Journal of Pharmacognosy and Phytochemistry
Available online at www.phytojournal.com

E-ISSN: 2278-4136
P-ISSN: 2349-8234
Impact Factor (RJIF): 6.35
www.phytojournal.com
JPP 2025; 14(6): 270-277
Received: 04-09-2025
Accepted: 07-10-2025

Amit Kumar
Faculty of Pharmaceutical Sciences, Motherhood University, Roorkee, Haridwar, Uttarakhand, India

Jitendra Kumar Malik
Faculty of Pharmacy, P.K. University, Shivpuri, Madhya Pradesh, India

Corresponding Author:
Amit Kumar
Faculty of Pharmaceutical Sciences, Motherhood University, Roorkee, Haridwar, Uttarakhand, India

Shooting an arrow against inflammasome: Novel plant phenolic derivatives as phosphodiesterase-4 inhibitor

Amit Kumar and Jitendra Kumar Malik

DOI: https://doi.org/10.22271/phyto.2025.v14.i6d.15665

Abstract
Background: Inflammation refers to the body's typical physiological reaction to tissue injury. Such injuries can result from physical or mechanical harm, trauma, autoimmune responses, microbial infections, or burns. Inflammation can be categorized as either acute or chronic. PDE-4 is a key player in inflammation, as it regulates the levels of cyclic adenosine monophosphate (cAMP) within inflammatory cells. This regulation is vital for the immune system's proper functioning and the resolution of inflammation. Phenolic compounds exhibit remarkable pharmacological and nutritional benefits, including antimicrobial, antibacterial, antiviral, anti-sclerosis, antioxidant, and anti-inflammatory effects, which have garnered increasing interest from the scientific community.
Aim: This study seeks to examine the effectiveness of plant phenolic like chlorogenic acid, rutin, quercetin and gallic acid against PDE-4 to clarify their anti-inflammatory potential.
Method: PDE-4 was chosen as the target proteins in the current investigation. The bond was found using the Auto Dock software using a grid-based docking method. Compounds' 2D structures were generated, converted to 3D, and subsequently energetically lowered up to an arms gradient of 0.01 using the Merck Molecular Force Field (MMFF).
Results: The binding energy was found to be -4.06, -5.74, -6.76 & -3.55 kcalmol^{-1} for chlorogenic acid, rutin, quercetin & gallic acid respectively against PDE4 enzyme.
Conclusion: The finding of the *in-silico* molecular docking showed that selected lead compound is effective binds & inhibitory action on target protein.

Keywords: Molecular docking, Phosphodiesterase-4 Inhibitor (PDE-4), chlorogenic acid, rutin, quercetin & gallic acid

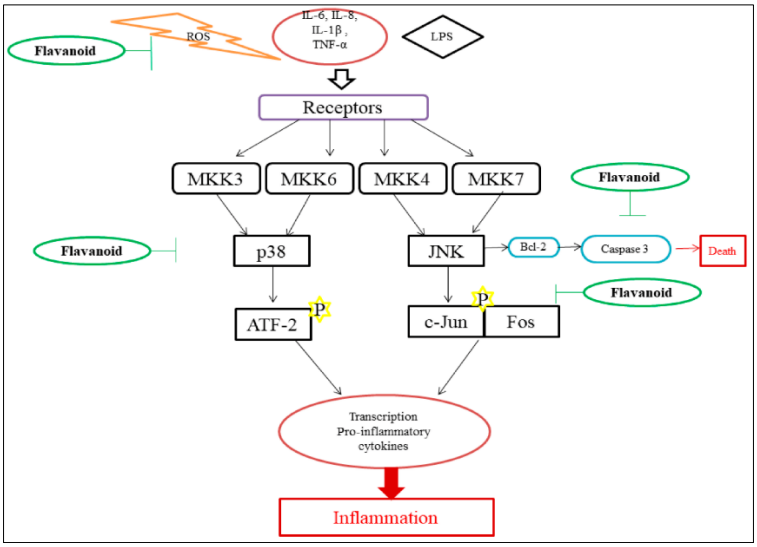
Introduction
Inflammation denotes the body's standard physiological response to tissue damage. The injury may come from physical or mechanical damage, trauma, autoimmune response, microbial invasion, or burns. Inflammation may be classified as either acute or chronic. [1-5]. During an acute inflammatory response, lipoxins, leukotrienes, bradykinin, platelet-activating factor, and lymphokines are involved [6]. Histamine enhances tissue permeability, induces smooth muscle contraction, and results in bronchoconstriction [7]. Chronic inflammatory conditions, such as arthritis and hemorrhoids, persist in disrupting cellular and molecular processes that mitigate potential harm or infection. This mitigation process aids in the restoration of tissue homeostasis and the resolution of acute inflammation. Unregulated acute inflammation may, however, progress to a chronic state, contributing to many chronic inflammatory disorders [8]. Inflammation and the immune system are intricately linked. Mediators of inflammation (autacoids) encompass serotonin, histamine, and prostaglandins, highlighting humanity's reliance on nature's medicinal plant resources. Numerous botanicals utilized in traditional medicine for the treatment of inflammation remain scientifically unassessed. The existing models for studying anti-inflammatory activity possess significant limitations and problems. Phenolic acids are hydroxyl derivatives of aromatic carboxylic acids which have a single phenolic ring and can be further divided into two main types, the benzoic acids and cinnamic acids, based on the C1-C6 or C3-C6 backbone. About 30% of the free or bound forms of dietary phenolics in plants are phenolic acids. Flavonoids contain two phenolic rings (Ring A and Ring B) linked by a three-carbon bridge that is usually an oxygenated heterocycle (Ring C), having a common C6-C3-C6 skeleton structure [9]. Phenolic compounds have been demonstrated anti-inflammatory properties to treat skin diseases, rheumatoid arthritis, and inflammatory bowel disease [10].

