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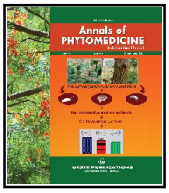

Original Article : Open Access

Molecular docking studies of COX-2 protein with 8-deoxylactucin of *Cichorium intybus* L. involved in anti-inflammation activity

Mamta Arya, Keena Singh Rathour, Apoorv Tiwari*, Vishwajeet Singh Chauhan and Gohar Taj◆

Department of Molecular Biology and Genetic Engineering, College of Basic Sciences and Humanities, Govind Ballabh Pant University of Agriculture and Technology, Pantnagar-263145, U.S. Nagar, Uttarakhand, India

**Department of Computational Biology and Bioinformatics, Jacob School of Biotechnology and Bio-Engineering, Sam Higginbottom University of Agriculture, Technology and Sciences, Prayagraj-211007, India*

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Abstract

Cichorium intybus L., commonly known as Chicory, is an everlasting herb with immense therapeutic activity and is used in traditional medicine. Due to the presence of 8-deoxylactucin, this plant has anti-inflammatory activity. This study demonstrates the structural and physicochemical properties of Cyclooxygenase-2 (COX-2) through various bioinformatics approaches along with docking studies. Through, the docking studies, it was found that COX-2 protein interacts with the 8-deoxylactucin with the lower energy – 4.44 kcal/mol with the threonine – 212 interactive amino acid residue showed hydrogen bonding interactions. For validation of our results, we have gone through the docking of COX-2 protein with the available anti-inflammatory drug aspirin and the docking score was found – 4.9 which is approx similar to the docking score of 8-deoxylactucin. Molecular docking results of 8-deoxylactucin and COX-2 protein clinical studies may give justification for the active participation of 8-deoxylactucin as an anti-inflammatory compound in chicory. This study is progressively useful for further wet-lab experiments to discover the mechanism of 8-deoxylactucin in the inhibition of COX-2 protein which is involved in inflammation.

1. Introduction

The trending research in Chicory (*Cichorium intybus* L.) is gaining interest because of its extensible features in the food and pharmaceutical industry. Chicory is an essential plant, grown in different parts of the world, having numerous medicinal and nutritional properties. Chicory is a well-known coffee substitute with no caffeine in earlier times, but is now also used for medicinal purposes ranging from wounds to diabetes (Street *et al.*, 2013). In India, it has been used as a medicine to treat various diseases like fever, diarrhea, spleen enlargement, jaundice, liver enlargement, gout, and rheumatism (Ali *et al.*, 2018). Chicory leaves can be used as a source of natural antioxidants for pharmaceutical or dietary needs. Chicory seeds consist of high levels of minerals K, Ca, P, Mg, Cu, Zn, and Mn, and these elements are believed to have important pharmacological activity (Nwafor *et al.*, 2017).

Natural herbs are widely used for medicinal purposes since ancient times (Nupur Mehrotra, 2021). Chicory root consists of some phytochemicals such as inulin (starch-like polysaccharide), coumarins, flavonoids, and sesquiterpene lactones (lactucin and lactucopicrin), tannins, alkaloids, vitamins, minerals, and volatile oils. The secondary metabolites (flavonoids, tannins, and coumarins) found in chicory, have been revealed to exhibit some pharmacological activities such as antioxidant, anticancer, anti-inflammatory, antiparasitic, antihepatotoxic, which result in positive health effects on humans and livestock (Ripoll *et al.*, 2017; Munnithum *et al.*, 2018). These findings suggest that chicory extract could be developed as a functional food. Cyclooxygenase (COX-1 and COX-2) enzymes are essential for the conversion of arachidonic acid into inflammatory prostaglandins. Cyclooxygenase-2 (COX-2), an inducible form of the enzyme is known to play role in inflammation (Rouzer *et al.*, 2009). Inflammation is responsible for the excretion of mediators like interleukin-1, histamines, prostaglandins, leukotrienes (LTs), *etc*, and is linked to all chronic and degenerative diseases (Abdulkhaleq *et al.*, 2018). Large numbers of nonsteroidal anti-inflammatory drugs (NSAIDs) are known to work as inhibitors of the COX-2 enzyme. Overexpression of COX-2 has been reported in many malignant tumors including breast cancer (Zarghi *et al.*, 2011).

