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Presuming the Probable Anti-inflammatory Mechanism of Ursolic Acid: a plant derived pentacyclic triterpenoid, using molecular docking

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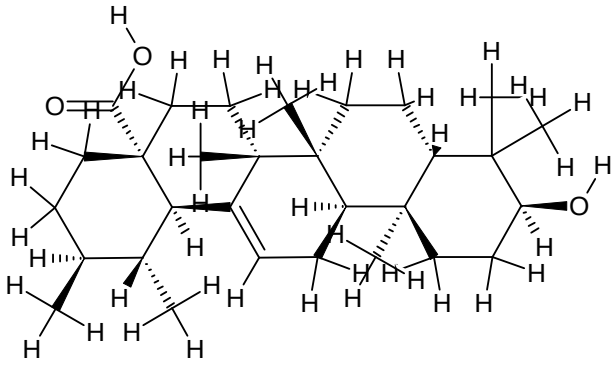
ABSTRACT

Diverse Non-steroidal anti-inflammatory drugs and COX-2 inhibitors selectively binds to COX-2 and provide relief from the symptoms of pain and inflammation. However, they lack anti-thrombotic activity and hence lead to cardiovascular and renal liabilities apart from gastrointestinal irritation. To ameliorate the situation, the search can be focused on plant originated natural products that could offer better relief from inflammation than currently used commercial drugs. As an attempt to identify such natural alternates with anti-inflammatory activity, Ursolic acid, a pentacyclic triterpenoid was studied against human COX-2 enzymes using MOE programme. The Docking analysis reveals that Ursolic acid inhibit COX-2 enzyme by hydrophobic and hydrogen bonding interactions.

Keywords: NSAID, COX-2, Docking, Hydrophobic, Ursolic acid.

INTRODUCTION

Triterpenoids exist widely in nature and are used for medicinal purposes in many Asian countries. Ursolic acid, a pentacyclic triterpenoid found in rosemary, possesses anticancer and anti-inflammatory effects [1,2,3,4]. It inhibits PMA-induced inflammation and tumor promotion in mouse skin[1].



Optimized Structure of Ursolic Acid

These effects have been attributed, in part, to inhibition of PG synthesis [1,3]although the mechanisms are incompletely understood. In this paper we are reporting probable binding mechanism of Ursolic acide with cox-2 by molecular docking.

Docking Algorithms

Docking programs are of two classes, “direct” and “unbiased.” Despite of the disadvantage of making assumptions about the potential energy landscape to save computational time direct docking softwares such as DOCK have the benefit of speed. Unbiased methods such as AutoDock, FTDOCK and MOE-Dock perform with few assumptions about the potential energy landscape. Thus at the expense of computation time, they find final docked solutions that the direct method might have missed. Here we report the use of MOE-Dock by Chemical Computing Group Inc.[5], which has the advantage flexible docking as well as integration with a graphical interface as well as with other modules, such as analysis, molecular mechanics, and molecular dynamics.

Docking Simulations

In MOE London dG scoring is used as default setting to calculate the exact confirmation and configuration of the ligand to find the best molecule with minimum binding energy and it can be used to develop potential drug molecules against the disease. The London dG scoring function estimates the free energy ΔG of binding of the ligand from a given pose. The functional form is a sum of terms:

$$\Delta G = c + E_{flex} + \sum_{h-bonds} c_{HB} f_{HB} + \sum_{m-lig} c_M f_M + \sum_{atoms\ i} \Delta D_i$$

where C represents the average gain/loss of rotational and translational entropy; E_{flex} is the energy due to the loss of flexibility of the ligand (calculated from ligand topology only); f_{HB} measures geometric imperfections of hydrogen bonds and takes a value in [0,1]; C_{HB} is the energy of an ideal hydrogen bond; f_M measures geometric imperfections of metal ligations and takes a value in [0,1]; C_M is the energy of an ideal metal ligation; and D_i is the desolvation energy of atom i. The difference in desolvation energies is calculated according to the formula

$$\Delta D_i = c_i R_i^3 \left\{ \iiint_{u \notin A \cup B} |u|^{-6}\, du - \iiint_{u \notin B} |u|^{-6}\, du \right\}$$

Where *A* and *B* are the protein and/or ligand volumes with atom *i* belonging to volume *B*; R_i is the solvation radius of atom *i* (taken as the OPLS-AA van der Waals sigma parameter plus 0.5 Angstrom); and C_i is the desolvation coefficient of atom *i*. Atoms are categorized into ~12 atom types for the assignment of the C_i coefficients. MOE 2008.10 was run on a Windows XP based Pentium IV 2·66 GHz PC (with 1GB RAM).

