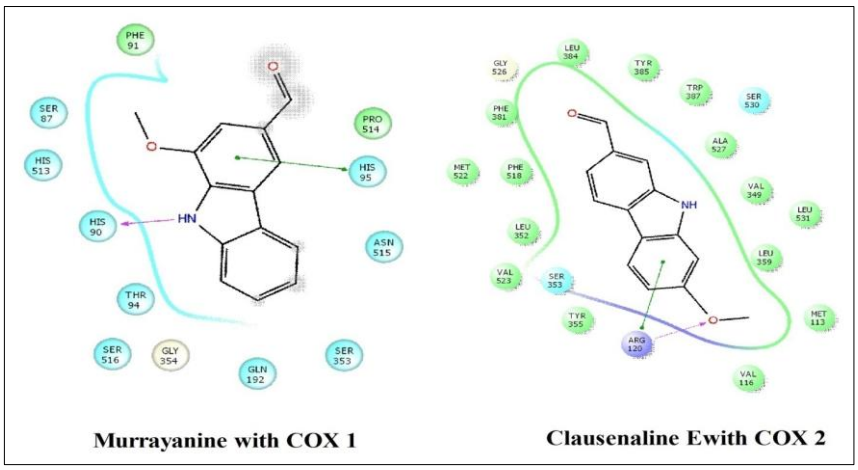

Fig 1: Docking figure of compounds with the receptors.

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 claulamines E, clausemarin B, Clausenaline C, Clausenaline E, Murrayanine, vanillic acid and Xanthotoxol. Were evaluated with QikProp module of Schrodinger, shown in Table 2. The selected properties are known to influence metabolism, cell permeation, and bioavailability. Among all the compounds Clausenaline E and Murrayanine was highly considered as safe drug.

Table 2: ADME/T Properties of claulamines E, clausemarin B, Clausenaline C, Clausenaline E, Murrayanine, vanillic acid and Xanthotoxol.

Name of molecules	MW[α]	HB donor[β]	HB acceptor[€]	Log P[¥]	Molar Refractivity[µ]
Claulamines E	335	2	4	4.060449	95.428986
Clausemarin B	404	1	5	4.741090	118.817764
Clausenaline C	225	1	2	1.802800	58.026188
Clausenaline E	225	1	2	1.802800	58.026188
Murrayanine	225	1	2	1.878820	56.704193
Vanillic acid	167	0	4	0.621940	34.646000
Xanthotoxol	202	0	4	1.055020	42.771999

[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.

Conclusion

Docking studies by Maestro v 10.1 (Schrodinger) showed that Murrayanine and Clausenaline E of *Clausena lansium* had the lowest docking score respectively against the COX-1 and COX2 which are -6.471 and -8.325. Murrayanine and Clausenaline E from *Clausena lansium* detected with significant docking score which may be a potent analgesic compound because the less docking score, the compound will be more potent.

Competing Interests

The authors declare that they have no competing interests.

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