The anti-inflammatory activity of chicory is contributed by the presence of 8-deoxylactucin (Rizvi *et al.*, 2014; Abdullah *et al.*, 2019). The root extract of chicory in ethyl acetate showed significant inhibition of prostaglandin E2 (PGE2) expression in human colon carcinoma HT29 cells treated with TNF-alpha a pro-inflammatory agent (Shirakami *et al.*, 2021). It was observed that chicory extract inhibits the COX-2 expression either through the TNF-alpha or direct inhibition of COX enzyme activities with a significantly higher selectivity for COX-2 activity (Alexanian *et al.*, 2017).

A major sesquiterpene lactone of chicory root, the guaianolide 8-deoxylactucin, was identified as the key inhibitor of COX-2 protein expression present in chicory extract (Shishodia *et al.*, 2004). Due to

Corresponding author: Dr. Gohar Taj
Department of Molecular Biology and Genetic Engineering, College of Basic Sciences and Humanities, GovindBallabh Pant University of Agriculture and Technology, Pantnagar-263145, U.S. Nagar, Uttarakhand, India
E-mail: gohartajkhan@rediffmail.com
Tel.: +91-7906553007

advanced *in silico* approaches (Kamalakkannan *et al.*, 2021) and computational methods, we can easily identify the structure and function of proteins (Kufareva *et al.*, 2012; Imad and Veeresh, 2020; Gezici *et al.*, 2021). Considering the anti-inflammatory activity of chicory extract, the present investigation was undertaken to determine various physicochemical properties of COX-2 protein as well as docking studies with aspirin (well-known anti-inflammatory drugs) and with an 8-deoxylactucin compound from chicory.

2. Materials and Methods

The following methodology was adapted to perform the current study.

2.1 Protein and ligand retrieval

PDB database was used to retrieve the 3D structure and amino acid sequence of COX-2 protein. The ligand 8-deoxylactucin was retrieved from Pubchem database (https://pubchem.ncbi.nlm.nih.gov) in.sdf format (Pub Chem CID: 442196)

2.2 Primary and secondary structure analysis

Primary structure analysis was done with the help of a ProtParam tool (Expasy) (Gasteiger *et al.*, 2005). The protparam tool requires the protein sequence in fasta format. The secondary structure analysis was done with the help of CFSSP (Chou and Fasman Secondary Structure Prediction Server) (Kumar *et al.*, 2013).

2.3 Protein-protein interaction

STRING is a biological database and web resource of known and predicted protein-protein interactions. The STRING database contains information from numerous sources, including experimental data, and computational prediction methods. STRING database (Szklarczk *et al.*, 2017) was used to find the interaction of COX-2 protein with other proteins.

2.4 Molecular docking studies

Molecular docking study was performed by Schrodinger software with of COX-2 protein and as target protein whereas aspirin and 8-deoxylactucin as ligand molecules through the following steps:

2.4.1 Active site prediction

A Site Map module in maestro12.1 of Schrodinger was used for binding site prediction. A minimized form of COX-2 protein was imported in SiteMap, which identified the top-ranked potential receptor binding sites based on site score value. The receptor with a high site score value was selected and used for further receptor grid generation (Schrodinger Release 2020-4: SiteMap).

2.4.2 Receptor grid generation

Receptor grid generation was performed on the glide module in maestro 12.1 in Schrodinger software. Receptor grid generated with the prepared structure of COX-2 protein with appropriate bond orders, Van der Waals radius, and the partial atomic charge was imported, scaling factor and partial charge cut-off values were selected. Residues that were specific to the active site were selected based on the highest site score in SiteMap.

2.4.3 Ligand Preparation

Ligand 8-deoxylactucin and aspirin were prepared by Ligprep module using Epik tool in Schrodinger software to expand protonation and tautomeric states at 7.0 ± 2.0 pH units, while "Lipinski rule of 5" conformations of co-crystal ligands were used in the present study. The correct protonation states and energy minimization were performed on Epik (pH 7.0 ± 2.0) using a force field (Schrodinger Release 2020-2: Maestro).

