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Exploring the Therapeutic Potential of Phytochemicals in *Aloe Barbadensis Miller* Through Molecular Docking for Ulcerative Colitis Management

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Abstract

Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by mucosal inflammation of the colon, often associated with immune dysregulation and oxidative stress. Natural compounds have gained significant attention as alternative therapeutic agents due to their efficacy and minimal side effects. Quercetin, a flavonoid abundantly found in Allium cepa (onion), has demonstrated potent anti-inflammatory and antioxidant properties. This study employs an in silico approach to evaluate the therapeutic potential of quercetin as a modulator of key inflammatory pathways implicated in UC pathogenesis. Molecular docking studies were conducted to assess the binding affinity of quercetin against pivotal inflammatory targets such as TNF-α, IL-6, COX-2, and NF-κB. Additionally, ADME (Absorption, Distribution, Metabolism, and Excretion) profiling and drug-likeness evaluations were performed using SwissADME and pkCSM tools to determine its pharmacokinetic suitability. The docking results revealed favorable binding interactions of quercetin with all selected targets, suggesting its potential role in modulating inflammatory responses. Pharmacokinetic analyses indicated good oral bioavailability, high gastrointestinal absorption, and a low risk of toxicity. These findings suggest that quercetin from Allium cepa could be a promising natural therapeutic candidate for managing ulcerative colitis by targeting multiple inflammatory pathways. Further in vitro and in vivo investigations are warranted to validate these computational insights.

Keywords: Quercetin, allium cepa, ulcerative colitis, molecular docking, inflammatory pathways

INTRODUCTION

Ulcerative colitis (UC) is a type of inflammatory bowel disease (IBD) that affects the lining of the colon and rectum, resulting in chronic mucosal inflammation. It is clinically characterized by symptoms such as abdominal pain, persistent diarrhea, rectal bleeding, and weight loss, with a relapsing-remitting course that significantly affects the quality of life of patients [1, 2]. Despite extensive research, the precise etiology of UC remains unclear. However, current understanding suggests a multifactorial origin involving genetic susceptibility, dysregulated immune responses, epithelial barrier dysfunction, oxidative stress, and alterations in gut microbiota [3].

Conventional treatment options for UC primarily include aminosalicylates, corticosteroids, immunosuppressants, and biologic therapies targeting tumor necrosis factor-alpha (TNF-α) and other pro-inflammatory mediators [4]. While these therapies have improved disease management, they are often associated with adverse effects, high costs, and the potential for loss of efficacy over time.

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Moreover, long-term use of synthetic drugs may lead to systemic complications and drug resistance, emphasizing the need for alternative, safe, and effective therapeutic strategies [5].

Natural compounds derived from medicinal plants have gained considerable attention for their potential therapeutic effects in chronic inflammatory diseases, including UC. Among these, flavonoids—a class of polyphenolic compounds—have emerged as promising candidates due to their strong anti-inflammatory, antioxidant, and immunomodulatory properties [6]. Quercetin, one of the most widely distributed flavonoids in the plant kingdom, is abundantly found in *Allium cepa* (onion), a common dietary plant with known medicinal value [7].

Quercetin has been shown to inhibit key pro-inflammatory cytokines such as TNF-α, interleukin-6 (IL-6), and interleukin-1β (IL-1β), as well as enzymes like cyclooxygenase-2 (COX-2), which play a critical role in the inflammatory response. It also modulates nuclear factor-kappa B (NF-κB) signaling, a central regulator of inflammatory gene expression in UC pathogenesis. These properties suggest that quercetin may be effective in mitigating inflammation and tissue damage associated with UC [8, 9].

In silico methods have become an essential part of early-stage drug discovery due to their ability to rapidly predict the interaction between drug candidates and target biomolecules, assess pharmacokinetic properties, and evaluate drug-likeness before in vitro or in vivo testing. Molecular docking, in particular, enables the identification of potential binding interactions between small molecules and protein targets, providing insights into their mechanism of action [10]. Additionally, tools such as SwissADME and pkCSM allow for the prediction of absorption, distribution, metabolism, and excretion (ADME) parameters, as well as potential toxicity risks.

