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Original Research Article

Therapeutic and Mechanistic Approaches of *Tridax procumbens* Flavonoids for the Treatment of Pyrexia: Molecular Docking

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Abstract: The perennial plant *Tridax Procumbens* is particularly intriguing, and its secondary metabolites, also known as T. procumbens flavonoids (TPFs), are well-known phytochemical agents due to their diverse medicinal uses, including their anti-inflammatory, anti-anemic, and anti-diabetic effects. The antipyretic potential of luteolin, a natural product isolated from the medicinal plant *Tridax procumbens*, was investigated for antipyretic action through molecular docking analyses with the target enzymes cyclooxygenase-2 (COX-2). The docking result of luteolin revealed that their docking scores was -7.24 kcal mol^{-1} and it can be predicted as good inhibitor of human COX2 receptor.

Keywords: *Tridax procumbens*, Luteolin, COX-2 & Molecular docking.

INTRODUCTION

Tridax Procumbens is a species of flowering plant in the daisy family, also known as coat buttons or tridax daisy. It is most well-known for being a pervasive weed and pest plant. Although it is indigenous to the tropical Americas, it has been spread throughout the world to tropical, subtropical, and mild temperate climates [1, 2]. *Tridax Procumbens* has historically been used in India as an anticoagulant, antifungal, and insect repellant in addition to being used to heal wounds. It is useful for dysentery and diarrhoea. In traditional treatments, its leaf extracts were known to treat infectious skin problems. Along with treating gastritis and heartburn, it is a well- known ayurvedic remedy for liver conditions or having a hepatoprotective nature. To confirm the accusations that indigenous people in the Udaipur district of Rajasthan were using the herb, research was conducted [3, 4].

Tridax procumbens

Flavonoids are found in the leaves and other organs and haves shown to be useful as anticoagulants, hair tonics, anti-fungal, against problems of bronchial catarrh, diarrhea, dysentery and wound healing. Luteolin and Quercetin were also isolated from Tridax, along with the flavonoid Procumbenetin. Lutein, glucoluteolin, and isoquercetin are found in the flowers of T. procumbens. Luteolin has anti-inflammatory and anti-carcinogenic activity [5], probably due to its anti-oxidant activity and its free-radical scavenging ability. In the present investigation as per literature survey Luteolin was selected for the molecular target against Cox-2 for elucidation of anti-pyretic potential.

EXPERIMENTAL WORKS

Ligand Preparation

2D Structure of ligand (luteolin) was drawn using ChemSketch [6], the two-dimensional structure of was converted into 3-D structure and optimized with 3D geometry. The optimized structure was saved in PDB format for AutoDock compatibility. The basic structure of ligand (luteolin) is given below:

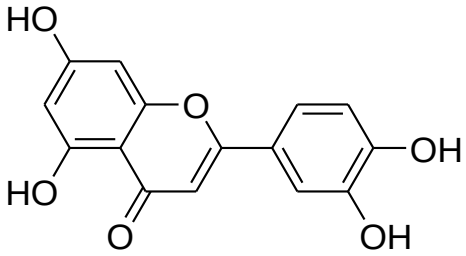


Figure 1: 2D structure of luteolin

Preparation of the Grid File

The regions of interest used by Autodock were defined by considering grid area by making a grid box around the active sites. Grid box plays a central role in process of docking as it is made to cover all the amino acids present in active sites necessary for binding other than those present in receptor. Grid box has 3 thumbwheel widgets which let us change the number of points in the x, y and z dimensions. The spacing between grid points can be adjusted with another thumbwheel, the value in the study taken is 0.375 Å and No. of points considered are 46, 44 and 46 points in the x, y, and z dimensions and 38.042, 2.131 and 61.28 as x, y, z centers.

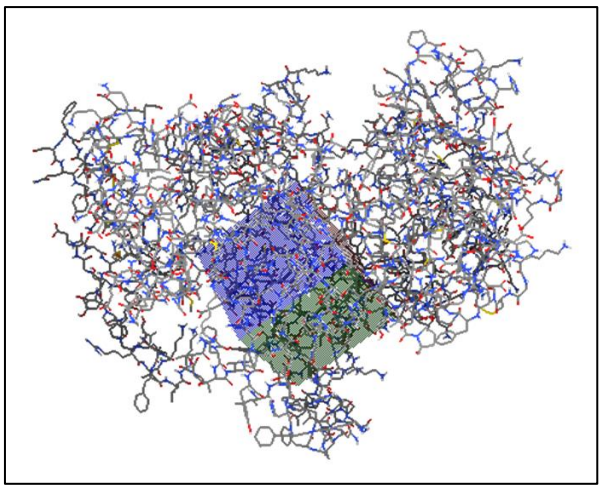


Figure 2: Grid box covering all active sites in receptor

Preparation of the Docking File

All the calculations were carried out by using Autodock 4.2 as docking tool. The visualization and other programs necessary for docking studies were performed out by means of Pymol, Chimera,[DS visualizer, MMP Plus [7].