2.4.4 Docking

Glide (grid-based ligand docking with energetics) require a set of previously calculated receptor grids and ligand, therefore, we prepared a receptor grid for COX-2 receptor protein. Glide application ligand docking module in maestro 12.1 in Schrodinger package was used for docking. A glide energy grid was generated for the prepared receptor and used for docking calculations considering the ligands as flexible but treating the receptor as a rigid structure. The "Glide XP" protocol was chosen during the docking, which deduces energy terms such as hydrogen-bond interactions, electrostatic interaction, hydrophobic enclosure, and pi-pi stacking interaction. XP score has the advantage that both the ligands and the active site (s) of the receptor can be flexible, allowing small structure rearrangements to reproduce the so-called "induced fit" when performing the score. The rest of the parameters were kept at default for the scoring (Schrodinger Release 2020-4: Glide).

3. Results

3.1 Primary and secondary structure determination

The ProtParam tool identified COX-2 protein as 604 amino acids long having 62 negatively charged amino acids and 61 positively charged amino acids and the formula of protein was given as $C_{3129}H_{4791}N_{823}O_{885}S_{28}$. The instability index (II), an indicator of the stability of protein was found at 37.67. This classifies the protein as a stable protein, as a value above 40 indicates the unstable nature of the protein (Guruprasad, *et al.,* 1990). The aliphatic index was found to be 80.70, showing the aliphatic side chain volume of protein, and the GRAVY (Grand Average of Hydropathicity) value was found as – 0.287, its negative sign indicates the nonpolar nature of the protein (Chang *et al.,* 2013).

The secondary structure determined by the CFSSP server showed that the linear peptide chain of protein had varying alpha helix, beta-pleated sheet, turns, and coils. The protein consisted of a total of 402 helices, 317 beta-sheet, and 83 turns and coils, and these secondary structures were 66.6% (α helix), 52.5% (β sheets), and 13.7% (turns and coils) (Figure 1). The three-dimensional structure of COX-2 protein (Figure 2) was retrieved from the PDB databank.

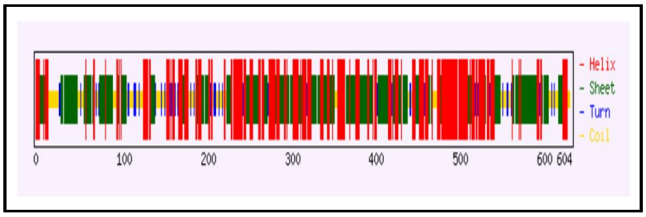

Figure 1: Secondary structure derived by CFSSP server.

3.2 Protein-protein interaction

COX-2 shares various metabolic associated networks with other proteins, shown in Figure 3. Here different associations indicated by different color edges and color saturation showed the functional association confidence score. The result showed the interaction with

a maximum score of 0.984 with prostaglandin-endoperoxide synthase (PTGS), indicating more strong interaction. Cyclooxygenase (COX) enzymes are also known as prostaglandin-endoperoxide synthase.

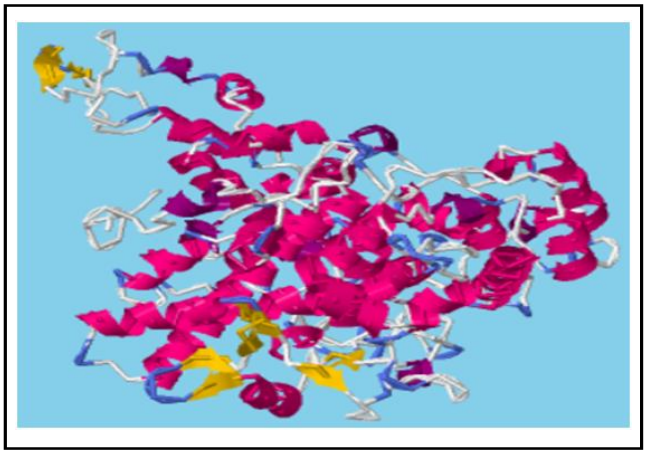

Figure 2: 3-D Structure of COX2 protein.

