# Virtual screening for potential COX-inhibiting constituents from *Mimosa pudica*

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## ARTICLE INFO

## ABSTRACT

Developing a new agent in the anti-inflammatory and 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 of *Mimosa pudica* Linn. to reveal its potentiality by molecular docking analysis to find out its potent compound against COX which was done by GOLD docking analysis. Docking studies by GOLD showed that vitexin of *Mimosa pudica* had the highest fitness score against the COX-1 which is 60.43 and 63.49 for COX-2 enzyme. Vitexin of *Mimosa pudica* detected with significant fitness score and hydrogen bonding against COX-1 and COX-2 which may be a potent analgesic compound.

## INTRODUCTION

Having the anti-inflammatory, analgesic and antipyretic effects, non-steroidal anti-inflammatory drugs (NSAIDs) form an important class of widely used therapeutic agents. Inflammation is a process involved in the pathogenesis of several disorders like arthritis and cardiovascular disease (Jiang and Ames, 2003). Cyclooxygenase (COX) is an endogenous enzyme which catalyses the conversion of arachidonic acid into prostaglandins and thromboxanes (Vane *et al.,* 1998; Smith *et al.,* 2000). The enzyme exists in at least two isoforms, COX-1 and COX-2. Although both the isoforms catalyze the same biochemical conversion, the two isoforms are subject to a different expression regulation (Smith- *et al.,* 1993). COX-1 is a constitutive enzyme and is responsible for the supply of prostaglandins which maintain the integrity of the gastric mucosa and provide satisfactory vascular homeostasis whereas COX-2 is an inducible enzyme and is expressed only after an inflammatory stimulus (Kurumbail *et al.,* 1996; Ishikawa *et al.,* 2009). Literature studies indicate that direct tissue contact of NSAIDs gives the side effects like gastric upset, irritation, and ulceration (Lanza, 1998), and also confirms that gastrointestinal side effects of NSAIDs such as irritation and GI bleeding are due to the presence of a free carboxylic group in the parent drug (Husain *et al.,* 2005; Metwally *et al.,* 2007). Thus, developing new agents with minimum or without side effects is an extensive research area in the present scenario. To find out a potent anti-inflammatory compound and we chose *Mimosa pudica* L. commonly known as 'Lajjabati' belonging to the family Fabaceae, is a stout strangling prostrate shrubby plant with compound leaves, sensitive to touch, spinous stipules and globose pinkish flower heads. It grows in almost all parts of Bangladesh (Akter *et al.,* 2010; Baghel *et al.,* 2013; Malayan *et al.,* 2013). It is originated in South America and naturalized almost throughout the tropical and subtropical parts of India (Akter *et al.,* 2010). The plant is regarded as diuretic, astringent and antispasmodic. Leaves and roots are used in the treatment of piles and fistula. Paste of leaves is applied to hydrocele. Cotton impregnated with juice of leaves is used for dressing sinus. The plant is also useful in the treatment of sore gums and is used as a blood purifier (Vaidya and Sheth, 1986). It is also used for treating convulsions of children. Ethanolic extract of *Mimosa pudica* showed nootropic (cognition enhancement) activity in Wistar Albino Rats (Ayissi Mbomo *et al.,* 2012) and also anti-helmintic (De Luccia, 2012).