Docking of Human COX-2 with Luteolin

Crystal Structure

The crystal structure of the protein consisting of receptor associated with bound ligand mefenamic acid is downloaded from the Protein Data Bank portal. All the primary information regarding receptor and structure (5ikr.pdb) registered in the Protein data bank was used. The bound ligand mefenamic acid is found within the receptor [8].

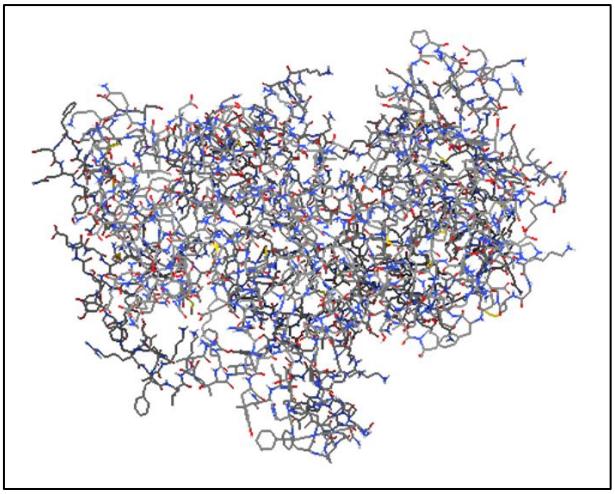


Figure 3: Crystal structure of human COX2 receptor with bound serotonin (PDB ID-5ikr)

Processing of Protein

The downloaded receptor protein is having two chains, i.e. chain A, and B. Out of these two chains, chain A was selected for experimental purpose and other chains were removed from it. The bound ligand mefenamic was separated from the macromolecular complex by using software Chimera [9].

Molecular Docking Simulation Studies

Docking of luteolin ligand on human COX-2 enzyme was performed by Autodock. All the bonds of ligand were kept flexible, while no residues in receptor were made flexible [10, 11].

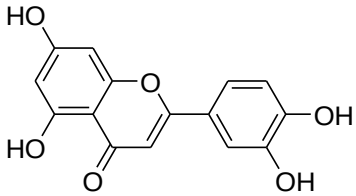
Toxicity & ADME-T Studies

The modified lead molecules are studied by online program OSIRIS, for prediction of presence of any toxic group as well as presence of any toxic group and ADME- T properties [12].

RESULTS AND DISCUSSION

Luteolin and Quercetin were also isolated from Tridax, along with the flavonoid Procumbenetin. Lutein, glucoluteolin, and isoquercetin are found in the flowers of T. procumbens. Luteolin has anti-inflammatory and anti-carcinogenic activity (Rao *et al.*, 2012), probably due to its anti-oxidant activity and its free-radical scavenging ability (Samantha Beck *et al.*, 2018). As per literature survey Luteolin was selected for the molecular target against Cox2 for elucidation of anti-pyretic potential. The outcome showed that the molecular docking of luteolin with human COX2 receptor revealed that (Table 1), it has exhibited the chemical interaction with the amino acids in the active pockets which is showed in Figure. 4. Theoretically, the ligand molecule has shown encouraging docking score. The docking result of luteolin revealed that their docking scores was -7.24 kcal mol^{-1} and it can be predicted as good inhibitor of human COX2 receptor. The pharmacokinetic profile of luteolin reveals that it is having good pharmacokinetic profile without presence of any major toxic effects. The pharmacokinetic and toxicity profiling results of luteolin were shown in figure 5.

Table 1: Results of docking of luteolin against human COX2 receptor

Sl. No	Compound Name	Structure	Binding Energy (Kcal/mole)	Ki
1	Luteolin		-7.24	4.9