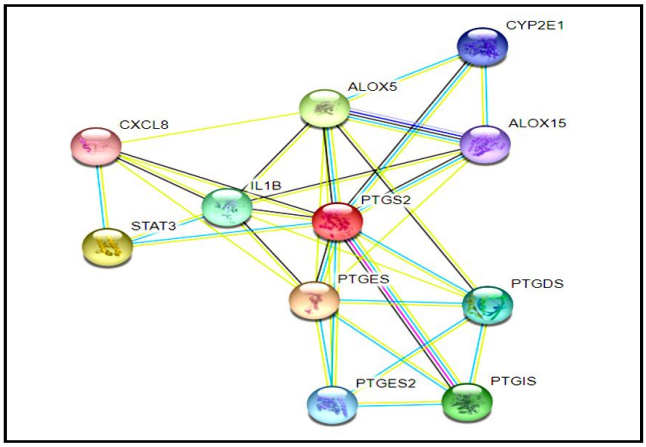

Figure 3: Protein-protein interaction network visualization. The color saturation of the edge represents the confidence score of a functional association, prostaglandin-endoperoxide synthase (PTGS) with a maximum score of 0.984.

3.3 Molecular Docking

Docking of COX-2 protein with the ligands 8-deoxylactucin and aspirin was done by Schrodinger software. The highest affinity of the ligand 8-deoxylactucin was found to be – 4.44 kcal/mol (Table 1) with theronine – 212 amino acid residue involved in hydrogen bonding interaction (Chen *et al.*, 2016). The docked protein-ligand complex structure was analyzed and it affirms the 8-deoxylactucin (anti-inflammatory compound) suitably bind to the COX-2 protein of human (Figures 4).

For validation of our results, we performed the docking of COX-2 protein with the available anti-inflammatory drugs like aspirin (Ghlichloo *et al.*, 2021), and the docking score was found –4.9 which is approx similar to the docking score of 8-deoxylactucin (Table 1). Aspirin drug showing interaction with three residues glutamine-454, histidine – 214, and threonine – 212. The amino acid threonine – 212 was found interact with both the ligand 8-deoxylactucin and aspirin (Figure 5).

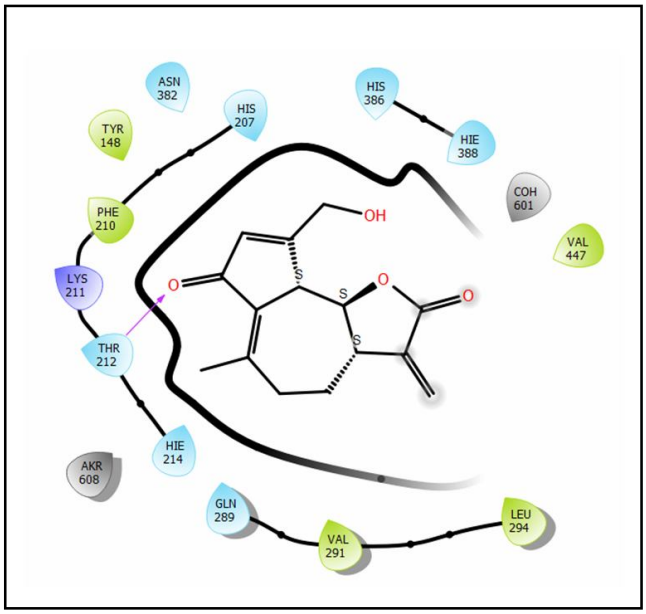

Figure 4: Interaction of COX-2 protein and 8-Deoxylactucin ligand docked complex structure. The 2D representation of the 3D structure shows the interaction of 8-Deoxylactucin with COX-2.

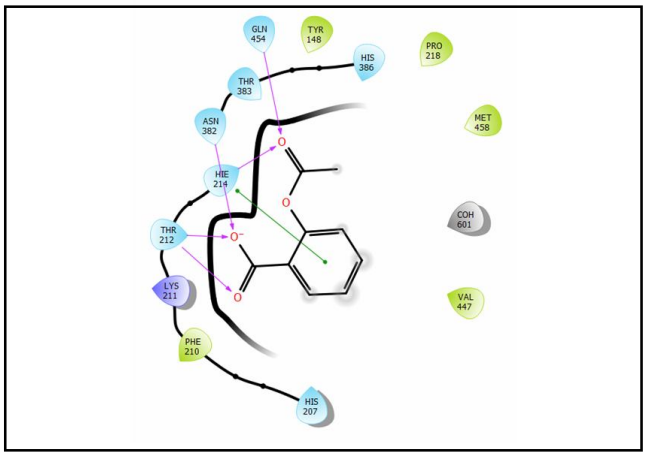

Figure 5: Interaction of COX-2 protein and aspirin ligand docked complex structure. The 2D representation of the 3D structure shows the interaction of aspirin with COX-2.