Experimental works

In-Silico molecular docking

Selection of lead molecules

Studies show that plant phenolic such as flavonoids activate antioxidant pathways that render an anti-inflammatory effect. They inhibit the secretions of enzymes such as lysozymes and β-glucuronidase and inhibit the secretion of arachidonic acid, which reduces inflammatory reactions. Phenolic acid such as chlorogenic acid and gallic acid is a bioactive compound ubiquitously present in the natural realm, lauded for its salient anti-inflammatory and antioxidant attributes. It executes its anti-inflammatory function by moderating the synthesis and secretion of inflammatory mediators, namely, TNF-α, IL-1β, IL-6, IL-8, NO, and PGE2. Flavonoids such as quercetin and rutin modulate the expression and activation of a cytokine such as interleukin-1beta (IL-1β), Tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8); regulate the gene expression of many pro-inflammatory molecules such s nuclear factor kappa-light chain enhancer of activated B cells (NF-κB), activator protein-1 (AP-1), intercellular adhesion molecule-1 (ICAM), vascular cell adhesion molecule-1 (VCAM), and E-selectins; and also inhibits inducible nitric oxide (NO) synthase, cyclooxygenase-2, and lipoxygenase, which are pro-inflammatory enzymes [11].



Role of flavonoid in Inflammation

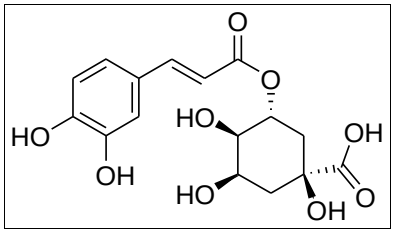
Selection of Target Protein

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 [12].

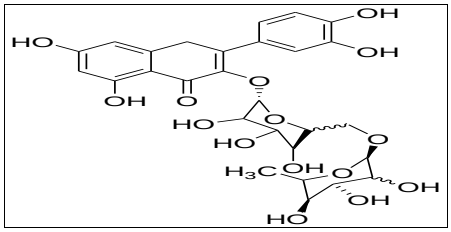
Molecular docking studies

Ligand Preparation

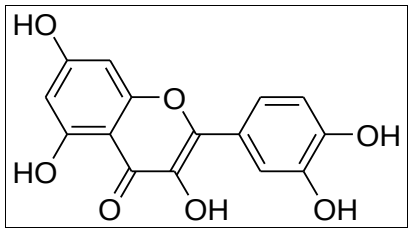
2D Structure of ligands like chlorogenic acid, rutin, quercetin, and gallic acid was drawn using Chem Draw [13].The two-dimensional structures of ligands were converted into 3-D structures with optimized 3D geometry by using Chem3D software. The optimized structure was saved in PDB format for AutoDock compatibility [14-16].



