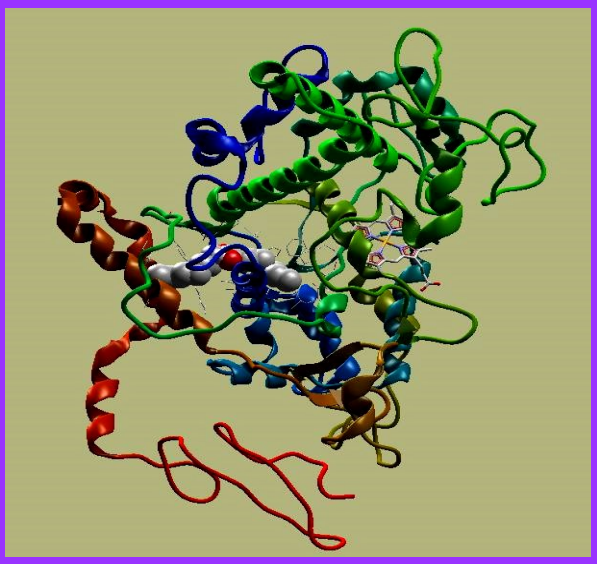

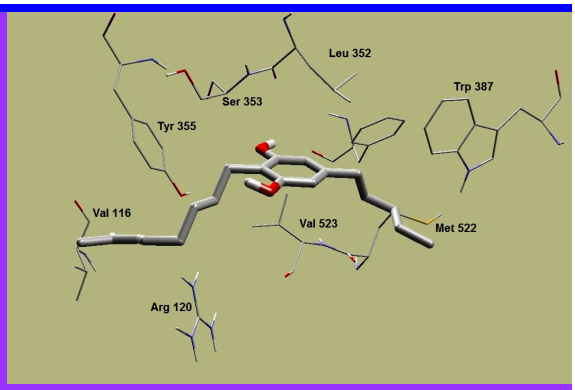

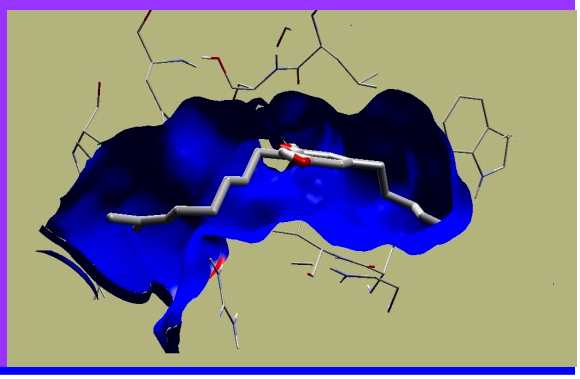

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In silico molecular mechanism of cannabigerol as a cyclooxygenase-2 inhibitor

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Abstract

Discovery of new cyclooxygenase-2(COX-2) inhibitors is a major area in anti-inflammatory drug discovery. Cannabigerol is a cannabinoid, which is recently discovered as a new COX-2 inhibitor. So far no work has been done to explore in depth mechanistic insights to understand its mechanism and binding mode. In the current investigation, molecular docking simulations were performed to explore its binding mode and is molecular interactions with the ligand binding site of COX-2 enzyme. Cannabigerol showed multiple molecular contacts with active of COX-2 especially withArg120, Tyr355, and Met522. Hydrogen bonding, dipole-dipole and hydrophobic interactions were the key attractive forces involved in macromolecular contacts. Molecular modifications in cannabigerol are discussed, which can lead to further improvement of the ligand as a new lead compound against COX-2 enzyme.

Introduction

Cannabinoids are well established bioactive compounds with a diverse set of pharmacological effects ranging from neurological aspects to cancer and inflammation (Zogopoulos et al., 2013). So far considerable work has been done on anti-inflammatory profile of cannabinoids and its source plant *Cannabis sativa*. Inflammation is a major condition often associated with a large number of diseases. Anti-inflammatory drugs are clinically used to control inflammation and adjoining conditions. The non-steroidal anti-inflammatory drugs (NSAIDs) have been among the most widely used drugs for the treatment of pain and inflammation. NSAIDs show their mechanism of action by inhibiting the cyclooxygenase (COX) enzyme and thus the biosynthesis of prostaglandins (PGs) (Vane, 1971). Two isoforms of the COX enzyme have been characterized: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) (Chen et al., 2005; O"Banion et al., 1991; Selvam et al., 2005; Habib et al., 2001). New and emerging COX-2 inhibitors are immensely investigated to develop better and safe anti-inflammatory drugs.

Recently a cannabigerol, a well-known cannabinoid is discovered to possess COX-2 inhibitory activity. So far no structural or computational insights have been investigated to know the molecular mechanism of cannabigerol as COX-2 inhibitor. In the current study, we have made an attempt to probe significant molecular interactions of CNL with its target protein COX-2 to explain its computational pharmacological mechanism behind inhibitory effect on COX-2 and arachidonic acid metabolism.

