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Original Research Article

Deciphering of Nature's Promising Warrior of Some Novel Flavonoid Derivatives against Psoriasis: *In-silico* Molecular Docking against *Phosphodiesterase* 4 Enzyme

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Abstract: ***Background*:** An inflammatory, prevalent, and chronic skin disease is psoriasis. The term "classic skin lesions" refers to the erythematous, scaly, and well-defined plaques that are frequently located on the extensor surfaces. There have also been several psoriasis variations reported, such as the guttate, erythrodermic, pustular, and palmoplantar types. Psoriasis is typically diagnosed clinically, although distinctive histologic findings include a lymphocytic infiltration, dilated blood vessels, and hyper- and parakeratosis of the epidermis. Although the exact cause of psoriasis is unknown, genetic and environmental factors have been linked to the immune-mediated disease. Many health advantages are associated with flavonoids, such as their antiviral, anticancer, and antioxidant qualities. They also have cardio- and neuroprotective properties. The kind of flavonoid, its (potential) method of action, and its bioavailability all affect these biological functions. These reasonably priced pharmaceutical ingredients contain substantial biological activities and have been shown to be beneficial for a range of illnesses. ***Purpose:*** The present study was conducted to evaluate the efficacy of new flavonoid derivatives for their anti-psoriatic potential. ***Methodology*:** The scientific validation of the present work was conducted using a computational molecular docking analysis of the lead compounds luteolin, baicalein, and myricetin against the PDE4 enzyme. ***Result*:** The results of the current analysis indicate that the selected lead compounds are efficient anti-psoriatic agents, demonstrating binding affinities to the target protein PDE4 with binding energies of -7.269, -7.16, and -6.64 kcal/mol for baicalein, luteolin, and myricetin, respectively. ***Conclusion*:** The results demonstrated that each chosen lead compound for further study exhibited substantial inhibitory efficacy against PDE4, hence indicating its potential as an anti-psoriatic drug.

Keywords: Psoriasis, flavonoids, baicalein, luteloin and myricetin & molecular docking.

INTRODUCTION

Psoriasis is a chronic autoimmune, non-communicable inflammatory disorder affecting the skin and joints. The term psoriasis is derived from the Greek word "psora," signifying itchiness, and "iasis," denoting a condition invalid input [1]. The disease exhibits a global frequency of two percent, with an elevated prevalence of approximately 4.6% in developed nations [2]. It is distinguished by strongly defined, scaly, red, coin-sized skin lesions, predominantly located on the elbows, knees, scalp, hands, and feet. Symptoms encompass pruritus, irritation, stinging, and discomfort. Infrequently, the entire integumentary surface of the body may be affected [3, 4]. Indicators for diagnosing psoriasis include the Koebner phenomenon and Auspitz's sign [5].

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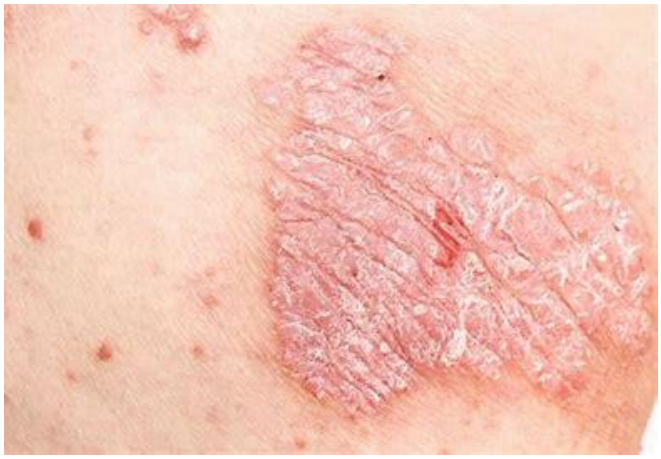


Psoriasis

The etiology of this persistent disease remains ambiguous. Stress is the predominant etiological cause, and individuals with chronic conditions such as Crohn's disease are at an increased risk of developing psoriasis [6, 7]. Medications that exhibit a significant causal association with psoriasis include beta-blockers, lithium, synthetic antimalarials, nonsteroidal anti-inflammatory medications (NSAIDs), and tetracyclines [8]. Individuals with the severe variant of this disease exhibit a heightened risk of cardiac comorbidities [9].

Flavonoids have been used in natural dyes in cosmetics and skin care products and anti-wrinkle skin agents. The most pronounced applications of these polyphenols, however, are in the field of medicine. Flavonoids have been used extensively as anticancer, antimicrobial, antiviral, antiangiogenic, antimalarial, antioxidant, neuroprotective, antitumor, and anti-proliferative agents. Apple peel extracts rich in flavonoids inhibits acetylcholinesterase (ACE) in vitro and is an effective antihypertensive agent. It also prevents cardio-metabolic disorders and displays better preservation of cognitive performance with aging [10].

In this work, a selected ubiquitous flavonoid (Luteolin, Baicalein and myrecetin) was considered to elucidate its anti-psoriatic potential by a molecular docking technique.

Experiment Work

Selection of Lead Molecules

Phytochemicals constitute a vast and varied category of naturally occurring molecules, bioactive nutrients, or phytonutrients generated by plants, commonly present in fruits, vegetables, whole grains, legumes, beans, herbs, seeds, nuts, tea, and dark chocolate. They are categorized based on their chemical structures and functional characteristics. Flavonoids are part of the phenolic category of phytochemicals, exhibiting significant pharmacological potential as modulators of many signal transduction pathways. Their advantageous impact on the human body is linked to their antioxidant, anti-inflammatory, antimutagenic, and anticarcinogenic characteristics. Flavonoids are extensively utilized in many dietary, pharmacological, medicinal, and cosmetic applications. It was examined the beneficial impact of flavonoids on chronic dermatological conditions, including vitiligo, psoriasis, acne, and atopic dermatitis [11].