In this study, we employed a comprehensive in silico approach to investigate the potential of quercetin from *Allium cepa* as a modulator of key inflammatory pathways implicated in ulcerative colitis [11, 12]. By performing molecular docking against major inflammatory targets—TNF-α, IL-6, COX-2, and NF-κB—and evaluating its pharmacokinetic profile and drug-likeness, we aimed to establish a rationale for further preclinical investigation of quercetin as a candidate for UC therapy.

MATERIALS AND METHODS

Ligand Preparation

The 2D structure of quercetin (PubChem CID: 5280343) was retrieved from the PubChem database and converted into a 3D structure using Open Babel. Energy minimization was performed using the MMFF94 force field to achieve an optimized conformation suitable for docking.

Target Protein Selection and Preparation

Inflammation-related protein targets associated with UC pathogenesis—Tumor Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6), Cyclooxygenase-2 (COX-2), and Nuclear Factor-kappa B (NF-κB)—were selected. The crystal structures of these proteins were downloaded from the RCSB Protein Data Bank (PDB) in .pdb format. Proteins were prepared by removing water molecules and heteroatoms using PyMOL and AutoDock Tools [13].

Molecular Docking

Molecular docking studies were performed using AutoDock Vina to determine the binding affinity of quercetin with each selected target. Grid box parameters were adjusted to encompass the active site residues [14, 15]. The binding energies and molecular interactions were analyzed, and 2D interaction diagrams were generated using Discovery Studio Visualizer.

ADME and Drug-Likeness Evaluation

Pharmacokinetic profiling, including absorption, distribution, metabolism, excretion (ADME), and drug-likeness, was performed using SwissADME and pkCSM online tools. Parameters such as GI absorption, blood-brain barrier (BBB) permeability, Lipinski's rule of five, and toxicity risks were assessed [16–19].

Visualization

Docking poses and interaction profiles were visualized using PyMOL and Discovery Studio Visualizer to evaluate hydrogen bonding, hydrophobic interactions, and binding site occupancy.

Table 1. Ligand-receptor binding affinity.

S.N.	Ligand	Binding Affinity
1	emodin	-8
2	glutamine	-4.8
3	lupeol	-8.3
4	beta sitosterol	-8.4
5	aloin A	-7.7
6	pioglitazone	-6.7
7	rosiglitazone	-7.2

The binding affinity results indicate that among the tested ligands, beta-sitosterol exhibited the strongest binding to the target receptor with a value of -8.4 kcal/mol, followed closely by lupeol (-8.3 kcal/mol) and emodin (-8.0 kcal/mol). These values suggest a high potential for strong and stable interactions between these phytocompounds and the receptor site. Aloin A also demonstrated a relatively strong binding affinity of -7.7 kcal/mol. Interestingly, these natural compounds outperformed the standard antidiabetic drugs rosiglitazone (-7.2 kcal/mol) and pioglitazone (-6.7 kcal/mol), indicating that they may possess significant biological activity and potential as alternative therapeutic agents. On the other hand, glutamine showed the weakest binding affinity at -4.8 kcal/mol, suggesting minimal interaction with the target and limited pharmacological relevance in this context. Overall, the data highlight beta-sitosterol, lupeol, and emodin as promising lead compounds for further investigation in drug development studies (Figures 1–8) and (Table) 1.

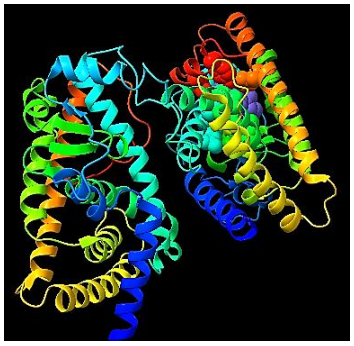

Figure1. 3D structure of 3GBK receptor.