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Various studies suggested that this plant have therapeutic activities such as urolithiasis, ovulation, vibriocidal, anti-depressant, estrogenic and antiestrogenic activities, anti-implantation and antiestrogenic activity, effects on oestrous cycle and ovulation, hyperglycemic, anticonvulsant activity, hyaluronidase and protease activities (Sanberg, 1976; Molina *et al.,* 1999; Ngo Bum *et al.,* 2004; Ganguly *et al.,* 2007; Kokane *et al.,* 2009; Ahmad *et al.,* 2012). However, the analgesic and anti-inflammatory activity of *Mimosa pudica* has been established reported in earlier studies (Ayissi Mbomo *et al.,* 2012). Various literature suggested that *Mimosa pudica* contain compounds like Crocetin, Mimosine, Norepinephrine, Thiamin (Ahmad *et al.,* 2012), Turgorin (Varin *et al.,* 1997), Isorientin, Orientin, Isovitexin, Vitexin (Zhang *et al.,* 2011), D-pinitol, Jasmonic acid (Tsurumi and Asahi, 1985) and Quercetin (Shrinivasan *et al.,* 2012). This work was aimed to describe described the anti-inflammatory and analgesic activity of *Mimosa pudica* by *in silico* molecular docking analysis to find out the novel compound having the inhibitory activity against COX-1 and COX-2 enzymes. The docking analysis involves the prediction of ligand conformation and orientation (or posing) within a targeted binding site. In the main, there are two aims of docking studies: accurate structural modeling and correct prediction of activity. However, the identification of molecular features that are responsible for specific biological recognition, or the prediction of compound modifications that improve potency, are them are much more focused on capturing energetic than entropic effects (Kitchen *et al.,* 2004; Dash R, 2014).

## MATERIALS AND METHODS

### Ligand preparation

From the literature review, all compounds, Crocetin, Mimosine, Norepinephrine, Thiamin, Turgorin, Isorientin, Orientin, isovitexin, Vitexin, D-pinitol, Jasmonic acid and Quercetin was drawn in Symyx Draw 4.0 represented in figure 1 and then prepared for docking using the Sybyl 7.3 Molecular Modeling Suite of Tripos, Inc. 3D conformations (here only shows 2D structures) were generated using Concord 4.0 (Hevener *et al.,* 2009), hydrogen atoms were added and charges were loaded using the Gasteiger and Marsili charges calculation method (Hristozov *et al.,* 2007).

The ligand were minimized with the Tripos Force Field prior to docking using the Powell method with an initial Simplex (Osolodkin *et al.,* 2011) optimization and 1000 iterations or gradient termination at 0.01 kcal/(mol*A). Input ligand file format was mol2 for all docking programs investigated.

### Protein preparation and active site determination

The crystal structure COX-1 and COX-2 enzymes were collected protein data bank (Berman *et al.,* 2000) pdb id: 2OYE (COX-1) and 6 COX (COX-2). Two enzymes were prepared according to the docking protocol of GOLD. The active site of these enzyme were identified according to the giving information by Harman *et al.* 2007 (Harman *et al.,* 2007) for COX-1 and Kurumbail *et al.,* 1996 (Kurumbail *et al.,* 1996) for COX-2.
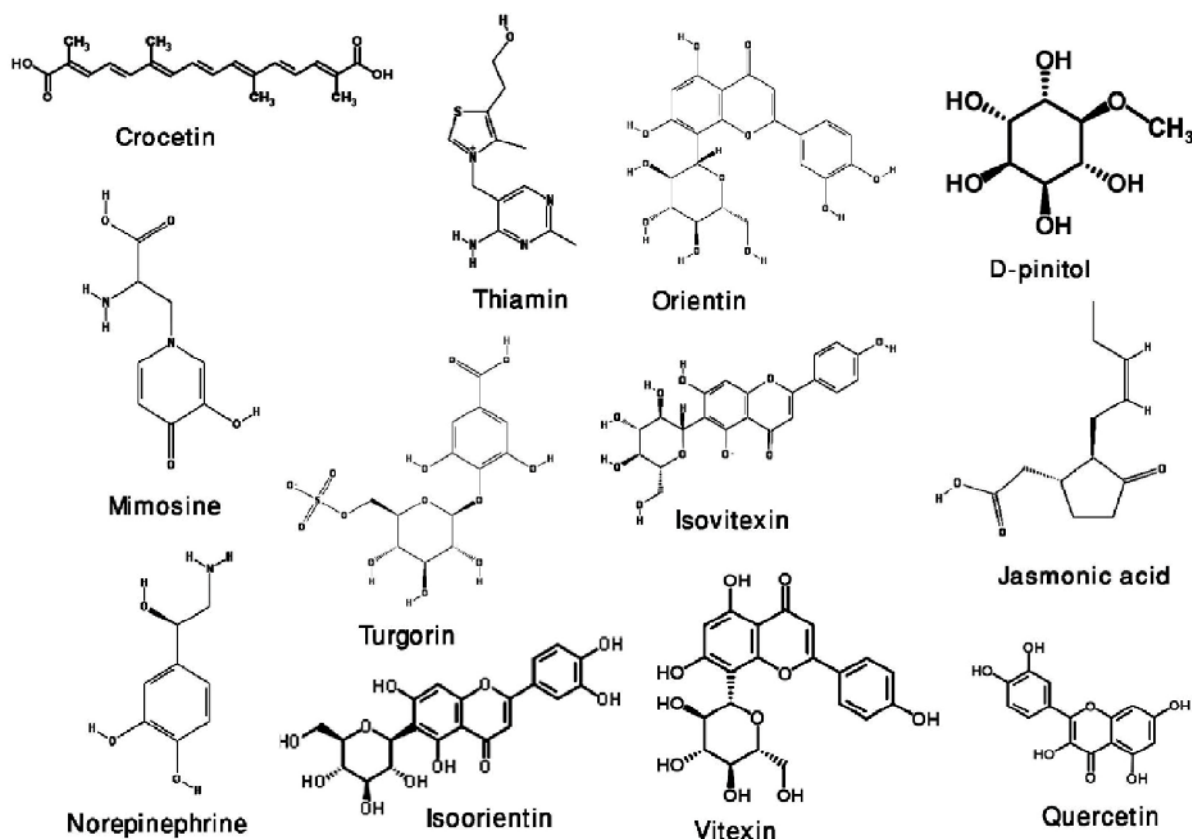