- According to the literature review, *luteolin* can inhibit proinflammatory mediators (e.g., IL-1β, IL-6, IL-8, IL-17, IL-22, TNF-α, and COX-2) and modulate numerous signaling pathways (e.g., NF-κB, JAK-STAT, and TLR signaling pathways). Luteolin regulates numerous inflammatory processes in the skin [12].
- *Baicalin* has been shown to possess anti-inflammatory and immunomodulatory properties, primarily by inhibiting the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway and the nucleotide-binding oligomerization domain-like receptor pyrin domain protein 3 (NLRP3) inflammasome, as well as by suppressing the expression of pro-inflammatory factors such as interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor α (TNF-α), and cyclooxygenase 2 (COX-2) [13].
- *Myricetin* (Myr), scientifically designated as 3,3′,4′,5,5′,7-Hexahydroxyflavon, is a flavonoid compound prevalent in numerous natural plants. Myr has demonstrated several biological roles, including immunomodulatory and anti-inflammatory properties. Myr has demonstrated an inhibitory effect on LPS-induced inflammation in RAW 264.7 macrophages and TNF-α-induced A549 cells via the NF-κB signaling pathway [14].

Selection of Target receptor

- ***Phosphodiesterase 4 Inhibitors***

Phosphodiesterase 4 (PDE4) is a principal phosphodiesterase found in immune cells (dendritic cells, T cells, macrophages, and monocytes) and keratinocytes, and it catalyzes the hydrolysis of intracellular cyclic adenosine monophosphate (cAMP), a

second messenger that mediates immunoregulatory effects. The synthesis of cAMP is modulated by hormonal activation of G-protein coupled receptors, which stimulate membrane-bound adenylyl cyclases to convert ATP into cAMP. PDE4 inhibitors are tiny compounds that target PDE4, resulting in elevated cytosolic cAMP levels, which then activate protein kinase A (PKA), exchange proteins 1/2 triggered by cAMP, and cyclic nucleotide-gated channels. PKA stimulates transcription factors such as cAMP-response element-binding protein (CREB), cAMP-responsive modulator (CREM), and ATF1 via phosphorylation, resulting in enhanced production of anti-inflammatory cytokines. The activation of these transcription factors results in the recruitment of coactivators CREB binding protein (CBP) or its homolog p300, which inhibits the proinflammatory transcription factor NF-κB by competing for these coactivators (CBP or p300). PDE4 modulates the production and signaling of essential cytokines implicated in the development of psoriasis [15].

Designing of *In-Silico* molecular docking in current investigation

- Psoriasis is an autoimmune inflammatory dermatological condition that impacts 0.5–3% of the global population, and existing treatment modalities are constrained by restrictions. The diminished likelihood of failure in clinical trials for repositioned drug candidates, together with time and cost efficiency, has popularized drug repositioning and computational approaches within the pharmaceutical research community.

Molecular Docking Studies

Ligand Preparation:

2D Structure of baicalin, luteolin and myricetin was drawn using ChemSketch [16], the two-dimensional structure of the prepared ligand was converted into their 3-D structures optimized with 3D geometry. The optimized structure was saved in PDB format for AutoDock compatibility. The basic structures of the prepared ligand were given below:

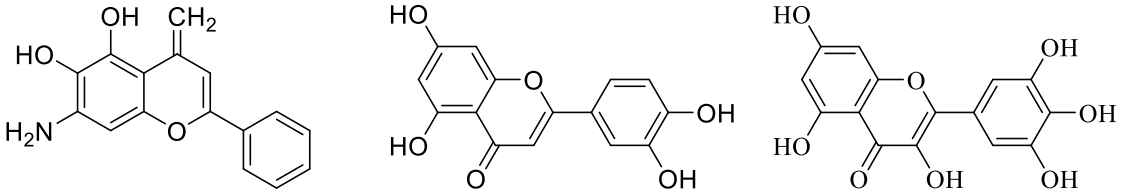


Figure 1: 2D structure of baicalin, luteolin and myricetin

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 and grid points for all the considered receptors in the current study are given in table 1 [17, 18].

Table 1: Grid parameters used in current docking analysis of PDE4 receptor

S. No.	Receptor	x-axis	y-axis	z-axis	Spacing	x center	y center	z center
1	PDE4	40	40	40	0.447	-26.196	-5.786	-26.62

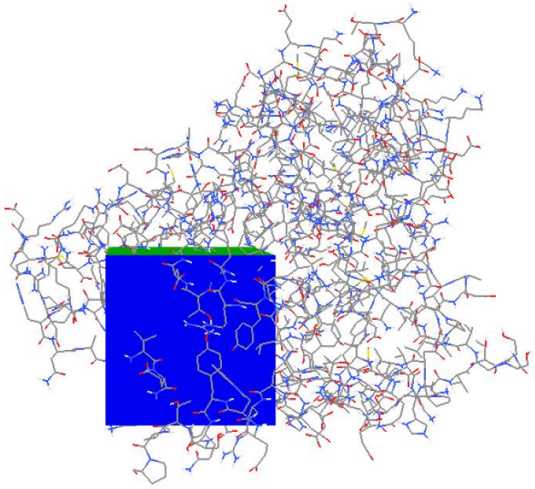


Figure 2: Grid box covering all active sites in PDE4 receptor

Preparation of the docking file

All the calculations were carried out by using Autodock 4.2 as docking tool. The visualization and other programs necessary for docking studies were performed out by means of Pymol, Chimera, DS visualizer, MMP Plus [19-21].