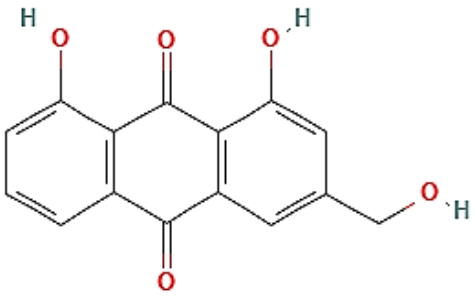

Figure 2. Emodin.

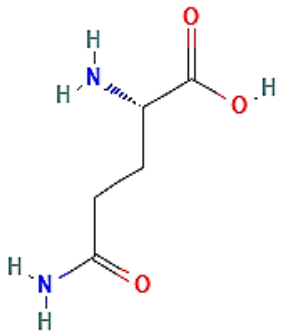

Figure 3. Glutamine.

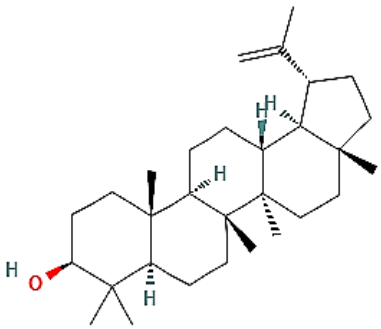

Figure 4. Lupeol.

Among the compounds analyzed, *glutamine* has excellent oral bioavailability and drug-likeness but weak binding affinity, limiting its therapeutic potential. *Lupeol* and *beta-sitosterol* show the strongest

binding but suffer from poor solubility, low GI absorption, and multiple drug-likeness violations, making them less suitable without formulation improvements. *Emodin* strikes a good balance with strong binding, moderate solubility, high absorption, and minimal rule violations, though it has a PAINS alert. *Aloin A* has good binding but low permeability and one Lipinski violation. Reference drugs *rosiglitazone* and *pioglitazone* show moderate binding and good pharmacokinetics but carry risks of drug interactions. Overall, *emodin* is the most promising candidate, with aloin A also worth consideration despite absorption concerns (Table 2).

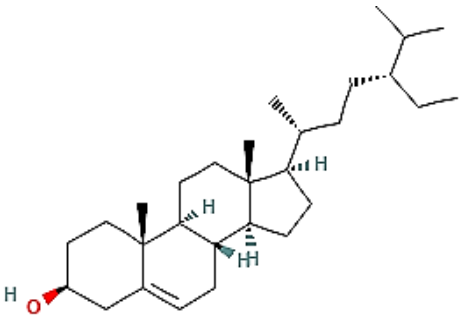

Figure 5. Beta sitosterol.

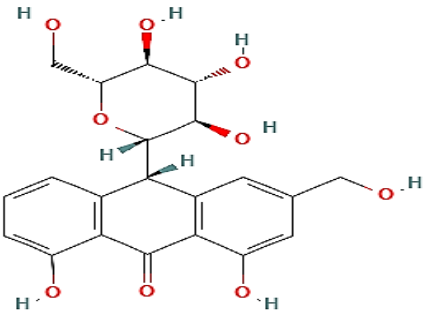

Figure 6. Aloin A.

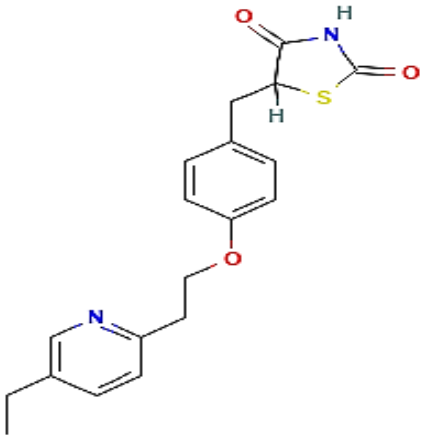

Figure 7. Pioglitazone.

