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Original Research Article

Mechanistic Insights an Anti-Inflammatory Potential of Quercetin by Molecular Docking

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Abstract: ***Background*:** Inflammation is a biological response to a series of chemical reactions whose major function is protection from infection and the resolution of tissue damage caused by injury. There are several mediators released during the process of inflammation. Flavonoids are universal in photosynthesizing cells and are often found in vegetables, fruit, nuts, seeds, stems, tea, flowers, honey and wine preparations. This class of natural products is becoming the subject of anti-infective research, and many groups have isolated and identified the structures of flavonoids possessing, antiviral, antifungal antibacterial activity and anti-inflammatory activity. This study has been carried out to rationally design quercetin was assayed for anti-inflammatory potential by using *in-silico* molecular docking approach. ***Methods*:** Molecular docking of Phosphodiesterase 4 (PDE4) with quercetin was carried out by AutoDock. ***Result*:** The molecular docking result revealed that quercetin showed encouraging docking score. The docking score found to be -7.67 kcal mol^{-1} respectively.

Keywords: Quercetin, docking score, molecular docking & Phosphodiesterase 4 (PDE4).

INTRODUCTION

Inflammation is a biological response to a series of chemical reactions whose major function is protection from infection and the resolution of tissue damage caused by injury. There are several mediators released during the process of inflammation. Activation of phospholipase –A2 (PLA2) family is a key step in the production of precursor in biosynthesis of inflammatory lipid mediators, Platelet activating factor, cyclooxyginase-2, leukotriens, nerve growth factor, inducible nitric oxide synthase, bradykinins, cytokines and adhesion molecules [1]. Most of the essential components of the inflammatory process are found in the circulation, and most of the early mediators (facilitators) of inflammation increase the movement of plasma and blood cells from the circulation into the tissue surrounding the injury. These substances known collectively as exudates defined the host against infection and facilitate tissue repair and healing.

The superficial hallmark of inflammation included:

- Rubor (redness)
- Tumor (swelling)
- Calor (Heat)
- Dolor (pain)
- Functiolaesa (loss of function)

Types of inflammation

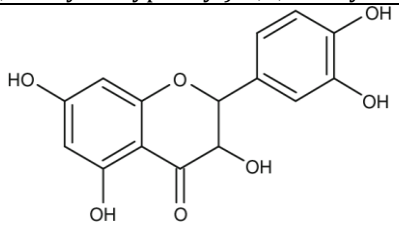
Depending upon the cause and duration of response, inflammation can be classified as acute and chronic [2].

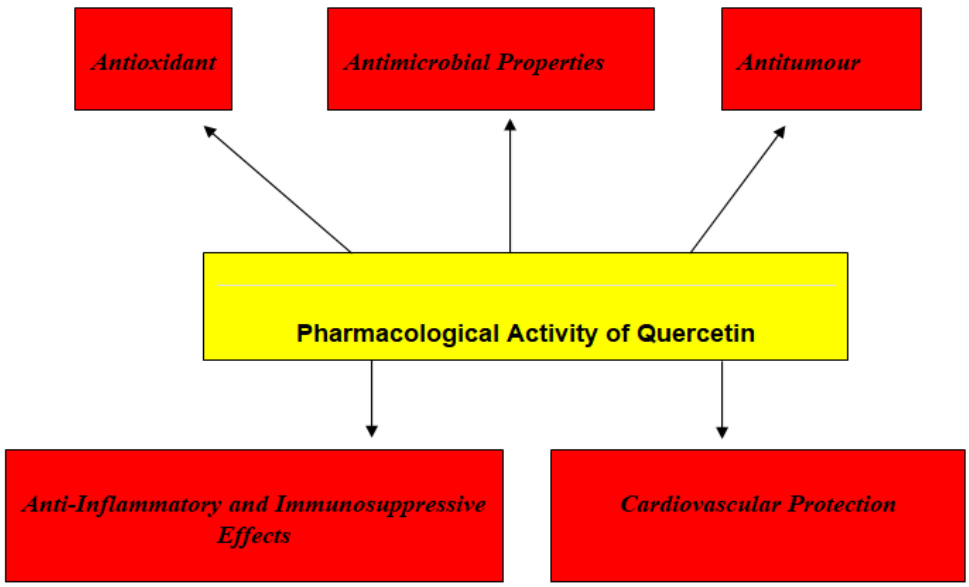
Acute inflammation	The inflammation is of relatively short duration, lasting for a few min, several hrs., or one to two days, and its main characteristics are the exudation of fluid and plasma protein (oedema) and the emigration of leukocytes, predominantly neutrophils.
Chronic inflammation	It is generally of longer duration and is associated histologically with the presence of lymphocytes and macrophages and the proliferation of small blood vessels and fibroblasts.

