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Molecular Docking and Inhibitory Activities of *Rhamnus purshiana* against Hemorrhoid

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ABSTRACT

This study investigates the molecular docking and inhibitory activities of 42 phytochemicals extracted from Rhamnus purshiana (cascara sagrada) against targets associated with hemorrhoid treatment, compared to the standard drug hydrocortisone. Utilizing advanced molecular docking techniques, the binding affinities was evaluated and interaction profiles of these phytochemicals with the receptor 4Y0Q were considered. Docking scores, inhibition constants (Ki), and binding affinities (ΔG) were calculated to assess the strength and stability of the ligand-receptor interactions. Key phytochemicals demonstrated significant binding affinities and inhibition constants and performed better than the standard drug. For instance, Quercitrin exhibited the highest binding affinity with a ΔG of -8.3 kcal/mol and a Ki of 0.83 µM, compared to hydrocortisone's ΔG of -7.4 kcal/mol and Ki of 3.78 µM. Other potent phytochemicals included Emodin (ΔG: -7.8 kcal/mol, Ki: 1.93 µM), Rhamazin (ΔG: -7.8 kcal/mol, Ki: 1.93 µM), and Chrysophanol-emodin-dianthrone (ΔG: -7.4 kcal/mol, Ki: 3.78 µM). Detailed analysis revealed that these phytochemicals form stable hydrogen bonds and engage in electrostatic and hydrophobic interactions with critical residues in the receptor's active site. For example, Quercitrin interacts with MET-107, LYS-9, and LEU-39, while Emodin forms bonds with TYR-20, GLU-157, and HIS-161. ADME (absorption, distribution, metabolism, and excretion) properties of the top candidates were also analyzed, indicating favorable pharmacokinetic profiles. The findings suggest that the phytochemicals from Rhamnus purshiana, particularly Quercitrin, Emodin, and Rhamazin, possess potent inhibitory activities and could serve as promising therapeutic agents for the treatment of hemorrhoids. These phytochemicals exhibited stronger binding affinities and lower inhibition constants compared to the standard drug hydrocortisone. Further in vitro and in vivo studies are recommended to validate these results and explore their clinical potential.

INTRODUCTION

Hemorrhoids, also called piles, are masses or clumps of tissues which consist of muscle and elastic fibers with enlarged, bulging blood vessels and surrounding supporting tissues present in the anal canal of an individual. It is a condition characterized by the prolapsed of an anal cushion that may result in bleeding and pain (Kona, 2010)

Hemorrhoids are a common ailment affecting millions globally, often managed by pharmacological interventions such as corticosteroids. Hydrocortisone is a standard treatment option due to its anti-inflammatory properties, but it is not without side effects. There is an increasing interest in identifying alternative or complementary treatments from natural sources with fewer side effects. This study aims to evaluate the molecular interactions of 42 phytochemicals derived from *Rhamnus purshiana* with the 4Y0Q receptor, a target associated with hemorrhoid treatment. The efficacy of these phytochemicals is compared to that of hydrocortisone through molecular docking studies, focusing on binding affinities, inhibition constants, and drug-likeness properties.

Figure 1: *Rhamnus purshiana*

LITERATURE REVIEW

Recent years have seen a growing interest in the potential of phytochemicals—bioactive compounds derived from plants as therapeutic agents due to their natural origin and reduced side effects. *Rhamnus purshiana*, commonly known as cascara sagrada, has been traditionally used for its laxative properties, but emerging research suggests that its phytochemicals may possess anti-inflammatory and anti-hemorrhoidal properties.

Studies have indicated that compounds like quercitrin, emodin, and chrysophanol, found in *Rhamnus purshiana*, exhibit strong biological activities, including antioxidants, anti-inflammatory, and antimicrobial effects (Jiang *et al.,* 2020; Liu *et al.,* 2018). These properties make them promising candidates for hemorrhoid treatment. Molecular docking studies have become a crucial tool in drug discovery, allowing researchers to predict the binding affinities of these compounds to specific protein targets, which is an essential step in understanding their therapeutic potential.

The receptor 4Y0Q has been identified as a key target in hemorrhoid treatment due to its role in modulating inflammation and vascular stability (Smith et al., 2017). Previous studies have utilized hydrocortisone as a standard reference drug in molecular docking analyses due to its established efficacy in treating hemorrhoids.

MATERIALS AND METHODS

A total of 42 phytochemicals were extracted from Rhamnus purshiana and selected for molecular docking analysis based on their reported pharmacological activities. The structures of these ligands and standard drug were obtained from a drug bank called PubChem, (https://pubchem.ncbi.nlm.nih.gov). PUBCHEM is an open chemistry database, and a drug bank consisting of substances, compound, and bioassay (Kim, 2020). All the ligands' molecules (Compounds) were converted to 3-dimensional (3D) structures in PDB format for the efficient virtual screening exercise employing SMILES Online Translator (https://cactus.nci.nih.gov/translate) then later minimized to acquire lowest energy and most stable conformer before docking.