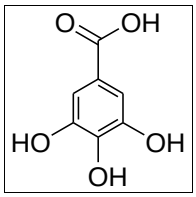
Chlorogenic acid



Rutin



Quercetin



Gallic acid

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[17-18].

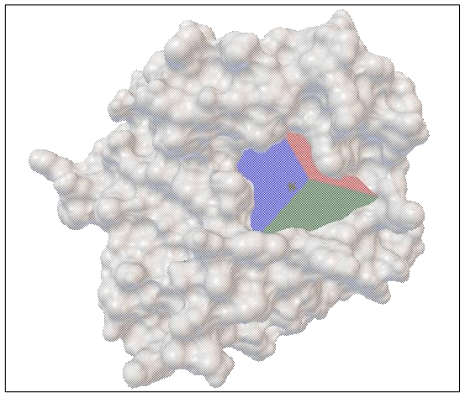


Fig 1: Grid box covering all active sites in receptor

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 [19-20].

Docking of Phosphodiesterase-4 (PDE4)

Crystal 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 [21].

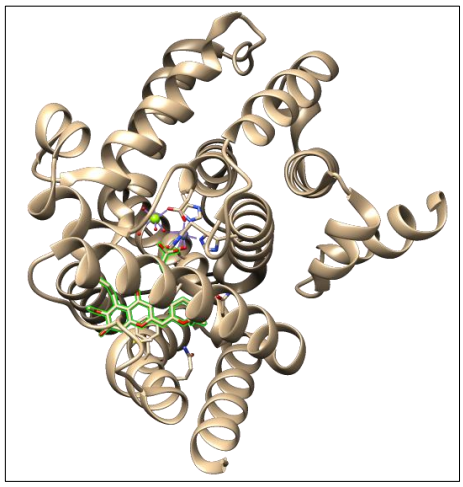


Fig 2: Crystal structure of PDE4 enzyme with bound ligand 0X8(PDB ID-7F2K)

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 [22].

Molecular Docking Simulation Studies

Docking of ligand like chlorogenic acid, rutin, quercetin and gallic acid against PDE4 enzyme was performed by Autodock. All the bonds of ligand were kept flexible, while no residues in receptor were made flexible [23].

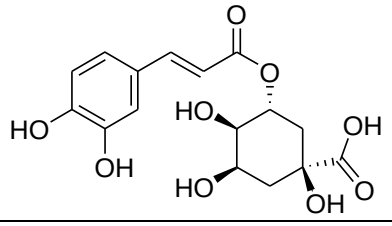
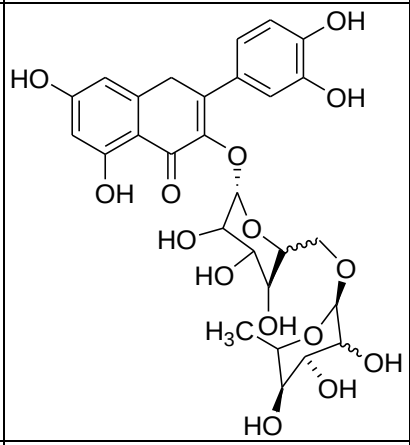
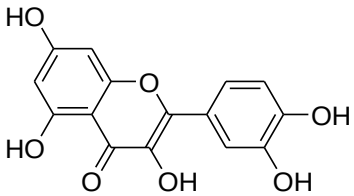
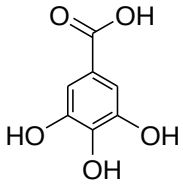
Toxicity & ADME-T Studies

The modified lead molecules are studied by online program OSIRIS, for prediction of presence of any toxic groups as well as presence of any toxic group and ADME- T properties[24].