Docking Study

Crystal structure

The crystal structure of the protein consisting of PDE4 receptor is downloaded from the Protein Data Bank portal. All the primary information regarding all the receptor's structure was registered in the Protein data bank [22-24]. The complex ligand was separated by using Chimera software for all the target receptors.

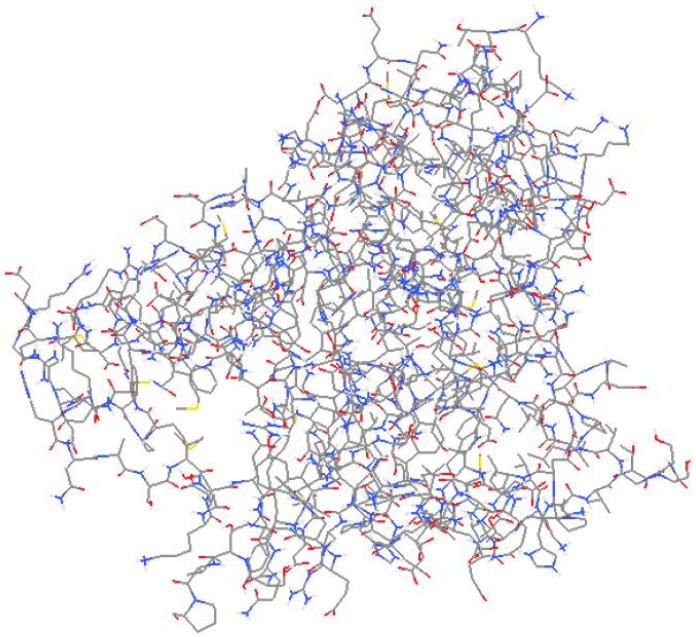


Figure 3: Crystal structure of PDE4 receptor (PDB ID-6kjz)

Processing of Protein

All the downloaded receptor proteins are having only one chains, i.e. chain A, which has been selected for experimental purpose and complex ligand was removed from it. The bound ligand was separated from the macromolecular complex by using software Chimera [25-29].

Molecular Docking Simulation Studies

Docking of ligands like baicalin, luteolin and myricetin against PDE4 receptor was performed by Autodock. All the bonds of each ligand were kept flexible, while no residues in receptor were made flexible [30-33].

Toxicity & ADME-T Studies

The ligand molecules viz. baicalein, luteolin and myricetin 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 [34].

RESULT AND DISCUSSION

Flavonoids are secondary metabolites, which mainly consists of a benzopyrone ring bearing a phenolic or poly-phenolic groups at different positions. They are most commonly found in fruits, herbs, stems, cereals, nuts, vegetables, flowers and seeds. The presence of bioactive phytochemical constituents present in these different plants parts gives them their medicinal value and biological activities. So far, over 10,000 flavonoid compounds have been isolated and identified. Most of the flavonoids are widely accepted as therapeutic agents. These are naturally synthesized through the phenylpropanoid pathway with bioactivity dependent on its absorption mechanism and bioavailability.

The most widely used applications of flavonoids, however, are in the field of medicine. They have been used extensively as anticancer, antimicrobial, antiviral, antiangiogenic, antioxidant, neuroprotective, antitumor, and anti-proliferative agents. Apple peel extracts rich in flavonoids inhibit acetylcholinesterase (ACE) in vitro and are an effective antihypertensive agent. They also prevent cardio-metabolic disorders and display better preservation of cognitive performance with aging.

Psoriasis is a prevalent, chronic inflammatory dermatosis. The characteristic skin lesions are characterized by clearly defined, scaly, erythematous plaques typically seen on the extensor surfaces. Various psoriasis varieties have been identified, including

palmoplantar, pustular, erythrodermic, and guttate types. Psoriasis is typically diagnosed clinically; however, distinctive histological features are hyperkeratosis, parakeratosis, and acanthosis of the epidermis, accompanied by dilated blood vessels and a lymphocytic infiltration. Psoriasis is an immune-mediated disorder, and while the etiology remains incompletely elucidated, both genetic and environmental factors have been implicated. Psoriasis is significantly linked to several systemic problems and comorbidities that profoundly affect patients.

Psoriasis is a chronic condition without a known cure; thus, the available medications are solely utilized to alleviate symptoms and enhance patients' quality of life. Consequently, medications for the treatment of psoriasis must be safe for prolonged use. They ought to be economically viable and highly convenient to administer. Nevertheless, the existing pharmacological treatments for psoriasis exhibit limitations, including insufficient efficacy (topical agents), significant toxicity (anticancer agents), elevated costs, and comparatively large molecular dimensions. Moreover, biologics necessitate the manipulation of living, specialized cells. Owing to these constraints, these medications are not easily accessible to patients, and those who can afford them still encounter compliance issues due to significant adverse effects. This circumstance prompted the pursuit of improved, economical, and safer anti-psoriatic medications.