Role of Phosphodiesterase 4 (PDE4) in inflammation

Phosphodiesterase 4 (PDE4) and phosphodiesterase 7 (PDE7), PDE superfamily associate, increase inflammatory processes in immunomodulatory as well as pro-inflammatory cells via breakdown of cyclic adenosine monophosphate. Dual inhibitors of PDE4 and PDE7 are a novel class of drug candidates which can regulate pro-inflammatory as well as T-cell function and can be particularly advantageous in the treatment of a wide-ranging disorders associated with the immune system as well as inflammatory diseases with fewer unwanted adverse effects [3]. Quercetin is found in abundance in onions, broccoli, apples and berries. The second group is flavanones, which are mainly found in citrus fruits [4]. Quercetin (3,3',4',5,7-pentahydroxyflavone) belongs to an extensive class of polyphenolic flavonoid compounds almost ubiquitous in plants and plant food sources.

Description of Quercetin [5]

IUPAC Name	2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one
Structure	
Mol. Wt.	302.23
Mol. Formula	$C_{15}H_{10}O_7$
M.P.	601-603^{0}F
Appearance	yellow, crystalline solid
Taste	a bitter taste
Class	Polyphenolic flavonoid



Pharmacological Activity of Quercetin [6]

The present research work was planned to design the molecular docking of quercetin flavonoids as dual inhibitors of PDE4 followed by evaluation of their anti-inflammatory activity and *in-silico* docking studies.

EXPERIMENTAL WORK

Docking Study of Quercetin with Phosphodiesterase-4 (PDE4) Enzyme

Molecular docking studies

Ligand Preparation:

2D Structure of ligand quercetin was drawn by using ChemDraw. The two-dimensional structures of ligand were converted into 3-D structures with optimized 3D geometry by using Chem3D software. The optimized structure was saved in PDB format for AutoDock compatibility [7].

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 0.392 Å and No. of points considered are 40, 40 and 40 points in the x, y, and z dimensions are -44.16, -34.73 and -54.88 as x, y, z centers [8].

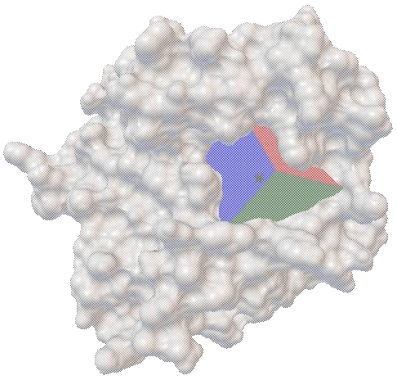


Figure 1: Grid box covering all active sites in receptor

Preparation of the docking file

All the calculations were carried out by using Autodock4.2 as docking tool. The visualization and other programs necessary for docking studies were performed out by means of Pymol, Chimera, DS visualizer, MMP Plus [9].

Macromolecular structure

The crystal structure of the protein consisting of receptor associated with bound ligand is downloaded from the Protein Data Bank portal. All the primary information regarding receptor and structure (7F2K.pdb) registered in the Protein data bank was used. The bound ligand 4-[8-methoxy-2,2-dimethyl-7-(3-methylbut-2-enyl)-9-oxidanyl-6-oxidanylidene-pyrano[3,2-b]xanthen-5-yl]oxybut-2-enoic acid (0X8) was found within the receptor (10).

