MOLECULAR DOCKING 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 (Schrodogering) docking analysis. Docking studies by Maestro v 10.1 (Schrodogering) 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, Murrayanine, Clausenaline.

INTRODUCTION

Pain may be a complicated expertise consisting of a particular sensation and also the reactions evoked by that Sensation.\(^1\) It is a specific enteroreceptive sensation; it can be perceived as arising from a selective portion of the body, its temporal properties can be 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.\(^2\) An analgesic or medicine is any member of the cluster of medication accustomed win physiological condition, relief from pain. Analgesic medication act in numerous ways in which on the peripheral and central nervous systems, they're distinct from anesthetics, that briefly have an effect on, and in some instances fully eliminate, sensation. Analgesics embody Paracetamol (known in North America as Panadol or just APAP), the anti-inflammatory drug medication (NSAIDs) like the salicylates, and opioid medication like painkiller and oxycodone.\(^3\)

*Clausena lansium* (Lou.) belongs to the family Rutaceae and is originated from Southern China and found also in Bangladesh, India etc. The pulp can be used to prepare fruit cups, desserts, jam, or jelly. In addition, the fermented fruit can be used to prepare carbonated beverages similar to champagne, although dried *Clausena lansium* is a more desirable product.\(^4\) Previous studies of bioactivities, particularly the extracts of its leaf and seed, mainly focused on the hepatoprotective,\(^5\) antiplatelet,\(^6\) hypoglycemic,\(^7\) antifungal and antiviral activities.\(^8, 9\) However, no systematic study has been conducted on the *Clausena lansium* peel even though it is used as a folk medicine in China for the treatment of stomachic, and bronchitis as well as it acts as a vermifuge. For the first time, this study investigated the antioxidant and anticancer activities of the *Clausena lansium* peel extracts and demonstrated the potent bioactivities of the extracts suitable to be used as natural antioxidant compounds or pharmaceutical supplements.

*In silico* is an expression meaning "performed on the computer or via computer simulation". It is a scientific research journal aiming to advance the use of computational models and simulations in studies applied to advanced biological phenomena. *In silico* computer-based modeling technologies have also been applied in: Whole cell analysis of prokaryotic and eukaryotic hosts, Bioprocess development and improvement e.g. improvement of product...
yields. Besides it have also applied in Analysis, interpretation and visualization of heterologous information sets from numerous sources e.g. genome, transcriptome or proteome data, Protein design.\textsuperscript{[10, 11]}

The aim of the study to find the mechanism of action of the isolated compounds from \textit{Clausena lansium} was explored the $\alpha$-amylase inhibitory activity by molecular docking analysis and ADME/T property studies used to measure the safety of the compounds as drug.

\textbf{MATERIALS AND METHODS}

\textit{In silico} analysis

\textbf{Molecular docking analysis of isolated compounds}

\textbf{Protein Preparation}

Three-dimensional crystal structure of COX 1 (PDB id:2OYE) and COX 2 (PDB id:6COX) was downloaded in pdb format from the protein data bank. After that, the 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.\textsuperscript{[12, 13]}

\textbf{Ligand Preparation}

Compounds were retrieved from PubChem databases, i.e. Claulamines E, Clausemarin B, Clausenaline C, Clausenaline E, Murrayanine, Vanillic acid and Xanthotoxol.\textsuperscript{[14-16]}

\textbf{Glide Standard Precision (SP) ligand docking}

SP flexible ligand docking was carried out in Glide of Schrödinger-Maestro v10.1 within which penalties were applied to non-cis/trans amidebonds. Van der Waals scaling factor and partial charge cutoff were 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.\textsuperscript{[17][18][19]}

\textbf{Ligand-based ADME/Toxicity prediction}

This test was carried out using Lipinski’s “Rule of Five”.\textsuperscript{[20]} This analysis was done by following server,

RESULTS AND DISCUSSIONS

In silico analysis

Molecular docking analysis

In this study, the binding mode of COX 1 and COX 2 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. Binding energy is the primary parameter which is generated as a result of molecular docking. It gives us the idea of strength and affinity of the interaction between the ligand and the receptor. The greater the binding energy is, the weaker the interaction is and vice versa. Thus during any docking study, we intend to look for the ligand which displays the least binding energy, thus the best affinity among the test molecules.[21] Among all the compounds, Murrayanine and Clausenaline E showed well docking score against COX 1 and COX 2 respectively.

Table 1: Docking score of Claulamines E, Clausemarin B, Clausenaline C, Clausenaline E, Murrayanine, Vanillic acid and Xanthotoxol with the receptors (COX 1 and COX 2).