PDE4 inhibitors are small molecules targeting PDE4 leading to increased cytosolic cAMP, which activates protein kinase A (PKA), exchange protein 1/2 activated by cAMP and cyclic nucleotide-gated channels. Through phosphorylation, PKA activates transcriptional factors including cAMP-response element-binding protein (CREB), cAMP-responsive modulator (CREM) and ATF1, which leads to increased expression of anti-inflammatory cytokines

The outcome of current investigation showed that selected lead molecules effective anti-psoriatic agent and their lead molecules effectively binds to be target protein *PDE4* with binding energy -7.269,-7.16 and -6.64 kcal/mol for baicalein, luteloin and myricetin respectively and ki value was found to be 12.25,12.017 and 11.20 for baicalein, luteloin and myricetin respectively .By using ki value IC50 was determined which was found to be 0.086,0.087 and 0.094 for baicalein, luteloin and myricetin respectively. The result was tabulated in table 2. The binding mode of selected lead molecules showed in fig.4-6. The 2D and 3D interaction of selected compound displayed in fig.7-12. The affinity of lead molecules with receptor was found to be more or less similar. The interaction of luteloin, baicalein and myricetin with active site at *PDE4* showed as follows:

Compound	Conventional Hydrogen bounding	Pi-alkyl	Pi-Pi	Week Vander's interaction
Luteloin	Thy271 Asp318 Thy 109 His204 Glu230 Met273	Ile336	Phen372	Asp201 His200 Asn321 Gln364 Phen340 Ser208 Thr271 Leu229
Baicalein	Glu230 His204 Thy271 Asp 318 Thy159	Ile 336	Phe372	Asp201 His200 Asp272 His164 Asn321 Glu364 Ser208 Leu340 Phe340 Leu229
Myricetin	Thy271 Asp318 Thy 109 His204 Glu230 Met273	Ile336	Phen372	Asp201 His200 Asn321 Gln369 Leu340 Phen340 Ser208 Leu229 Asn209 Ap272

The pharmacokinetic profile reveals that it is having good pharmacokinetic profile but with the presence of any major toxic effects including mutagenicity, tumorogenicity and reproductive effects.

The pharmacokinetic and toxicity profiling results of ligands like luteloin, baicalein and myricetin were shown in figure 13-15 & table 3-5. Theoretically, all the ligand molecules have shown encouraging docking score.

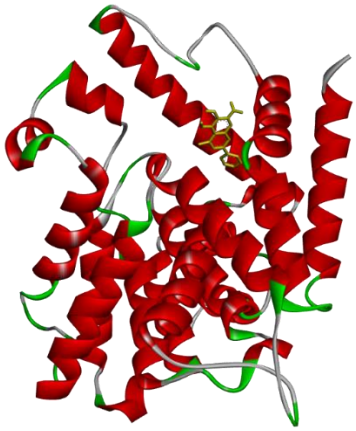


Figure 4: Binding mode of baicelin within the active site of PDE4 receptor

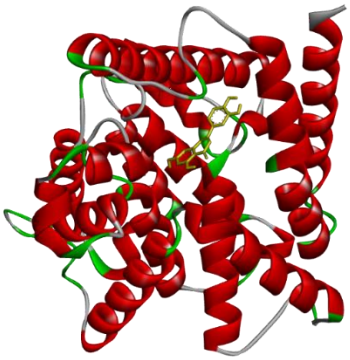


Figure 5: Binding mode of luteolin within the active site of PDE4 receptor

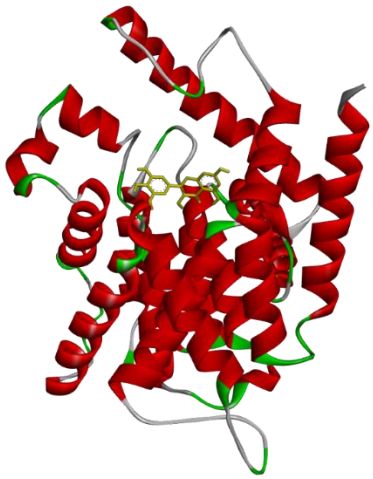
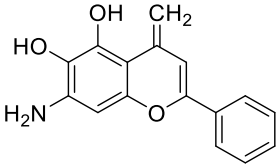
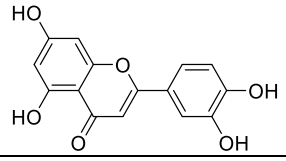
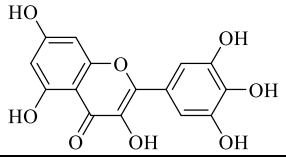


Figure 6: Binding mode of myricetin within the active site of PDE4 receptor

Table 1: Results of docking of ligands like baicalein, luteolin and myricetin against PDE4 receptor

S. No.	Compound Name	Structure	BE	Ki value	IC50
1	Baicelein		-7.26	12.25	0.086
2	Luteolin		-7.12	12.017	0.087
3	Myricetin		-6.64	11.20	0.094

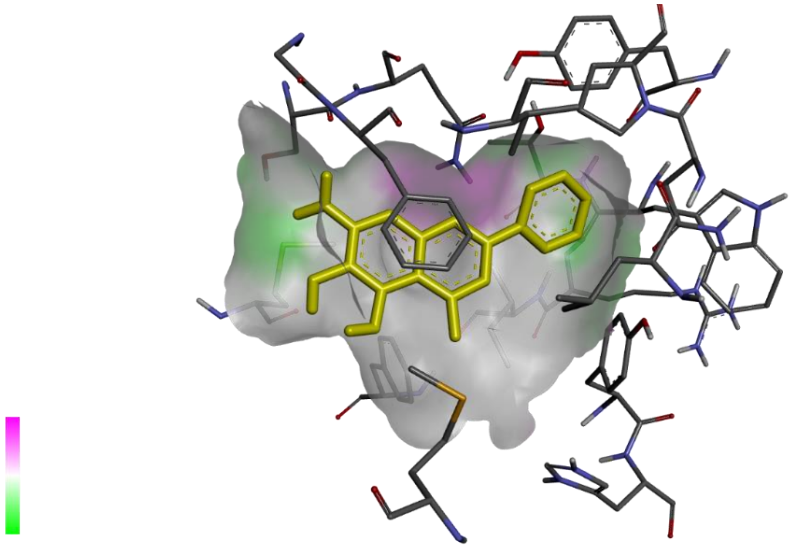


Figure 7: Three-dimensional binding mode of baicelein within the active site of PDE4 receptor