Table 1: Docking score of ligand 8-deoxylactucin, aspirin with the COX-2 protein

S.No.	Ligand	G score	Dock_Score
1	8-deoxylactucin_442196	– 4.47	– 4.44
2	Aspirin_2244	– 4.9	– 4.9

4. Discussion

Traditional medicines are an important source for drug discovery in past and now a days. However, many challenges faced by the scientific community to develop novel drugs from natural compounds, (Gezici 2022; Belkhodja *et al.*, 2017). For a long time,

medicinal plants have been the primary treatment for a variety of diseases, and numerous medications have been produced from traditional medicine. This study examines the medicinal properties of the chicory plant along with its anti-inflammatory properties. Chicory is a perennial plant that is planted all over the world and utilized as cattle feed, folkloric medicines, and a vegetable supplement to human diets. The chicory plant comes in a variety of types, each with its unique set of medicinal, culinary, and nutritional properties. Chicory plants include inulin, coumarins, tannins, monomeric flavonoids, and sesquiterpene lactones, among other phyto-compounds. Chicory's health-promoting properties include anti-inflammatory, anticarcinogenic, antiviral, antibacterial, and immune-stimulating, properties, as well as its antioxidative capabilities. To investigate the rationale behind the medical legacy of centuries of precious knowledge from traditional medicine, we aimed to perform virtual screening and identified the potential lead molecule 8-deoxylactucin from chicory which has anti-inflammatory activity. The total molecular weight of the COX-2 protein was found at 68996.12 Da with a theoretical isoelectric point (pI) of 7.02 which directly affect the solubility of the protein in water or salt solution and is useful for protein purification (Shaw *et al.*, 2001). The protein-protein interaction network of COX-2 protein with the central node, *i.e.*, PTGS2 which interacts with other proteins also is the target of nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin (Ricciotti *et al.*, 2011). PTGS2 is responsible for the production of inflammatory prostaglandins. Up-regulation of PTGS2 is also associated with increased cell adhesion, phenotypic changes, resistance to apoptosis, and tumor angiogenesis. In cancer cells, PTGS2 is a key step in the production of prostaglandin E2 (PGE2) (Gonçalves *et al.*, 2021). The docking results showed that 8-deoxylactucin can be taken as an herbal drug (Das, 2019), acting as an anti-inflammatory agent (Alam and Khan, 2020). As the available anti-inflammatory drug in the market may cause some side effects in adults in long time usage, so taking *C. intybus* daily dietary habits may prove to be beneficial against inflammation as well as other disorders of the liver and digestive tract (Maroon *et al.*, 2010).

5. Conclusion

Chicory has anti-inflammatory activity due to the presence of 8-deoxylactucin. The various active sites present on the surface of protein with the maximum area to volume ratio by forming tetrad of nonpolar amino acids shows the maximum interaction with the solvent or the exterior environment. With the help of STRING, interaction among different proteins was also studied. The successful docking between COX-2 protein and 8-deoxylactucin along with the anti-inflammatory drugs indicates active participation of 8-deoxylactucin in providing anti-inflammatory activity. As most the anti-inflammatory drug, sometimes shows side effects to adult due to continuous long time consumption, so taking *C. intybus* in daily dietary routine can help in keeping healthy homeostasis of the body as the plant is known for its tremendous nutritional and medicinal dietary features. Moreover, as the plant has abundant nutritious value, through food technology experimentation, any delicious foodstuffs can be produced by the chicory plant with abundant 8-deoxylactucin, which people charm to have in their diet. An additional different part of the plant including the leaf and roots can be included in dietary habits in the form of salads, vegetables, and root beverages. In some countries like India, whole plant chicory is used as a digestive, stomach, and liver tonic, as well as a diuretic and anti-inflammatory agent. In literature, it was also found that chicory is more effective in inflammatory conditions. As per similar docking results of 8-deoxylactucin and anti-inflammatory drugs with COX-2 protein of humans involve in inflammation, proceeding clinical trials with 8-deoxylactucin may give more clues and justification for the active participation of 8-deoxylactucin as an anti-inflammatory compound and employ information of some anti-inflammatory allopathic medicine like aspirin.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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