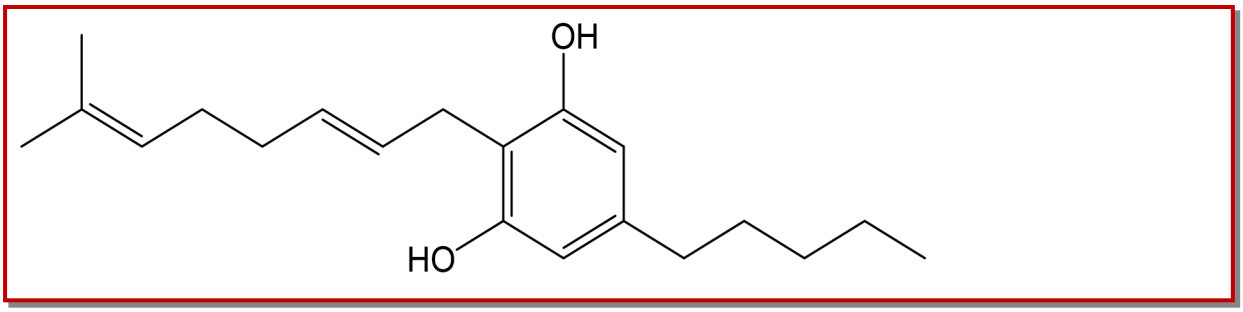

Figure 1: Chemical structure of cannabigerol

Figure 2: Binding mode of cannabigerol penetrated deeply into active site of COX-2 enzyme

Material and Methods

Molecular docking simulations

Ligand file (cannabigerol, Figure 1) was designed and optimized using dreading force field was implemented in Marvin Sketch V5.1. Molecular coordinates were further optimized using MMFF force field. FRED 2.1 (Khan et al., 2011) was used to dock the OMEGA pre-generated multicon-former library. Default FRED protocol was used except for the size of the box defining the binding sites. In an attempt to optimize the docking-scoring performance, exhaustive docking was performed with shapegauss applying the "Optimization" mode. The "Optimization" mode involves a systematic solid body optimization of the top ranked poses from the exhaustive docking. 3 different boxes were explored for COX-2 (PDB ID: 3PGH). Three different simulations were carried out with an added value of 9Å around the active site. After completion, best scoring pose was selected to study molecular interactions behind significant enzyme inhibitory activity of cannabigerol.

Results and Discussion

PGs belongs to a class of autacoids that are involved in various biochemical and physiological function. Over-production of these PGs is often associated with pathological conditions. Prostaglandin E_2 synthase is a key enzyme in the biosynthesis of PGs mediating inflammation and other important physiological processes. COX-1, described as a "housekeeping" enzyme, is expressed in the gastrointestinal tract, kidneys and platelets. Under the influence of COX-1, prostaglandins maintain the integrity of the gastric mucosa, mediate normal platelet function and regulate renal blood flow (Crofford et al., 1997). The isoenzyme COX-2 is primarily associated with inflammation. Cytokines and growth factors increase the expression of COX-2, mainly at inflammatory sites, producing prostaglandins that mediate inflammation, pain and fever (Crofford et al., 1997). Discovery of the COX-2 isoenzyme led to the theory that COX-2 selective inhibition would provide the potent anti-inflammatory and analgesic effects of traditional NSAIDs without influencing COX-1 (Needleman et al., 1997). The COX molecule consists of three independent folding units: An epidermal growth factor-like domain, a membrane binding site, and an enzymatic domain (Picot et al., 1994). COX-2 specific inhibitors retain some platelet thromboxane A2 inhibitory properties, but their antiplatelet potency is far less than that of traditional NSAIDs (McAdam et al., 1999). Celecoxib, the first highly selective COX-2 inhibitor approved by US FDA is indicated against osteoarthritis and rheumatoid arthritis (Chen et al., 2005). NSAIDs administration in animal models resulted in inhibition of angiogenesis and proliferation, induction of apoptosis and prevention of metastasis. In clinical setting, NSAIDs and selective COX-2 inhibitors have the capacity to prevent the development of colorectal adenomas. Herein, we reported our structural studies on a cannabigerolto investigate its *in silico* interactions against COX-2 active site by employing protein-ligand docking.

Anti-inflammatory drug discovery are timely required by humanity around the globe to successfully tackle the outcomes of inflammation and inflammatory disorders. In the present investigation, cannabigerol revealed