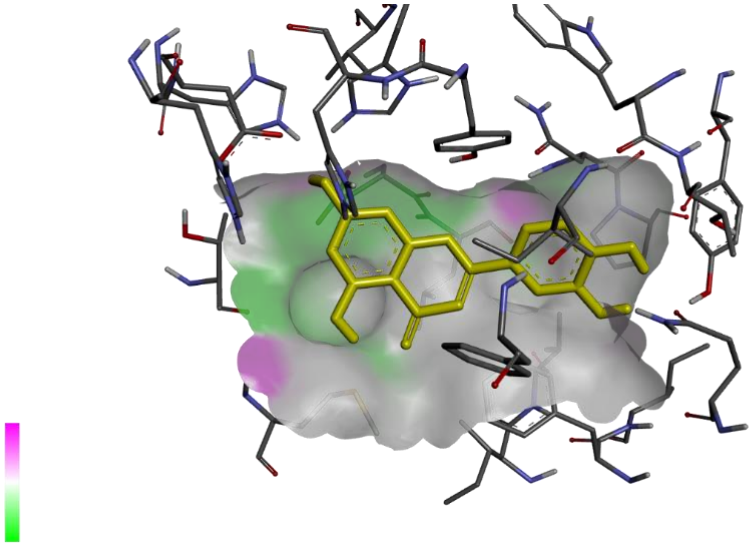


Figure 8: Three-dimensional binding mode of luteolin within the active site of PDE4 receptor

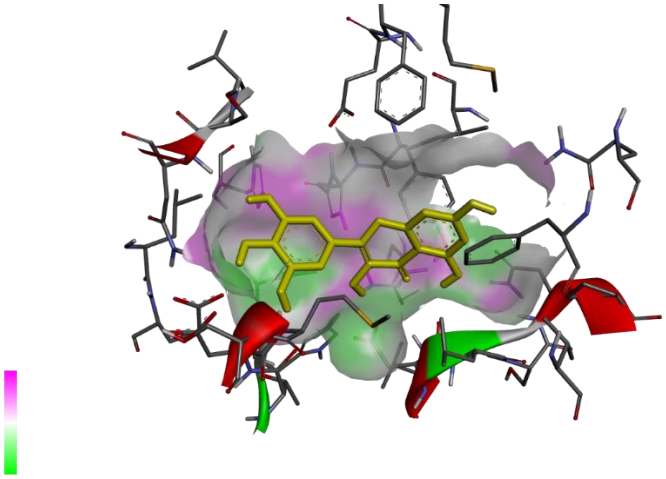


Figure 9: Three-dimensional binding mode of myricetin within the active site of PDE4 receptor

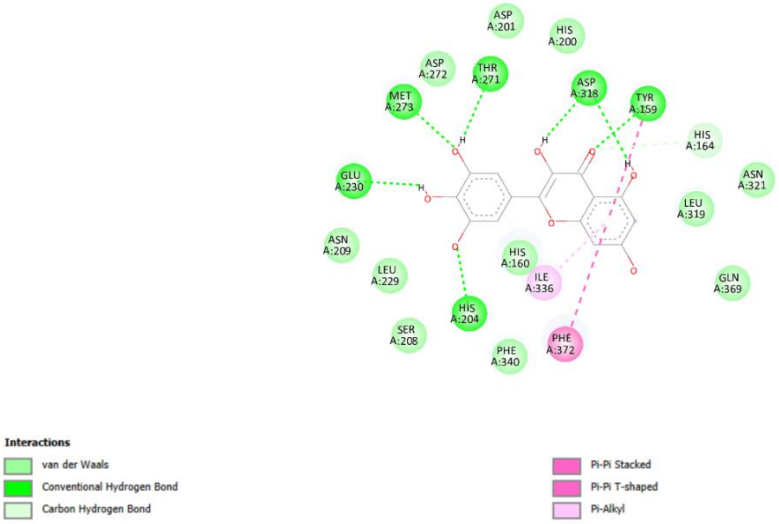


Figure 10: Two-dimensional binding mode of baicelein within the active site of PDE4 receptor

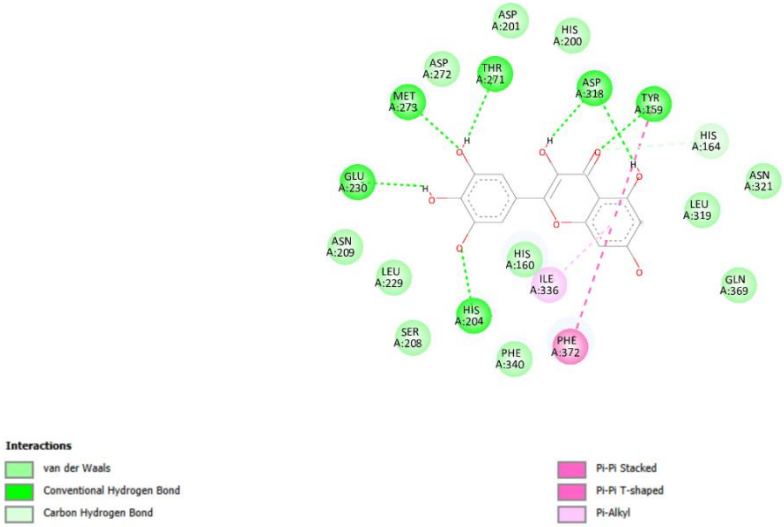


Figure 11: Two-dimensional binding mode of luteolin within the active site of PDE4 receptor