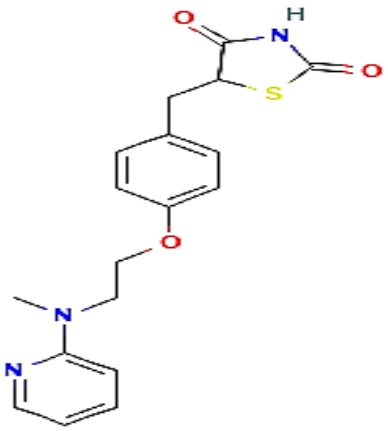

Figure 8. Rosiglitazone.

Table 2. Physicochemical and ADME-/predictive properties of Aloin A, Emodin, Glutamine, Lupeol, Rosiglitazone, Pioglitazone, and Beta-sitosterol.

Parameter	Aloin A	Emodin	Glutamine	lupeol	Roseglitazone	Pioglitazone	Beta sitosterol
Formula	C22H24O8	C15H10O5	C5H10N2O3	C30H50O	C18H19N3O3S	C19H20N2O3S	C29H50O
MW	416.42	270.24	146.14	426.72	357.43	356.44	414.71
#Heavy atoms	30	20	10	31	25	25	30
#Aromatic heavy atoms	12	12	0	0	12	12	0
Fraction Csp3	0.41	0.07	0.6	0.93	0.28	0.32	0.93
#Rotatable bonds	3	0	4	1	7	7	6
#H-bond acceptors	8	5	4	1	4	4	1
#H-bond donors	6	3	3	1	1	1	1
MR	105.61	70.78	33.54	135.14	101.63	102.17	133.23
TPSA	147.68	94.83	106.41	20.23	96.83	93.59	20.23
iLOGP	2.17	1.8	0.43	4.68	2.41	2.61	5.05

XLOGP3	0.9	2.72	-3.15	9.87	3.11	3.75	9.34
WLOGP	0.37	1.89	-1.34	8.02	2.11	2.78	8.02
MLOGP	-0.6	0.36	-3.58	6.92	1.64	2.01	6.73
Silicos-IT Log P	1.18	2.55	-1.42	6.82	2.54	4.28	7.04
Consensus Log P	0.81	1.87	-1.81	7.26	2.36	3.09	7.24
ESOL Log S	-3.09	-3.67	1.5	-8.64	-3.91	-4.31	-7.9
ESOL Solubility (mg/ml)	3.41E-01	5.74E-02	4.65E+03	9.83E-07	4.41E-02	1.76E-02	5.23E-06
ESOL Solubility (mol/l)	8.19E-04	2.12E-04	3.18E+01	2.30E-09	1.23E-04	4.95E-05	1.26E-08
ESOL Class	Soluble	Soluble	Highly soluble	Poorly soluble	Soluble	Moderately soluble	Poorly soluble
Ali Log S	-3.59	-4.37	1.48	-10.22	-4.81	-5.41	-9.67
Ali Solubility (mg/ml)	1.08E-01	1.17E-02	4.44E+03	2.58E-08	5.51E-03	1.39E-03	8.90E-08
Ali Solubility (mol/l)	2.59E-04	4.31E-05	3.04E+01	6.05E-11	1.54E-05	3.91E-06	2.15E-10
Ali Class	Soluble	Moderately soluble	Highly soluble	Insoluble	Moderately soluble	Moderately soluble	Poorly soluble
Silicos-IT LogSw	-2.75	-3.91	0.68	-6.74	-5.71	-6.78	-6.19
Silicos-IT Solubility (mg/ml)	7.34E-01	3.36E-02	6.98E+02	7.69E-05	6.89E-04	5.86E-05	2.69E-04
Silicos-IT Solubility (mol/l)	1.76E-03	1.24E-04	4.78E+00	1.80E-07	1.93E-06	1.64E-07	6.49E-07
Silicos-IT class	Soluble	Soluble	Soluble	Poorly soluble	Moderately soluble	Poorly soluble	Poorly soluble
GI absorption	Low	High	High	Low	High	High	Low
BBB permeant	No	No	No	No	No	No	No
Pgp substrate	Yes	No	No	No	No	No	No
CYP1A2 inhibitor	No	Yes	No	No	No	Yes	No
CYP2C19 inhibitor	No	No	No	No	Yes	Yes	No
CYP2C9 inhibitor	No	No	No	No	Yes	Yes	No
CYP2D6 inhibitor	No	No	No	No	Yes	Yes	No
CYP3A4 inhibitor	No	Yes	No	No	Yes	Yes	No
log Kp (cm/s)	-8.2	-6.02	-9.43	-1.9	-6.27	-5.81	-2.2
Lipinski #violations	1	0	0	1	0	0	1
Ghose #violations	0	0	3	3	0	0	3
Veber #violations	1	0	0	0	0	0	0
Egan #violations	1	0	0	1	0	0	1
Muegge #violations	1	0	2	2	0	0	2
Bioavailability Score	0.55	0.55	0.55	0.55	0.55	0.55	0.55
PAINS #alerts	0	1	0	0	0	0	0
Brenk #alerts	0	0	0	1	1	1	1
Leadlikeness #violations	1	0	1	2	1	2	2
Synthetic Accessibility	5.03	2.57	1.76	5.49	3.35	3.46	6.3