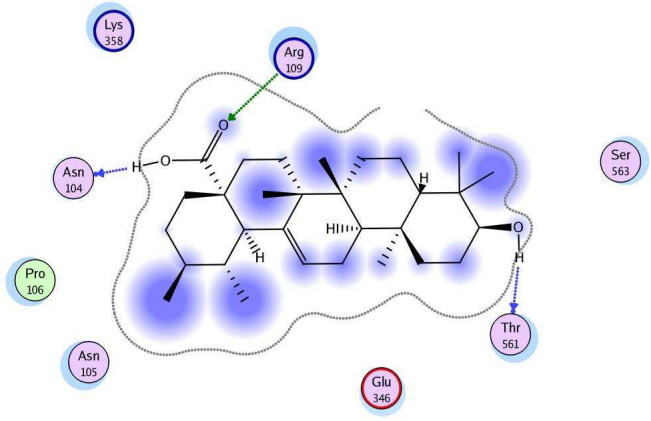
Docking run parameters:

Since the main goal of this study was to perform docking to understand binding between ligand (Ursolic acid) and receptor (COX-2 PDB ID-1cvu'a) was chosen to get fruitful results. During docking most of the default settings were applied except that the number of *Retain* were 10 instead of 30 during docking in MOE. Protein structures were first repaired and then appropriately protonated in the presence of ligand using the Protonate3D[6] process in MOE. Proteins prepared in this manner were applied directly for docking. It is well documented in literature[7] that if a crystallographic structure of the protein complexed with a relatively close analog of the ligand is available, "ligand-based docking" may be performed. In this procedure, one or more conformations of the candidate ligand are fitted to the crystallographic structure of the known ligand by optimizing the similarity in electrostatic and steric potentials. The experimental structure of the "template" ligand is then deleted, leaving the candidate ligand docked to the protein. In addition, the conformation of the fitted ligand may be simultaneously optimized during the fitting. The same strategy was used to get best docking results. The default procedure using Triangle Matcher placement method with London dG scoring was used for the docking runs.

RESULTS AND DISCUSSION

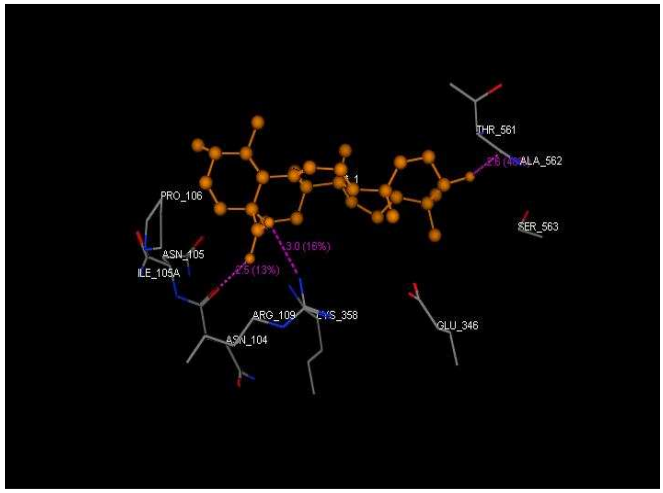
Molecular docking of ligands with target proteins are routinely and extensively used to reduced cost and time of drug discovery. The Carboxylic acid in ursolic acid is unteracting with asn-104, and OH group is showing same with Thr561 therefor these two groups are responsible for tight binding with cox-2 (as shown in figure 1).

Figure-1 Showing 2D hydrogen bonding of Ursolic acid with COX-2 enzyme.



To add further the two methyl groups are enhancing the interaction with cox-2 bacause of their hydrophobic nature and peculiar arrangement. The shape of ursolic acid matches excellent with the receptor pocket thus ursolic acid has best fit in the cox-2 .The Ursolic acid, a pentacyclic triterpenoid was docked deeply within the binding pocket region forming interaction with binding site residues of COX-2.

Figure-2 Showing 3D hydrogen bonding of Ursolic acid with COX-2 amino acids with interatomic distances and % of hydrogen bonding.



Hydroxy group may imparting pharmacophoric feature to the ursolic acid and act as hydrogen bond donar in drug receptor interaction therefore enhancing the affinity toward cox-2 enzyme.The percent of hydrogen bonding between OH and Thr 561 was found to be 48% and interatomic distance was maintained at 2.6 A^0. (as shown in figure no2).

In case of Carboxylic group, Carbony group of carboxylic moiety act as hydrogen bond acceptor with the percent of hydrogen bonding was 13 % and interatomic distance was 2.5 A^0 wheras OH group of carboxylic moiety act as hydrogen bond donor with the percent of hydrogen bonding was found to be 16% and interatomic distance was maintained at 3.0 A^0. (as shown in figure no2).

Further amino acids Residues lys 358, pro 106 , asn 105, glu 346 and ser 563 which approach closely to the ligand but do not have any qualifying strong interactions (i.e. hydrogen bonds) may be classified as non-bonded residues that have a significant effect on the orientation and binding of the ligand, but which may be spread out over a number of pairwise contacts, each of which is relatively weak.

Some false positives and false negatives were observed but considering the limitations of the available docking program, even the best software can not mimic the natural environment in the cell therefore the results are encouraging. The Ursolic acid may be considered as novel inhibitors of COX-2 and as promising lead-compounds for developing new anti-inflammatory drugs.

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