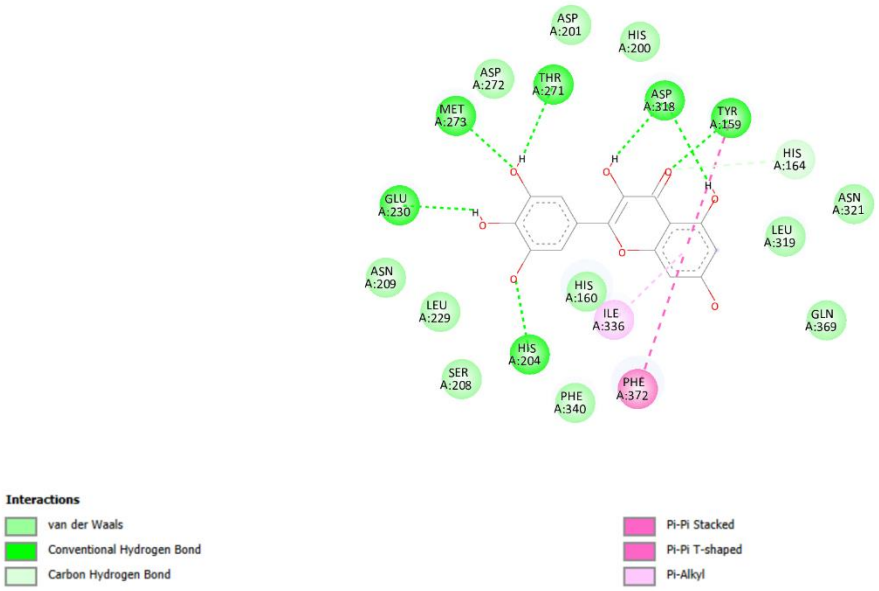


Figure 12: Two-dimensional binding mode of myricetin within the active site of PDE4 receptor

