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In Silico Molecular Estimation of Flavonoid as A Cyclooxygenase-2 Inhibitor

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Abstract:
The search for new COX-2 inhibitors is a prominent field of anti-inflammatory medication development. Quercetin is a flavonoid that has recently been identified as a COX-2 inhibitor. So yet, no research has been done to delve deeper into the mechanism and binding manner of the protein. The current study used molecular docking simulations to investigate its binding style and molecular interactions with the COX-2 enzyme's ligand binding site. Quercetin made numerous molecular connections with COX-2 active, particularly with Arg102, Tyr355, and Met252. The main attractive forces in macromolecular contacts were hydrogen bonding, dipole-dipole interactions, and hydrophobic interactions. Quercetin's molecular changes are explored, which could lead to the ligand's further improvement as a novel lead molecule against the COX-2 enzyme.

Keywords: COX-2 enzyme, Docking, Anti-inflammation

Introduction:
Quercetin is a well-known bioactive compound with a wide range of pharmacological effects ranging from neurological to cancer and inflammation (Zogopoulos et al., 2013). Significant research has been conducted on the anti-inflammatory profile of quercetin and its source plant, Euphorbia microphylla Linn. Inflammation is a major condition that is frequently linked to a wide range of diseases. Anti-inflammatory medications are used in the treatment of inflammation and related conditions. Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs for treating pain and inflammation.
NSAIDs work by inhibiting the cyclooxygenase (COX) enzyme and, as a result, the biosynthesis of prostaglandins (PGs) (Vane, 1971). The COX enzyme has two isoforms: COX-1 and 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 being thoroughly researched in order to develop more effective and safe anti-inflammatory drugs. A well-known quercetin has recently been discovered to have COX-2 inhibitory activity. No structural or computational insights into the molecular mechanism of quercetin as a COX-2 inhibitor have been investigated thus far. In this study, we attempted to investigate significant molecular interactions of quercetin with its target protein COX-2 in order to explain its.

Material and Methods:
Molecular docking simulations*:* Ligand file (quercetin, **Figure 1**) was designed and optimized using dreading

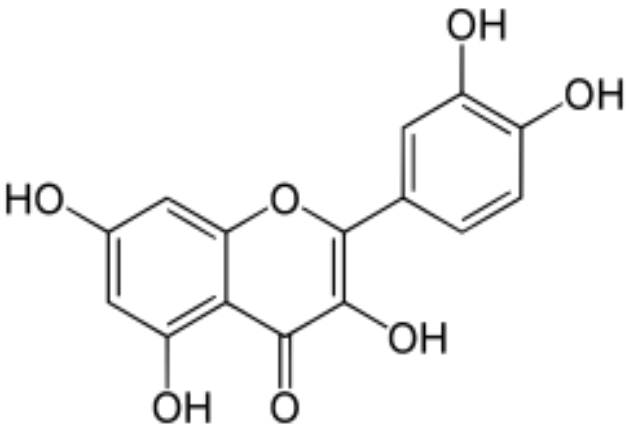

Figure 1: Chemical structure of quercetin

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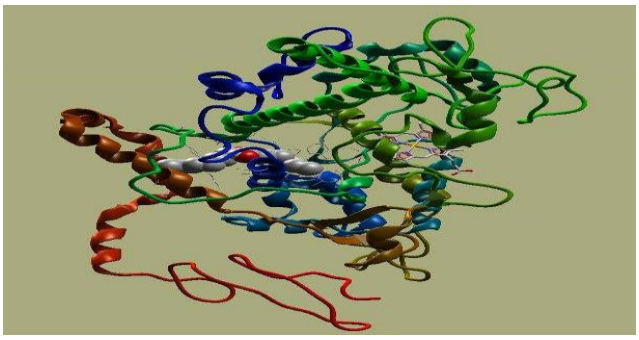

Figure 2: Binding mode of penetrated deeply into active site of COX-2 enzyme

Marvin Sketch V5.1 included a force field. The MMFF force field was used to further optimise the molecular coordinates. The OMEGA pre-generated multicon-former library was docked using FRED 2.1 (Khan et al., 2011). Except for the size of the box defining the binding sites, the default FRED protocol was used. Exhaustive docking was performed with shapegauss using the "Optimization" mode in an attempt to optimise docking-scoring performance. The "Optimization" mode entails systematic solid body optimization of the top ranked poses from exhaustive docking. COX-2 was investigated in three different boxes (PDB ID: 3PGH). Three different simulations with an added value of 9 were run around the active site. Following completion, the best scoring pose was chosen to investigate the molecular interactions underlying significant enzyme inhibitory effects.