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Docking Score with COX 1</th>
<th>Docking Score with COX 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claulamines E</td>
<td>-5.252</td>
<td>-6.93</td>
</tr>
<tr>
<td>Clausemarin B</td>
<td>-5.958</td>
<td>-6.479</td>
</tr>
<tr>
<td>Clausenaline C</td>
<td>-5.477</td>
<td>-6.412</td>
</tr>
<tr>
<td>Clausenaline E</td>
<td>-6.412</td>
<td>-8.325</td>
</tr>
<tr>
<td>Murrayanine</td>
<td>-6.471</td>
<td>-7.828</td>
</tr>
<tr>
<td>Vanillic Acid</td>
<td>-4.702</td>
<td>-6.592</td>
</tr>
<tr>
<td>Xanthotoxol</td>
<td>-6.336</td>
<td>-7.458</td>
</tr>
</tbody>
</table>

The Bold numbers indicated the best docking score in respective receptor.
ADME and Toxicity analysis
Ligand-based ADME/Toxicity prediction

Drug likeliness, log P, molar refractivity, molecular weight and toxicity risks may be used to judge the compound's overall potential to qualify a ligand as a potential drug candidate. The drug-like activity of the ligand molecule in this study was categorized using ADME properties by ACD/I-Lab and Molinspiration. This test was carried out using Lipinski’s “Rule of Five”\(^\text{[20]}\). The distributions of the compound molecular weights (MW), calculated lipophilicity (log P), the number of hydrogen bond acceptors (HBA) and the number of hydrogen bond donors (HBD) were used to assess the “drug-likeness” of the compounds. It is noteworthy that natural products exhibit a wide range of flexibility, from rigid conformationally constrained molecules to very flexible compounds. The ADME properties of the Claulamines E, Clausemarin B, Clausenaline C, Clausenaline E, Murrayanine, Vanillic acid and Xanthotoxol were evaluated with ACD/I-Lab and Molinspiration, shown in Table 2. The selected properties are known to influence metabolism, cell permeation, and bioavailability. Predicted properties of Vanillic acid was not within the range for satisfying all the Lipinski’s rule of five to be considered as a drug like potential and it failed to maintain Molar Refractivity rule. But all other compounds like Claulamines E, Clausemarin B, Clausenaline C, Clausenaline E, Murrayanine and Xanthotoxol were satisfying all the Lipinski’s rule of five to be considered as a drug like potential.

Table 2: ADME/T Properties of Claulamines E, Clausemarin B, Clausenaline C, Clausenaline E, Murrayanine, Vanillic acid and Xanthotoxol.

<table>
<thead>
<tr>
<th>Name of molecules</th>
<th>MW(^a)</th>
<th>HB donor(^b)</th>
<th>HB acceptor(^c)</th>
<th>Log P(^y)</th>
<th>Molar Refractivity(^\mu)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claulamines E</td>
<td>335</td>
<td>2</td>
<td>4</td>
<td>4.060449</td>
<td>95.428986</td>
</tr>
<tr>
<td>Clausemarin B</td>
<td>404</td>
<td>1</td>
<td>5</td>
<td>4.741090</td>
<td>118.817764</td>
</tr>
<tr>
<td>Clausenaline C</td>
<td>225</td>
<td>1</td>
<td>2</td>
<td>1.802800</td>
<td>58.026188</td>
</tr>
<tr>
<td>Clausenaline E</td>
<td>225</td>
<td>1</td>
<td>2</td>
<td>1.802800</td>
<td>58.026188</td>
</tr>
<tr>
<td>Murrayanine</td>
<td>225</td>
<td>1</td>
<td>2</td>
<td>1.878820</td>
<td>56.704193</td>
</tr>
<tr>
<td>Vanillic acid</td>
<td>167</td>
<td>0</td>
<td>4</td>
<td>0.621940</td>
<td>34.646000</td>
</tr>
<tr>
<td>Xanthotoxol</td>
<td>202</td>
<td>0</td>
<td>4</td>
<td>1.055020</td>
<td>42.771999</td>
</tr>
</tbody>
</table>

\(^a\)Molecular weight (acceptable range: <500).
\(^b\)Hydrogen bond donor (acceptable range: ≤5).
\(^c\)Hydrogen bond acceptor (acceptable range: ≤10).
\(^y\)High lipophilicity (expressed as LogP, acceptable range: <5).
\(^\mu\)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 respectively. Murrayanine and Clausenaline E from Clausena lansium detected with significant docking score which may be a potent analgesic compound because the better docking score, the compound will be more potent.

COMPETING INTERESTS
The authors declare that they have no competing interests.

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