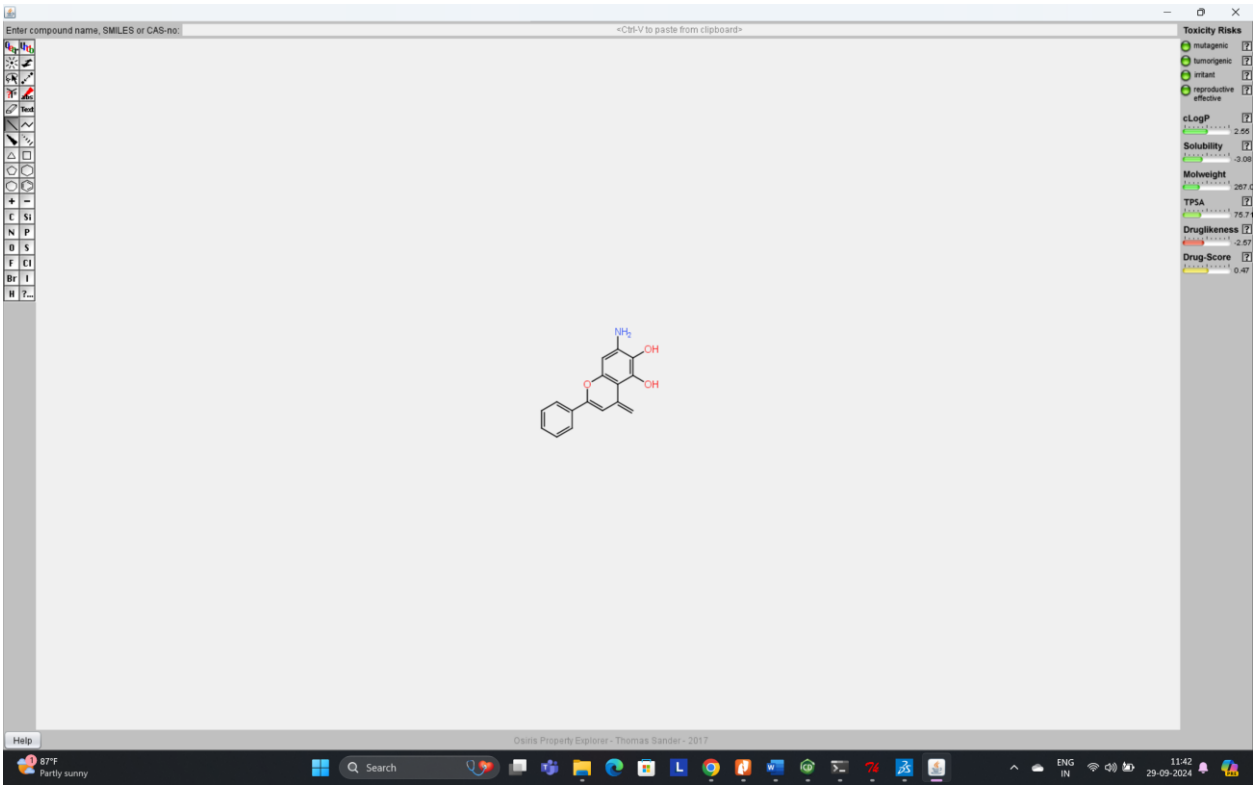


Figure 13: Pharmacokinetic and toxicity profiling of baicalein

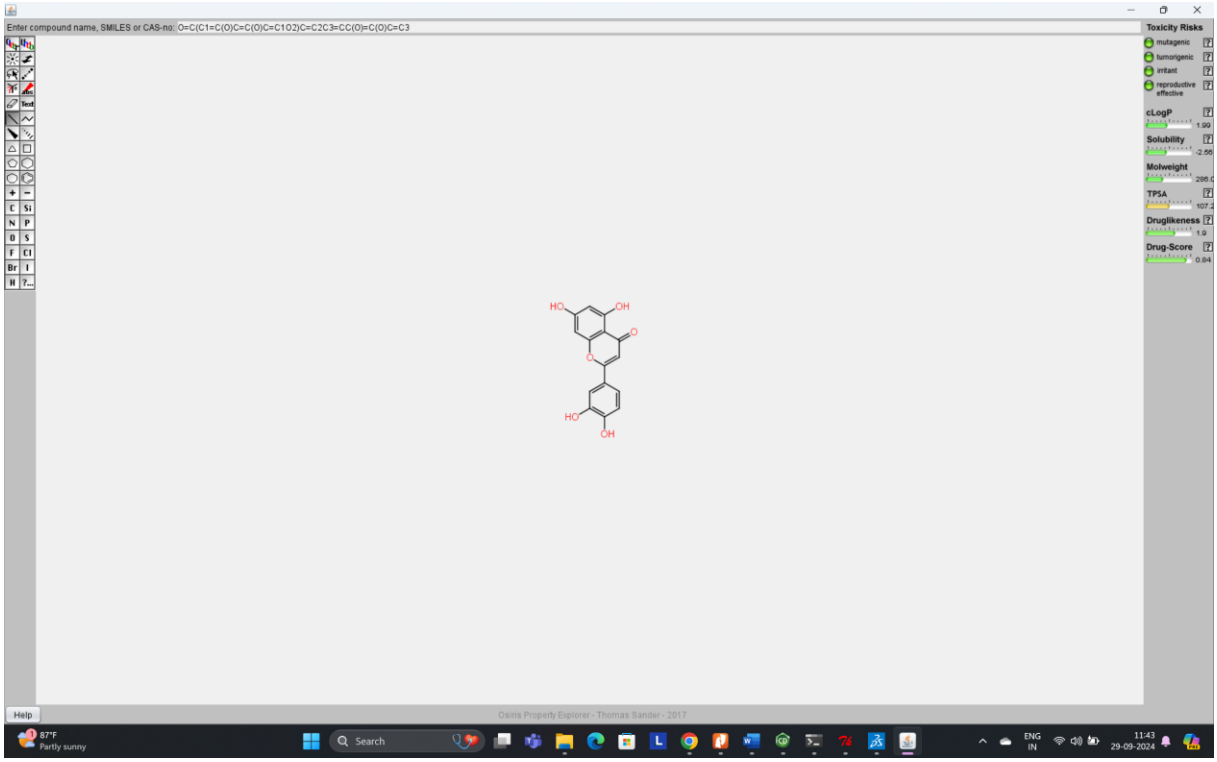


Figure 14: Pharmacokinetic and toxicity profiling of luteolin

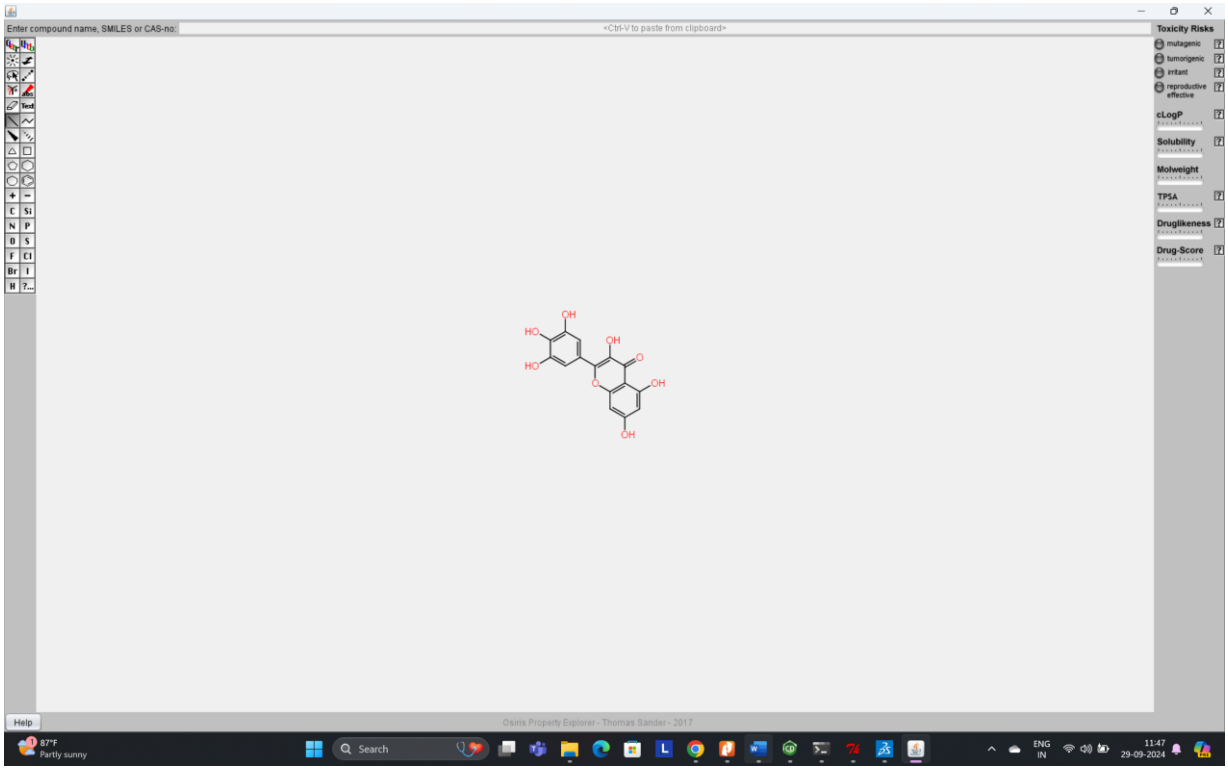


Figure 15: Pharmacokinetic and toxicity profiling of Myricetin

Table 3: Pharmacokinetic Profiling of lead molecules

Compound	ADMET			
	Mutagenic	Tumorigenic	Irritant	Reproductive effectivity
Baicelein	NO	NO	Yes	NO
Luteolin	NO	NO	NO	No
Myricetin	NO	NO	NO	No

Table 4: Lipinski Properties of lead molecules

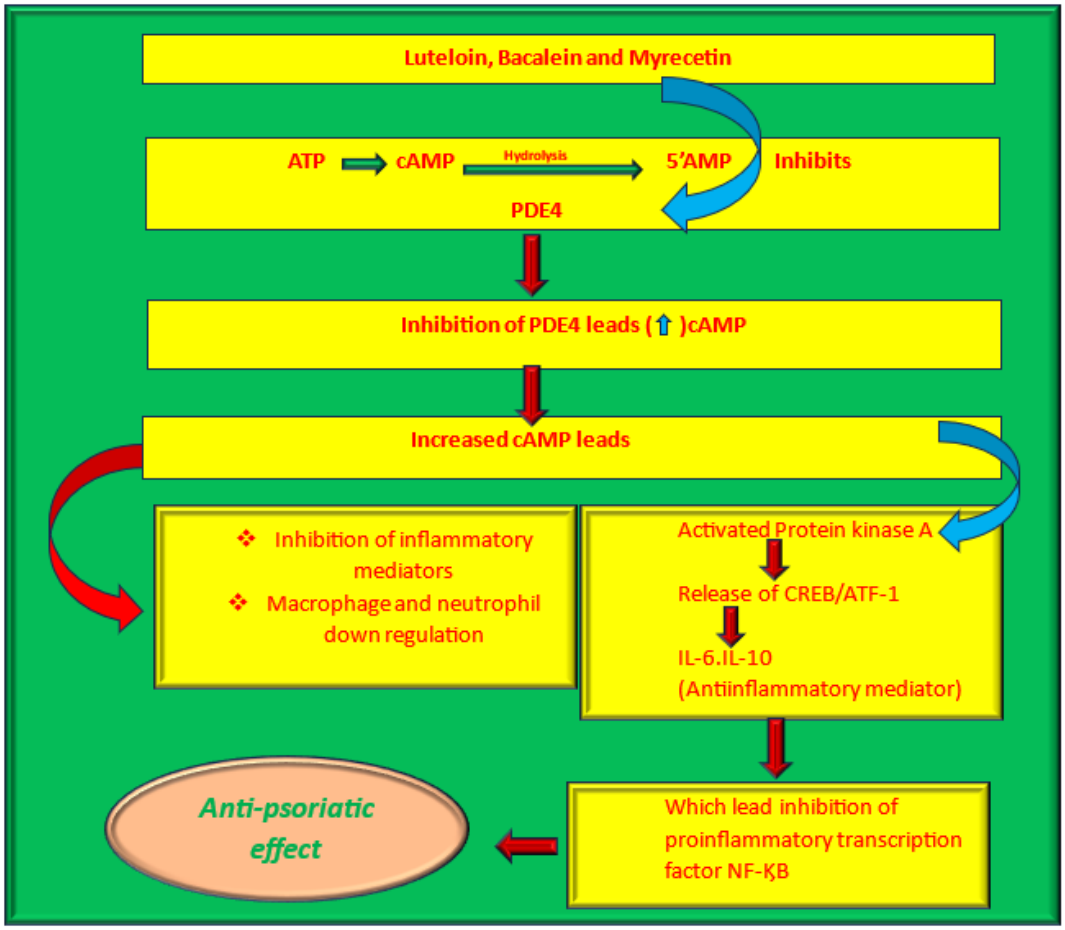
Compound	*cLogP*	Solubility	Mol.wt.	TPSA	Drug likeness	Drug score
Baicelein	2.56	-3	267	75.71	-2.57	0.47
Luteolin	1	-2.56	286	107.2	-0.19	0.14
Myricetin	1.2	-2.1	318	97.2	-1.6	0.12

Table 5: Drug likeness of lead molecules

Compound	Lipinski rule of five	H bond donar(<5)	H bond acceptor (<10)
Baicelein	Yes	3	5
Luteolin	Yes	4	6
Myricetin	Mild	6	8

Divulgence of Investigation

This study aims to investigate the efficacy of flavonoid (luteolin, baicalein and myrecetin) in treating psoriasis. The findings indicated that selected lead molecules demonstrated considerable inhibitory activity against the PDE4 enzyme, hence exhibiting anti-psoriatic effects. The suggested mode of action was illustrated in the following visuals:



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