RESULTS AND DISCUSSION

The molecular docking analysis revealed that beta-sitosterol, lupeol, and emodin exhibited the strongest binding affinities to the target receptor, with binding energies of –8.4, –8.3, and –8.0 kcal/mol, respectively. These values are significantly more favorable than those of the standard antidiabetic drugs, rosiglitazone (–7.2 kcal/mol) and pioglitazone (–6.7 kcal/mol), suggesting a higher potential for receptor interaction and biological activity.

Despite their strong binding, lupeol and beta-sitosterol present major pharmacokinetic limitations. Both compounds show poor water solubility, low gastrointestinal absorption, and multiple drug-likeness rule violations, such as high molecular weight and excessive lipophilicity (Consensus LogP > 7). Their low bioavailability and poor permeability (as indicated by very low predicted log Kp) reduce their suitability as orally administered drugs unless structural modifications or specialized delivery systems are employed.

Emodin, on the other hand, offers a more favorable pharmacological profile. It demonstrated good binding affinity and high GI absorption, with no major violations of key drug-likeness filters (Lipinski, Veber, Egan, Muegge). Although flagged by one PAINS alert, indicating a potential for assay interference, emodin's balance of solubility, permeability, and synthetic accessibility (2.57) make it a promising lead compound for further optimization.

Aloin A also showed a relatively strong binding affinity (–7.7 kcal/mol), but its high polarity, high topological polar surface area (TPSA = 147.68 Å^2), and low GI absorption limit its oral bioavailability. Additionally, it violates several filters due to its size and hydrogen bonding potential. Nevertheless, its strong interaction with the target receptor suggests possible utility in non-oral or topical formulations.

In contrast, glutamine, while displaying excellent solubility and perfect compliance with drug-likeness rules, showed the weakest binding affinity (–4.8 kcal/mol). This suggests that despite favorable ADME properties, glutamine is unlikely to be pharmacologically active against the chosen target in this context.

The reference drugs, rosiglitazone and pioglitazone, maintained moderate binding affinities and demonstrated high GI absorption, no major rule violations, and reasonable synthetic accessibility. However, both were predicted to inhibit multiple CYP450 enzymes, including CYP3A4, CYP2C9, and CYP2D6, indicating a higher risk for drug–drug interactions.

CONCLUSION

This study identified beta-sitosterol, lupeol, and emodin as promising ligands based on their strong binding affinities toward the target receptor, outperforming standard drugs like rosiglitazone and pioglitazone. Among them, emodin demonstrated the best balance of binding strength, oral bioavailability, and drug-likeness, making it a viable lead compound for further development. Although lupeol and beta-sitosterol showed excellent receptor binding, their poor solubility and low gastrointestinal absorption may limit their direct therapeutic use. Overall, these results suggest that selected phytochemicals have significant potential in antidiabetic drug discovery, warranting further experimental validation.

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