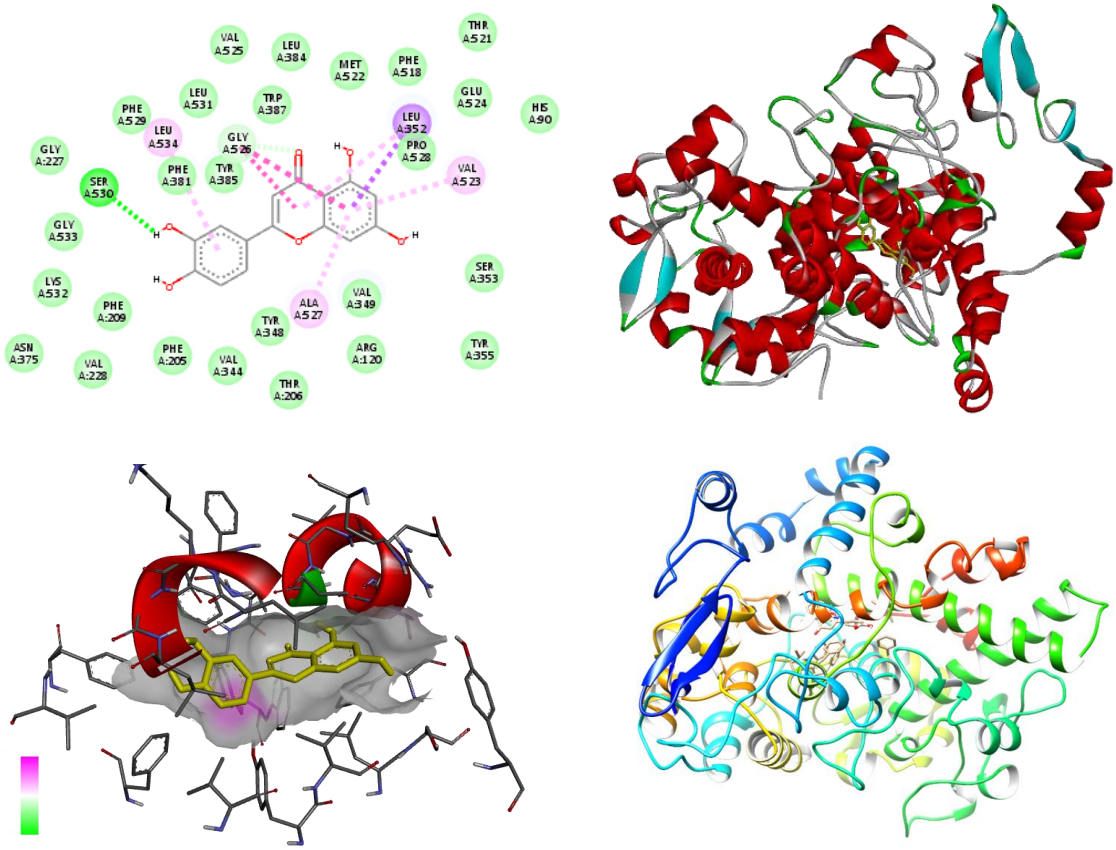


Figure 4: Binding mode of luteolin within the active site of COX2 Receptor

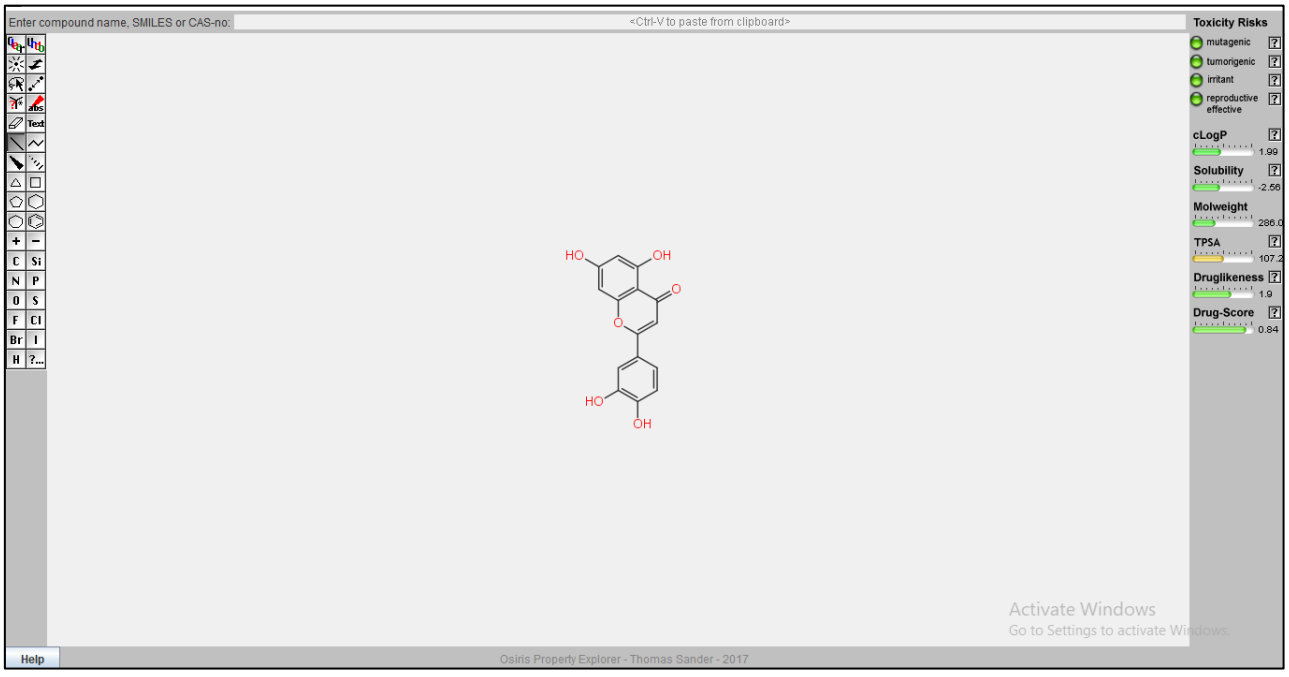


Figure 5: Pharmacokinetic and toxicity profiling of luteolin

CONCLUSION

The outcome of molecular docking elucidated the possible mechanism of luteolin present *Tridax Procumbens* for antipyretic action might be inhibition of prostaglandin synthesis by diminishing cyclooxygenase enzyme's activity. Antipyretic activity might be denoted by inhibition of pyrexia inducing mediated activity of COX-2 enzyme. The study will be further extended to identify and characterize the exact active phytoconstituents and to elucidate the exact mechanism of action, which is responsible for the observed significant analgesic and antipyretic activity.

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