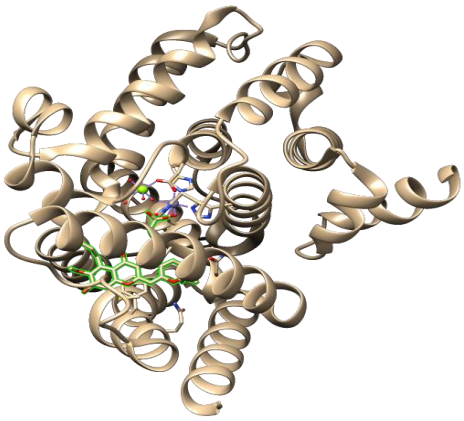


Figure 2: Crystal structure of PDE4 enzyme with bound ligand 0X8 (PDB ID-7F2K)

Processing of Protein

The downloaded receptor protein is having two chains A and B, out of which chain A has been selected for the experimental purpose. The bound ligand 0X8 was separated from the macromolecular complex by using software Chimera [11].

Molecular Docking Simulation Studies

Docking of ligand quercetin againstPDE4 enzyme was performed by Autodock. All the bonds of ligand were kept flexible, while no residues in receptor were made flexible [12].

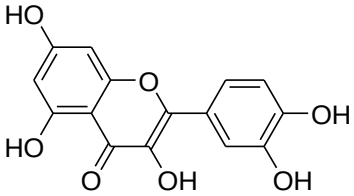
Toxicity & ADME-T Studies

The pharmacokinetics of ligand molecule was 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 [13].

RESULTS AND DISCUSSION

Inflammation is a biological response to a series of chemical reactions whose major function is protection from infection and the resolution of tissue damage caused by injury. There are several mediators released during the process of inflammation. Activation of phospholipase –A2 (PLA2) family is a key step in the production of precursor in biosynthesis of inflammatory lipid mediators, Platelet activating factor, cyclooxyginase-2, leukotriens, nerve growth factor, inducible nitric oxide synthase, bradykinins, and cytokines and adhesion molecules. Flavonoids are plant polyphenolic compound derivatives from natural origin found in fruits, grains, vegetables, roots, bark, flowers, stems, tea, and wine. Non-plant natural products such as mushrooms and honey, plant extracts, plant juices, plant powders, and essential oils have shown to possess anti-inflammatory activities and many of these plant natural products have polyphenols as their major compound. Flavonoids are a wide category of polyphenolic compounds that have a major role in the treatment of various inflammatory diseases, including arthritis, gastritis, nephritis, hepatitis, ulcerative colitis, Alzheimer's disease, atherosclerosis, and many allergic reactions. Flavonoids reported for the management of inflammatory disorders with their possible mechanism. These compounds also regulate the oxidative status and prevent damage caused by oxidative stress such as the antioxidant effect. The high levels of cytokines, such as tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6, are allied with chronic inflammatory diseases. Some flavonoids, namely luteolin, quercetin, and apigenin, reduce cytokine expression and their secretion. It suggests that these flavonoids may have a therapeutic benefit in the treatment of inflammation-associated diseases as cytokine modulators. Flavonoids also have wide pharmacological effects by inhibiting some enzymes such as cyclooxygenase, aldose reductase, xanthenes oxidase, $Ca2^{+}$ ATPase, phosphodiesterase, and lipoxygenase. In the present study quercetin was taken as selected compound for elucidation of anti-inflammatory mechanism. Quercetin or 3, 3′, 4′, 5, 7-pentahydroxyflvanone that falls into the category of flavonol is widely found in plants such as *Ginkgo biloba, Hypericum perforatum, and Sambucus canadensis* as well as vegetables such as apples, berries, grapes, onions, shallots, and tomatoes. Quercetin is one of the important bioflavonoids present in more than twenty plants material and which is known for its anti-inflammatory, antihypertensive, vasodilator effects, antiobesity, antihypercholesterolemic and antiatherosclerotic activities. Free-radical are one of the key factors for the development of the diseases such as hypertension, vascular disorders, and metabolic syndrome. The molecular docking result revealed that binding energy of quercetin with ,PDE4 was found to be -7.67 kcal mol^{-1}. Above finding showed that quercetin potent inhibitor of pro-inflammatory mediators. The result was tabulated in table.1.Furthur molecular dynamic studies showed interaction of quercetin with target protein (Fig.3-5).With endeavor of molecular dynamic interaction studied of quercetin with PED-4 enzyme. The interaction of quercetin structure on 2,3,6 position of H and 3-position of =O with Asp.318,Asn321,His200,His164,Glu230 and Met 273 of PED-4 enzyme showed strong H-bonding binding as compared to other targeted protein taken in consideration of present studied which revealed the potentiating of quercetin as an anti-inflammatory compound by inhibition of PED-4 enzyme. The brain, cardiovascular tissues, smooth muscles, keratinocytes, and immunocytes all have high levels of the c-AMP-specific PDE-4 (including T-cells, monocytes, macrophages, neutrophils, dendritic cells, eosinophiles). PDE4 inhibition can increase intracellular cAMP levels, which can then be used to control inflammatory reactions and keep the immune system in balance. The pharmacokinetic profiling of the quercetin ligand has revealed that it is having good pharmacokinetic profile associated with some mutagenic and tumorogenic properties. The pharmacokinetic and toxicity profiling results of quercetin was shown in figure 6.