Result & Discussion:

PGs are autacoids that play a variety of biochemical and physiological roles. Overproduction of these PGs is frequently associated with pathological conditions. Prostaglandin E2 synthase is a key enzyme in the biosynthesis of PGs that mediate inflammation and other important physiological processes. COX-1 is a "housekeeping" enzyme found in the gastrointestinal tract, kidneys, and platelets. Prostaglandins regulate renal blood flow and maintain the integrity of the gastric mucosa under the influence of COX-1 (Crofford et al., 1997). COX-2 is primarily associated with inflammation. Cytokines and growth factors increase COX-2 expression, primarily at inflammatory sites, where it produces prostaglandins that mediate inflammation, pain, and fever (Crofford et al., 1997). COX-2 isoenzyme discovery. The COX molecule is made up of three folding units: an epidermal growth factor-like domain, a membrane binding site, and an enzyme (Picot et al., 1994). Some platelet thromboxane A2 inhibitory characteristics are retained by COX-2 selective inhibitors, but their antiplatelet effectiveness is significantly reduced.

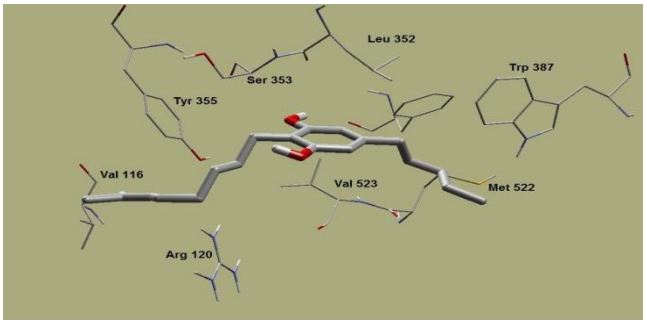

Figure 3: A closer view of molecular interactions of quercetin with important amino acid residues inside binding pocket of COX-2 enzyme

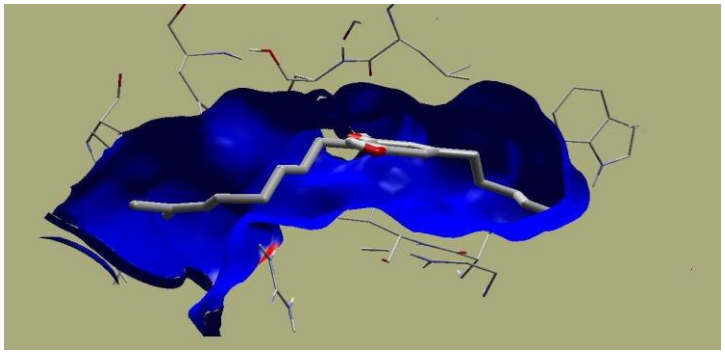

Figure 4: Favorable steric interactions of quercetin inside COX-2 binding pocket

NSAIDs (McAdam et al., 1999). The development of anti-inflammatory drugs is urgent. Celecoxib, the world's first highly selective COX-2 inhibitor, has been licenced by the US Food and Drug Administration for the treatment of osteoarthritis and inflammatory conditions. Rheumatoid arthritis and other autoimmune diseases (Chen et al., 2005). NSAIDs In this study, quercetin was found to block promising molecular interactions with crucial of angiogenesis and proliferation, induction of apoptosis, and prevention of metastasis in animal models. NSAIDs and selective COX-2 inhibitors have the capacity to suppress COX-2 and inflammation in a clinical context. Quercetin has been shown to have beneficial interactions with all major amino acid residues surrounding colorectal adenomas. The structural investigations on ligand, which includes Arg120, Phe518, Tyr355, bigerolto examine its in silico interactions against Val523, and Met522 are shown here (Figure 2 and 3). Using protein-ligand docking, it revealed the whole COX-2 active site. Hydrogen bonding, dipole-dipole interactions, **π**- **π**-aromatic interactions, and non-aromatic hydrophobic interactions are examples of molecular interactions. In terms of steric and electrostatic properties, the ligand's elongated and flexible skeleton was similar to the active site of an enzyme (Figure 4), which encouraged strong bonding contacts between the ligand and the protein. At a distance of 3.32°A, the oxygen atom of the phenyl group forms a hydrogen connection with Leu352. Dipole-dipole interactions were another important electrostatic interaction between ligand and protein. This was demonstrated by the interaction of the ligand's phenyl group with COX-2's Tyr355 amino acid side chain. One of the key factors at work in protein and nucleotide folding, which moulds proteins and DNAs into their 3D shapes, is hydrogen bonding. This potential interaction could partially explain the pharmacological activity of quercetin, according to our findings. Aside from hydrogen bonding, favourable hydrophobic interactions appear to be another important element in the compound's high bioactivity. The various alkyl carbon atoms of the ligand demonstrated hydrophobic interactions, which resulted in increased attraction to support the ligand-protein complex. For example, Leu384 made hydrophobic contact with the carbon 5 (C-5) pentyl side chain. Hydrophobic interaction was found between Trp387 and Met522 and carbon 3 of the pentyl side chain. The ligand-protein complex is aided by these hydrophobic interactions. These interactions could play a role in the macromolecular complex's stabilization. Val531, Val116, Leu93, Val89, and Leu359 all showed different hydrophobic interactions. Met522 and Phenyl518 have distinct pentyl side chain carbons. Finally, comprehensive structural study suggested that modest octyl chain shortening and the addition of some polar functional groups or polar aromatic rings could improve binding forces and hence improve the potency of future lead compounds.

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