Results and Discussion

Inflammation often arises when infectious microorganisms, including bacteria, viruses, or fungi, infiltrate the body, inhabit specific tissues, and/or disseminate through the bloodstream. Inflammation may also occur in reaction to events such as tissue injury, cellular necrosis, malignancy, ischemia, and degeneration. A variety of inflammatory mediators are synthesized and released during various types of inflammatory responses. Inflammatory chemicals are typically classified into two primary categories: pro-inflammatory and anti-inflammatory mediators. Plant phenolic have many biological functions, mainly including antioxidant and anti-inflammatory effects, and can produce a series of beneficial biological effects on the body, including antibacterial, lipid-lowering, anti-cancer, cardioprotective, neuroprotective and anti-diabetic, etc. 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. The binding energy -4.06, -5.74,-6.76 & -3.55 kcalmol^{-1} for chlorogenic acid ,rutin, quercetin & gallic acid respectively against PDE4 enzyme . The result was tabulated in table 1. The 2D interaction of selected compound displayed in fig.3-6. The result revealed that the minimum binding energies showed Quercetin>Rutin>Chlorogenic acid > gallic acid. For above finding it was concluded that these plant phenolic and flavonoid molecules could act as the starting hits for the design of effective, potent and selective PDE4 inhibitors for the promising treatment of inflammatory disorders. The pharmacokinetic profiling of the rutin, quercetin, chlorogenic acid and gallic acid ligand had revealed that it is having good pharmacokinetic profile associated without the presence of major toxic effects like mutagenic, reproductive effects, irritant effect, and tumorogenic properties. The pharmacokinetic and toxicity profiling results were shown in figure 7-10 & table 2-4. Theoretically, all the ligand molecules have shown encouraging docking score. All compound followed Lipinski rule and showed all most similar drug likeness score.

Table 1: Result of docking of againstPDE4 enzyme

S. No	Compound	Structure	B.E.	H-Bond	Residual Interaction	
					Pi-Interaction	Van der Waals
1	Chlorogenic acid		-4.06	Asp201, Asp318, His160, Pro322	Phe372, Tyr159	Glu230, Met273, His204, Asn209, Ser208, Asn321, Leu319
2	Rutin		-5.74	His204, His160, Met273, Glu230, Asp201, Asn321, Pro356	Asp318, Ile336, Leu319, Phe372	Gln343, Ser208, Asn209, Thr271, His200, Tyr159, Cys358, Phe340, Met357, Ser368
3	Quercetin		-6.76	Gln369, Asn321, Asp318	Ile336, His160	Tyr329, Val377, Tyr159, His164, Met273, Phe340
4	Gallic acid		-3.55	Gln369, Asn321, Asp318, Tyr159	Leu319	His160, Ser320, Pro322, Phe372