Table 1: Result of docking

S. No	Target Receptor	Structure (Quercetin)	B.E. kcal mol^{-1}	H-Bond	Residual Interaction	
					Pi-Interaction	van der Waals
1.	PDE4 enzyme		-7.67	Asp318, Asn321, Gln369	His160, Ile336	Tyr329, Val377, Tyr159, His164, Met273, Phe340

Interactions

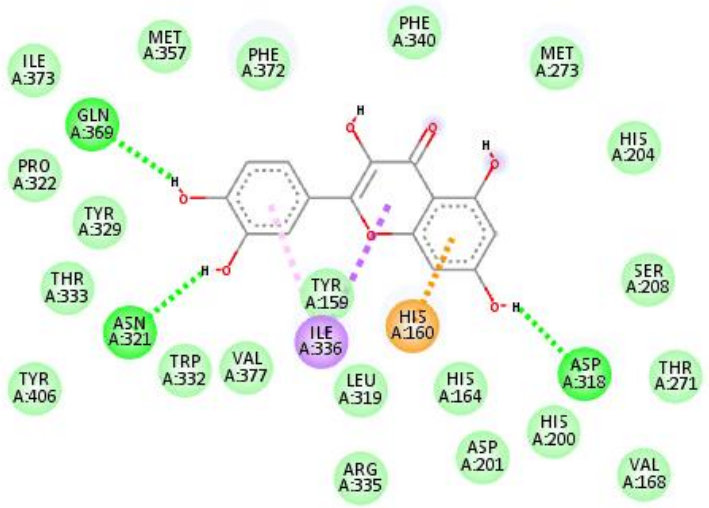


Figure 3: Two-dimensional binding interaction of quercetin with PDE4

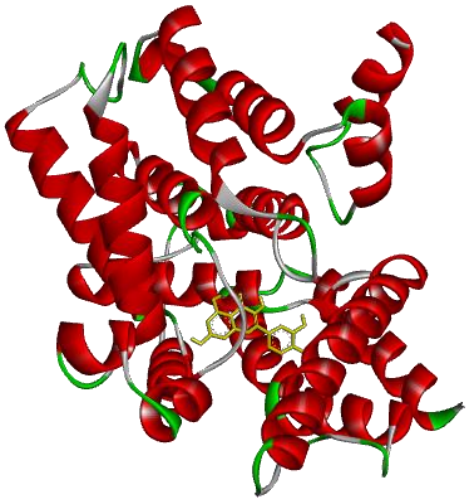


Figure 4: Three-dimensional binding interaction of quercetin with PDE4

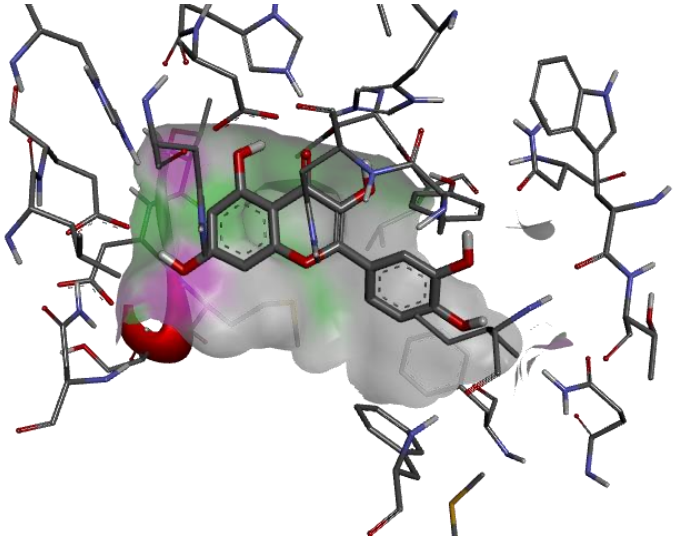


Figure 5: Binding conformation of ligand quercetin with PDE4

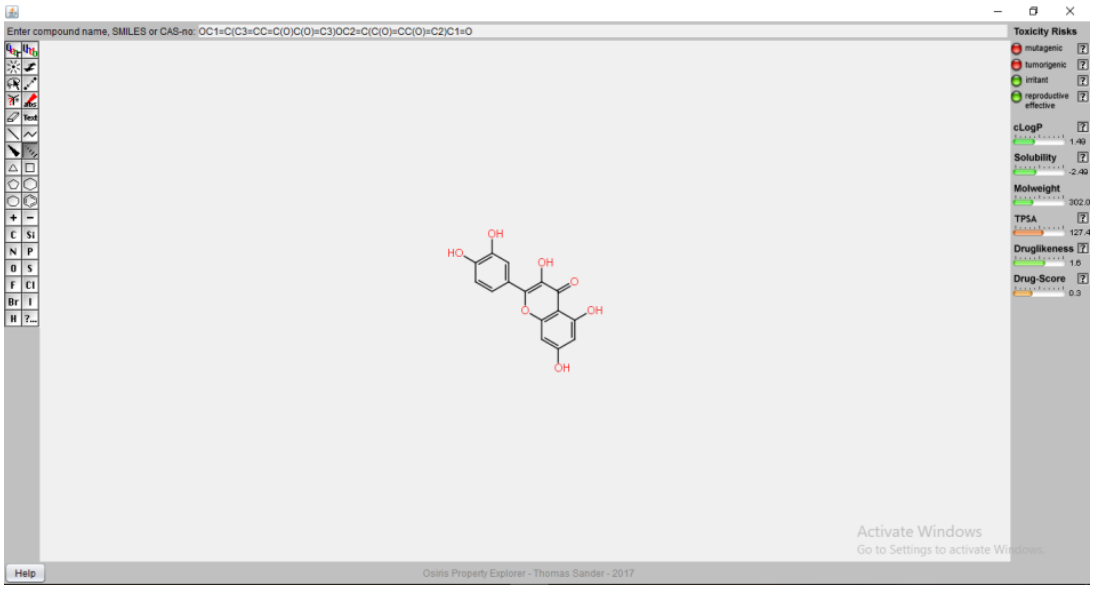


Figure 6: Pharmacokinetic and toxicity profiling of quercetin

CONCLUSION

Quercetin (Que) is an antioxidant flavonol belonging to the flavonoid group and generally present as Que glycoside. The Que aglycone is able to conjugate with glucose, xylose, or rutinose attaching to one of the Que's hydroxyl groups with the consequent creation of various Que glycoside forms. It shows a relatively higher bioavailability than other phytochemicals. The anti-inflammatory and antioxidant effects of Que are essential for its activity as oxidative, kinase, and cell cycle inhibitors, as well as for neuronal survival. Que apoptosis-inducing effects are the key for its anticancer potential.

The plants containing quercetin are traditionally utilized for the cure of inflammation and related disorders from the immortal time. The exact mechanism of action for the anti-inflammatory response of quercetin was still not revealed. With intent to propose the most probable mechanism of action of quercetin the docking based computational analysis has been performed against the anti-inflammatory drug targets PDE4. The docking analysis, chemical interactions, followed by the physicochemical based pharmacokinetic profiling has revealed that the quercetin is executing its anti-inflammatory response via inhibiting the PDE4 receptor. With the endeavor of molecular docking result quercetin is effectively used as therapeutic strategy for inflammatory conditions including asthma, chronic obstruction pulmonary disease (COPD), psoriasis, atropic dermantitis (AD), inflammatory bowel syndrome (IBS), rheumatic arthritis (RA), Lupus and neuro-inflammation. Thus present studied revealed the mechanistic insights into anti-inflammatory effect of quercetin via a inhibitory action on PED-4 enzyme.

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