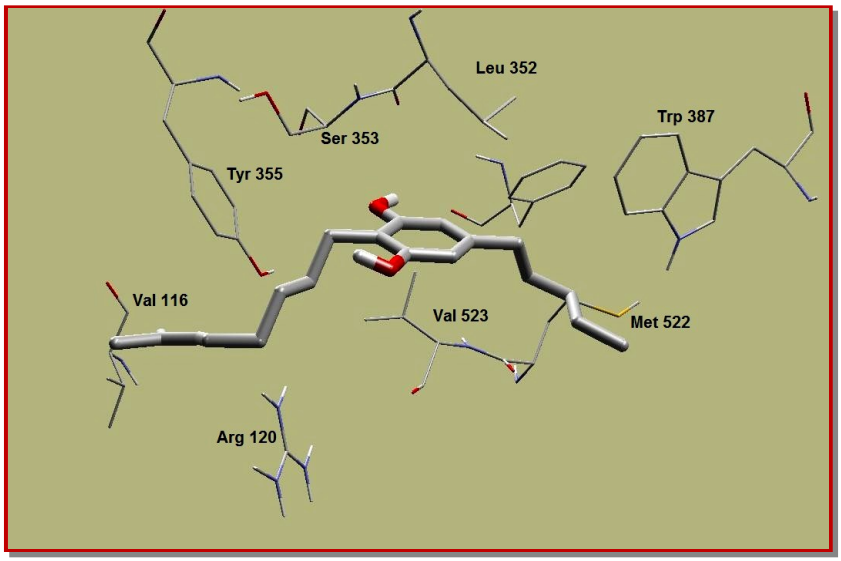

Figure 3: A closer view of molecular interactions of cannabigerol with important amino acid residues inside binding pocket of COX-2 enzyme

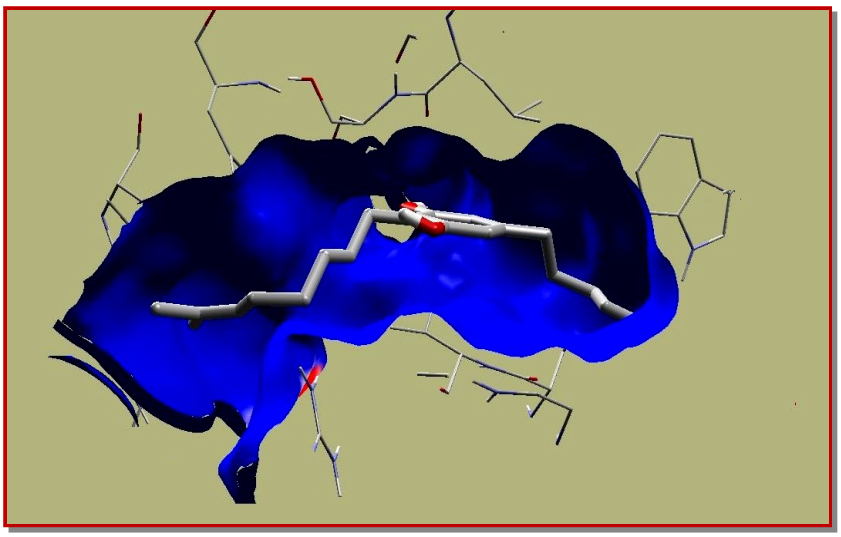

Figure 4: Favorable steric interactions of cannabigerol inside COX-2 binding pocket

promising molecular interactions with important components of the active site of COX-2 enzyme, which proved its significant COX-2 and inflammation inhibitory effects. Cannabigerol showed favorable interactions with all major amino acid residues surrounding the ligand, which includes Arg120, Phe518, Tyr355, Val523, and Met522 (Figure 2 and 3). It showed all classes of molecular interactions such as hydrogen bonding, dipole-dipole interactions, π- π aromatic interactions and non-aromatic hydrophobic interactions.

Elongated and flexible skeleton of the ligand was somewhat comparable active site of enzyme in terms of steric and electrostatic features (Figure 4) that ultimately favored the strong bonding interactions between ligand and the protein. Oxygen atom of phenyl group interacts with Leu352 via hydrogen bonding at a distance of 3.32°A. Another major electrostatic forces between ligand and protein was dipole-dipole interactions, which was shown between phenyl group of ligand with Tyr355 amino acid side chain of COX-2. Hydrogen bonding is one of the major forces working behind formation of protein and nucleotide folding and thus shaping the proteins and DNAs into their 3D shapes. Here in our data, this promising interactions could partially explain the pharmacological effect of cannabigerol.

Apart from hydrogen bonding, favorable hydrophobic interactions seems to be another major factor behind significant bioactivity of the compound. Interestingly, hydrophobic interactions were shown by the various alkyl carbon atoms of the ligand, which collectively resulted in enhanced attraction to support ligand-

protein complex. For instance, carbon 5 (C-5) pentyl side chain showed hydrophobic contact with Leu384. Trp387 and Met522 showed hydrophobic contact with carbon 3 of pentyl side chain. These hydrophobic interactions support the ligand-protein complex. These interactions might be partly responsible to stabilize the macromolecular complex. Similarly different hydrophobic interactions was shown between Val531, Val116, Leu93, Val89, Leu359. Met522 and Phenyl518, with different carbons of pentyl side chain.

Conclusion

Detailed structural analysis revealed the fact slight shortening of octyl chain and introduction of some polar functional groups or polar aromatic rings could further enhance the binding forces to show better potency of future lead compound.

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Conflict of Interest

Authors declare no conflict of interest

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