Interactions

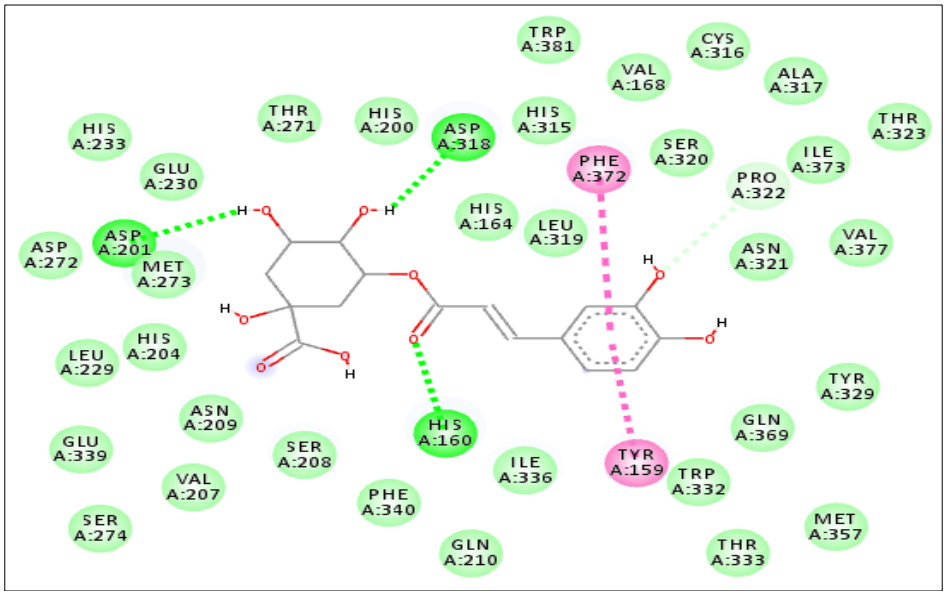


Fig 3: Binding interaction of chlorogenic acid with PDE4

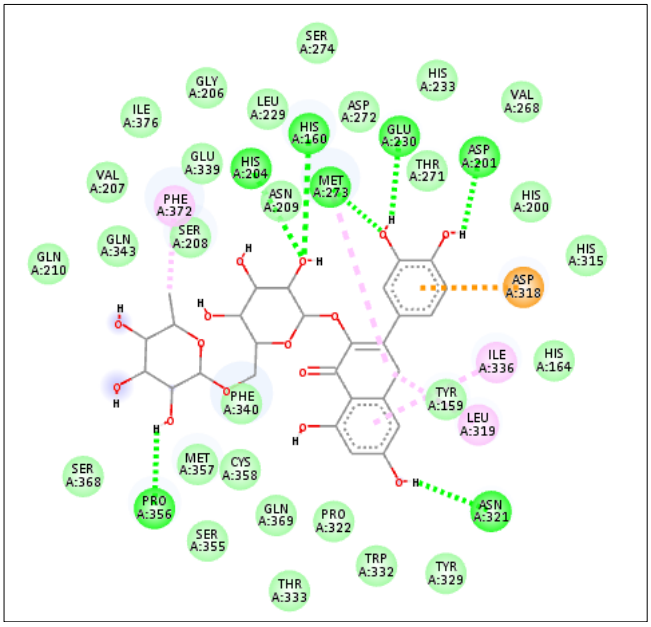


Fig 4: Binding interaction of rutin with PDE4

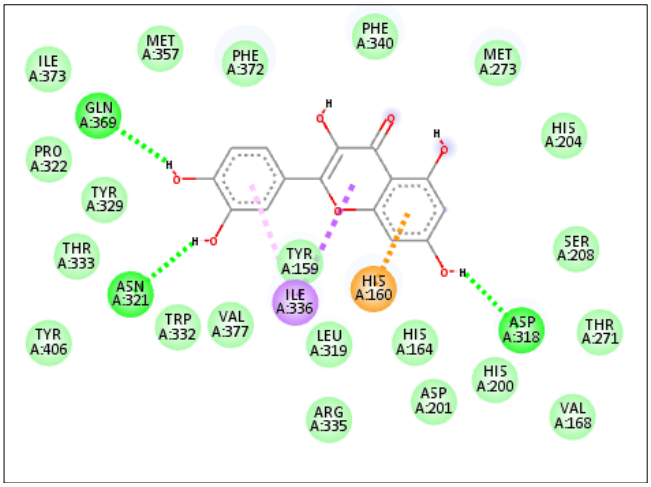


Fig 5: Binding interaction of quercetin acid with PDE4

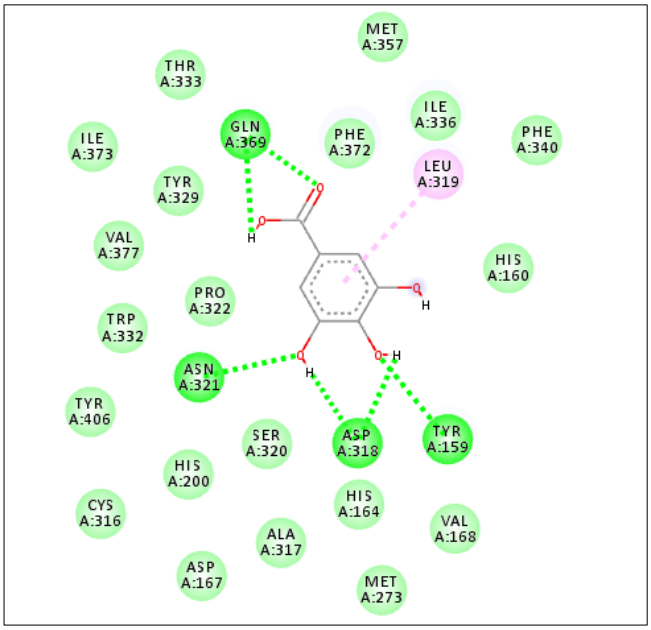


Fig 6: Binding interaction of gallic acid with PDE4

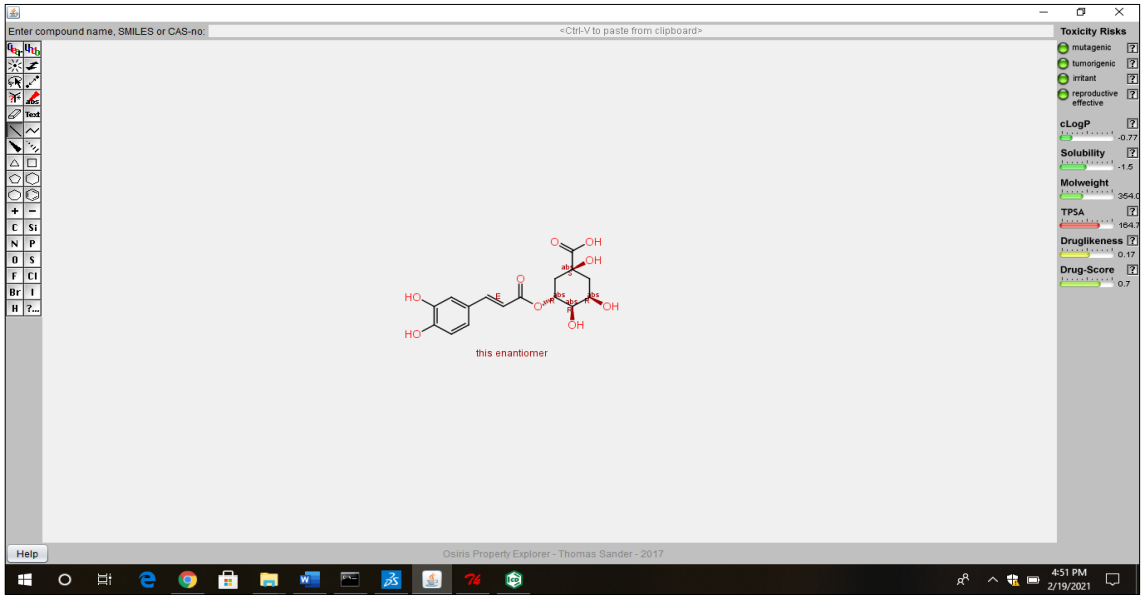


Fig 7: Pharmacokinetic and toxicity profiling of chlorogenic acid

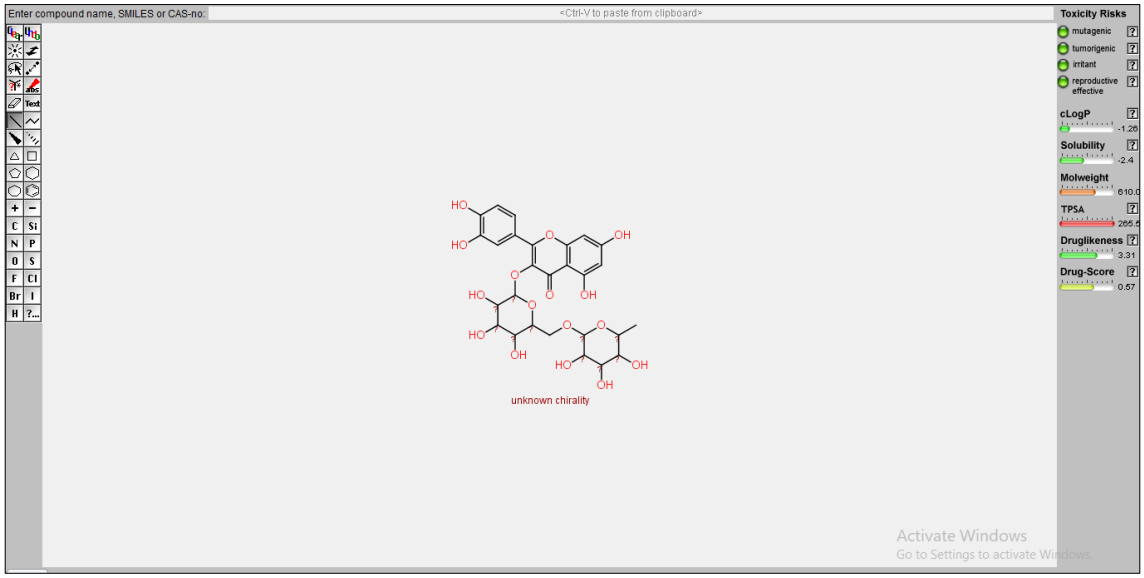