**Fig. 1:** Two-dimensional structure of all compounds isolated from *Mimosa pudica*

**Table 1:** Gold fitness score of all compounds of *Mimosa pudica* against COX-1 and COX-2 protein.

| Compounds Name | COX-1 | | | | | COX-2 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Gold Fitness | S(hb_ext) | S(vdw_ext) | S(hb_int) | S(int) | Gold Fitness | S(hb_ext) | S(vdw_ext) | S(hb_int) | S(int) |
| Crocetin | 35.82 | 0.01 | 44.88 | 0.00 | -25.90 | 34.33 | 0.00 | 43.70 | 0.00 | -25.77 |
| Mimosine | 36.04 | 2.59 | 28.40 | 0.00 | -5.60 | 36.39 | 9.01 | 24.17 | 0.00 | -5.85 |
| Norepinephrine | 33.26 | 2.61 | 27.53 | 0.00 | -7.20 | 32.32 | 2.37 | 26.66 | 0.00 | -6.70 |
| Thiamin | 51.33 | 3.36 | 38.76 | 0.00 | -5.32 | 50.36 | 1.95 | 40.88 | 0.00 | -7.80 |
| Turgorin | 50.50 | 7.68 | 41.62 | 0.00 | -14.42 | 58.04 | 12.84 | 43.19 | 0.00 | -14.19 |
| Isorientin | 44.11 | 2.93 | 41.11 | 0.00 | -15.34 | 36.01 | 1.83 | 36.55 | 0.00 | -16.07 |
| Orientin | 38.84 | 1.85 | 38.59 | 0.00 | -16.06 | 32.02 | 4.09 | 42.16 | 0.00 | -30.04 |
| Isovitexin | 46.70 | 1.08 | 41.96 | 0.00 | -12.08 | 44.37 | 9.10 | 51.02 | 0.00 | -34.88 |
| Vitexin | 60.43 | 3.76 | 49.93 | 0.00 | -11.98 | 63.49 | 7.54 | 50.85 | 0.00 | -13.97 |
| D-pinitol | 30.78 | 4.31 | 23.70 | 0.00 | -6.12 | 30.82 | 1.98 | 24.08 | 0.00 | -4.28 |
| Jasmonic acid | 37.40 | 0.00 | 31.17 | 0.00 | -5.45 | 41.76 | 6.00 | 30.15 | 0.00 | -5.70 |
| Quercetin | 48.53 | 5.36 | 40.20 | 0.00 | -12.11 | 45.44 | 8.82 | 36.19 | 0.00 | -13.15 |
| Crocetin | 35.82 | 0.01 | 44.88 | 0.00 | -25.90 | 34.33 | 0.00 | 43.70 | 0.00 | -25.77 |

**Table 2:** Protein Ligand Interaction of vitexin with COX

| COX-1 | | COX-2 | |
|---|---|---|---|
| Interacted Amino acid residue | Hydrogen bond Distance (Å) | Interacted Amino acid residue | Hydrogen bond Distance (Å) |
| SER 530 | 2.904 | SER 530 | 2.722 |
| TYR 385 | 2.747 | SER 530 | 2.682 |
| SER 530 | 2.048 | TYR 385 | 2.349 |
| | | TYR 355 | 2.275 |
| | | ARG 120 | 3.055 |

## Docking using GOLD (Genetic Optimization for Ligand Docking)

GOLD utilizes genetic algorithm to explore the rotational flexibility of receptor hydrogens and ligand conformational flexibility (Jones *et al.,* 1997). In GOLD docking was carried out using the wizard with default parameters population size (100); selection pressure (1.1); number of operations (10,0 00); number of islands (1); niche size (2); and operator weights for migrate (0), mutate (100), and crossover (100) were applied. The active site with a 10 Å radius sphere was defined by selecting an active site residue of protein.

Default Genetic Algorithm settings were used for all calculations and a set of 10 solutions were saved for each ligand. GOLD was used by a GoldScore fitness function. GoldScore is a molecular mechanism like function and has been optimized for the calculation of binding positions of ligand. It takes into account four terms:

**Fitness = S$_{(hb\_ext)}$ + 1.3750*S$_{(vdw\_ext)}$ + S$_{(hb\_int)}$ + 1.0000*S$_{(int)}$**

S$_{(int)}$ = S$_{(vdw\_int)}$ + S$_{(tors)}$

Where, S$_{hb\_ext}$ is the protein-ligand hydrogen bonding and s$_{vdw\_ext}$ are the vanderwaals interactions between protein and ligand. S$_{hb\_int}$ are the intramolecular hydrophobic interactions where as S$_{vdw\_int}$ is the contribution due to intra molecular strain in the ligand (Uddin *et al.,* 2014).

## RESULTS

After preparing the compounds of *Mimosa pudica* mentioned above were subjected to dock in the active site of COX-1 and COX-2 enzyme by GOLD docking method. The results of docking analysis are listed in Table 1. After docking the ligand protein complex having best fitness score was saved in pdb format than subjected to be analyzed in the Accelrys Discovery Studio

Visualizer and result of protein and ligand interactions are listed in Table 2. Docking studies showed that vitexin had the best gold fitness score against the COX-1 which was 60.43 and 63.49 for.