Fig 8: Pharmacokinetic and toxicity profiling of rutin

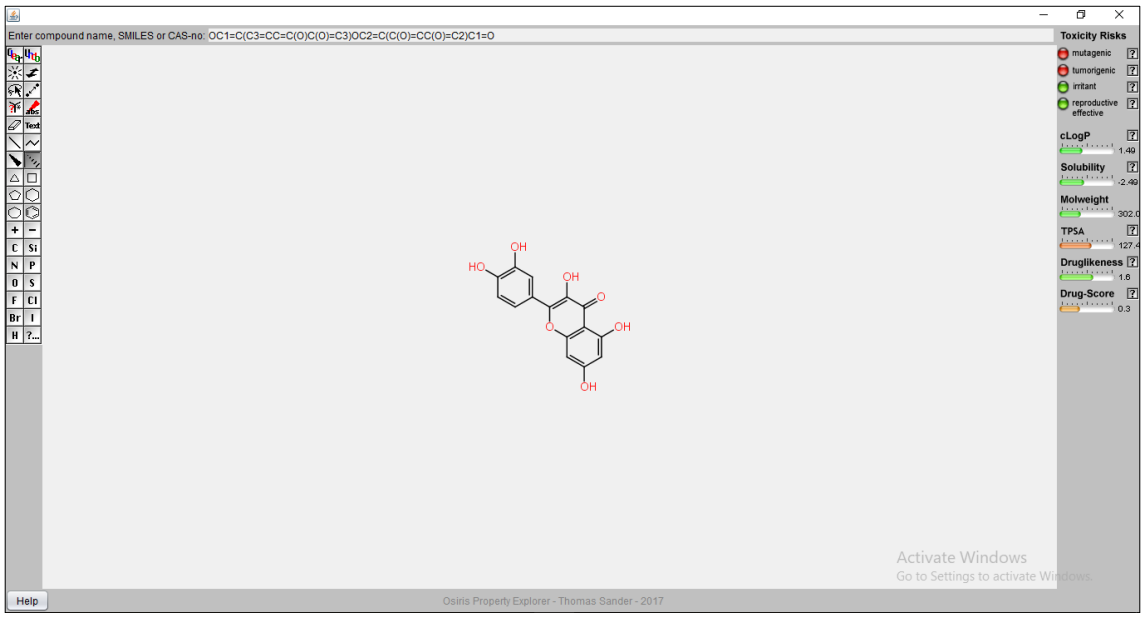


Fig 9: Pharmacokinetic and toxicity profiling of quercetin

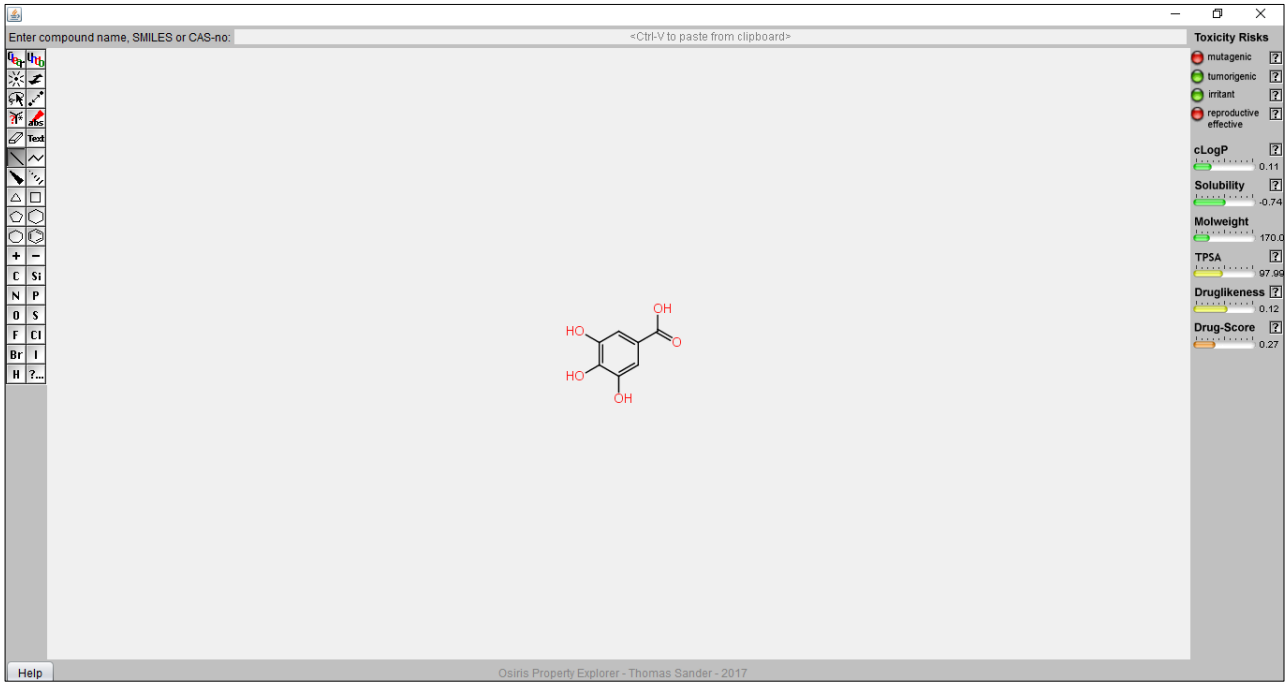


Fig 10: Pharmacokinetic and toxicity profiling of gallic acid

Table 2: Pharmacokinetic Profiling of lead molecules

Compound	ADMET			
	Mutagenic	**Tumorigenic**	**Irritant**	**Reproductive effectivity**
Quercetin	NO	NO	Yes	NO
Rutin	NO	NO	NO	No
Chlorogenic acid	NO	NO	NO	No
Gallic acid	NO	NO	NO	No

Table 3: Lipinski Properties of lead molecules