## DISCUSSION

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 (Franca *et al.,* 2013). To identify a potential analgesic lead molecule, we have subjected the docking analysis of the active compounds of *Mimosa pudica* to the active site cyclooxygenase enzymes viz. COX-1 and COX-2. Gold fitness score suggested that vitexin had the highest affinity to the COX-1 and COX-2 enzymes corresponding to the other compounds. Literature based studies suggested that several structural features are considered to be an important for efficient COX inhibition: (i) a carboxylate moiety that interacts with the Arg 120 side chain; (ii) a carbonyl moiety that interacts via a hydrogen bond with the side chain of Ser 530 and (iii) a distal aromatic ring filling a hydrophobic pocket beneath the Tyr 385 side chain (Luong *et al.,* 1996; Llorens *et al.,* 2002; Pouplana *et al.,* 2002; Michaux and Charlier, 2004). Protein ligand interaction of vitexin with COX-1 and COX-2 represented in Table 2 and shown in Figure 2 and 3 has been postulated that vitexin has the enzyme catalysis activity in two enzymes but active in COX-2 enzyme due to formation of three hydrogen bonds with three residues Arg 120, Tyr 385 and Ser 530 which lead to process anti-inflammatory action by inhibiting biosynthesis of prostaglandins and thromboxanes from arachidonic acid.
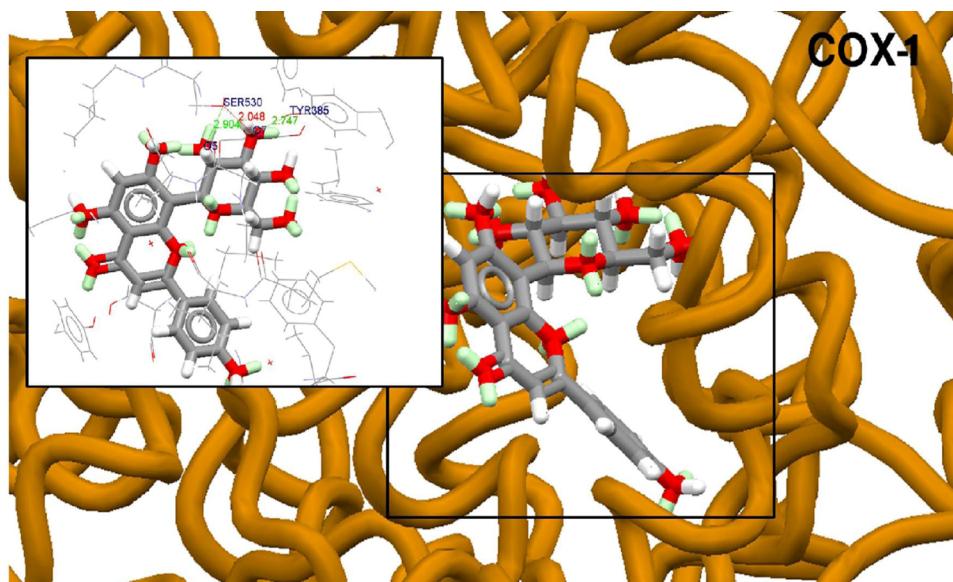
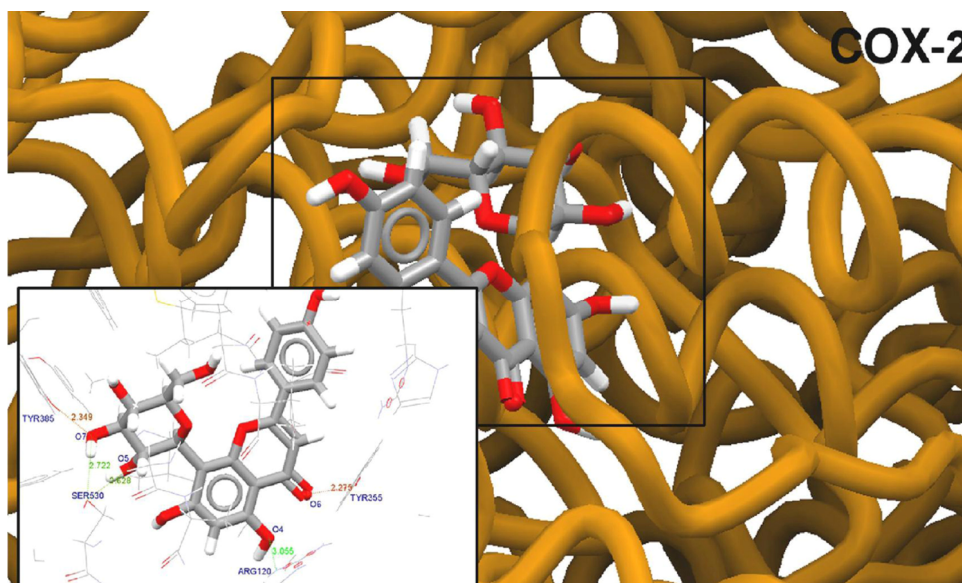**Fig. 2:** Interaction of vitexin with COX-1 protein



**Fig. 3:** Interaction of vitexin with COX-2 protein

## CONCLUSION

The present study revealed that *Mimosa pudica* has the compound named vitexin, 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.

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## COMPETING INTERESTS

All authors declare that they have no competing interests.

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