Compound	*cLogP*	Solubility	Mol.wt.	TPSA	Drug likeness	Drug score
Chlorogenic acid	0.77	1.5	354	164.2	0.17	0.7
Quercetin	6.7	1.5	302	104	0.57	0.3
Rutin	1.28	0.8	610	344	-3.34	0.08
Gallic acid	0.11	0.74	170	97.99	-0.12	0.27

Table 4: Drug likeness of lead molecules

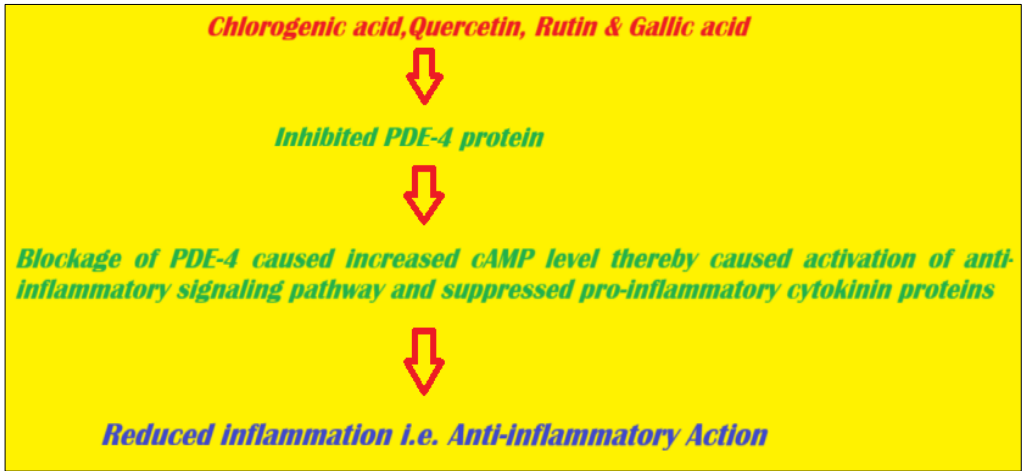
Compound	Lipinski rule of five	H bond donar	H bond acceptor
Chlorogenic acid	Yes	6	9
Quercetin	Yes	5	7
Rutin	Yes	10	16
Gallic acid	Yes	4	5

Conclusion

The scientific validation of anti-inflammatory action was conducted using *in-silico* molecular docking targeting PDE-4 as the proteins of interest. The chosen lead compound exhibited inhibitory activity on the PDE-4 enzyme, thereby the levels of cAMP increase, leading to the activation of anti-inflammatory signaling pathways and the suppression of pro-inflammatory cytokines. The outcome of finding demonstrated the anti-inflammatory potential of plant phenolic shooting against inflammasome and their related disorders.

Divulgence of Investigation

The proposed mechanism of action of lead molecules against inflammation showed as:



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