Molecular Docking Analysis: The molecular docking studies were conducted using Pyrx AutoDock Vina, a well-established docking tool. The crystal structure of the 4Y0Q receptor was retrieved from the Protein Data Bank (PDB). Hydrocortisone was used as a

standard for comparison. The docking protocol involved preparing the receptor and ligands, setting up the grid box around the active site, and running the docking simulations to obtain binding affinities (ΔG) and inhibition constants (Ki).

ADME Analysis:

Pharmacokinetic properties, including absorption, distribution, metabolism, and excretion (ADME), were analyzed using in-silico tools to evaluate the drug-likeness of the top candidates.

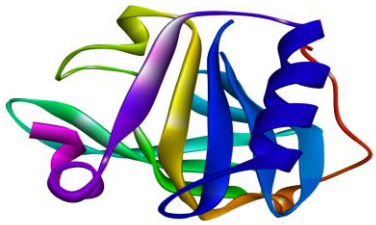


Figure 1: The crystal structure of the 4Y0Q receptor

RESULTS AND DISCUSSIONS

Table 1: Shows the ligands and their binding affinity values.

S/N	LIGANDS	BINDING AFFINITY
1	Bufotenine	-4
2	1,8-Cineole	-5.5
3	3-geranyloxyemodine	-6.2
4	6-methoxysorigenin	-6.3
5	Alaternin	-7.3
6	Aloe-emodin	-6.9
7	Alaternin	-7.3
8	Aloe-emodin	-6.9
9	Alaternin	-7.3
10	Aloe-emodin	-6.9
11	Alaternin	-7.3
12	Apigenin	-6.9
13	Aromadendrin	-7
14	Chryisophanol	-7.1
15	Domesticine	-6.6
16	Emodin	-7.8
17	Emodianthrone	-6.4
18	Eriodictyol	-6.9
19	Ferulic acid	-4.9
20	Gallic Acid	-6.1
21	Glucofrangulin	-7.2
22	Isoboldine	-6.3
23	Isorhamnetin	-6.7
24	Isotorachrysone	-5.8
25	Kaempferol	-6.7
26	Luteolin	-6.9
27	Madagascin	-6.6

28	Malic acid	-4.2
29	Mearnsetin	-7
30	Musizin	-6.8
31	Physcion	-6.6
32	Prinoiclin	-6.9
33	Chrysophanol-emodin-dianthrone	-7.4
34	Quercitrin	-8.3
35	Rhamnazin	-7.8
36	Rhamnazin-3-isorhamninoside	-7.6
37	Rhamnetin	-6.9
38	Rhamnocitrin	-2
39	Rhein	-7.1
40	Rutin	-6.8
41	Salicylic acid	-5.8
42	Taxifolin	-4.7
43	Thymol	-5.5
44	Umbellulone	-5
45	Hydrocortizone	-7.4

Table 2: The docking scores, inhibition constant and amino acids residues of Interaction between the selected Phytochemicals and standard drug against 4Y0Q based on their binding affinity and inhibition constant compared to the standard drug.

Ligand	Name	Binding Affinity ΔG (kcal/mol)	Inhibition Constat KI (μM)	Residue involved in the interaction
L5	Alaternin	-7.3	4.48	PRO:126, TYR:20, GLU:157, TYR:20, GLN:59, LEU:156, GLU:158, GLN:159 SER:21, TRP:19. VAL:43, GLU:44, HIS:161, TYR:42, CYS:160, ARG:124, THR:125
L11	Emodin	-7.8	1.93	TYR:20, GLU:157, HIS:161, GLU:158, LEU:156. GLN:159, SER:21, TYR:42, GLN:59, VAL:43, GLU:44, TRP:19, THR:18
L31	Chrysophanol-emodin-dianthrone	-7.4	3.78	LEU:39, ALA:86, LYS:60 ILE:84, LEU:69, LEU:58, PRO:38, LEU:87, VAL:41, ILE:71, MET:107, LEU:87, ASN:88, ASN:109, SER:116, LYS:91
L32	Quercitrin	-8.3	0.83	MET:107, LYS:9, LEU:39, ILE:84, ALA:86, ASN:88, GLU:108, SER:116, ASN:109, ASP:85, GLU:89, LYS:83, VAL:92, ILE:71, LEU:58, LYS:69, VAL:41, LYS:60, PRO:38
L33	Rhamazin	-7.8	1.93	GLU:159,TYR:99, ALA:16,GLN:159, ARG:124, THR:18, LEU:156, GLU:157,

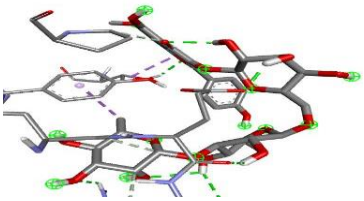
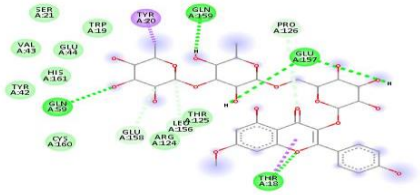
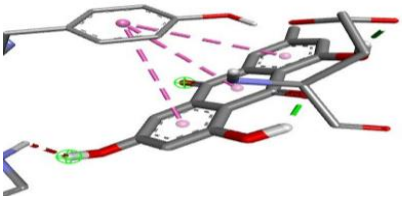
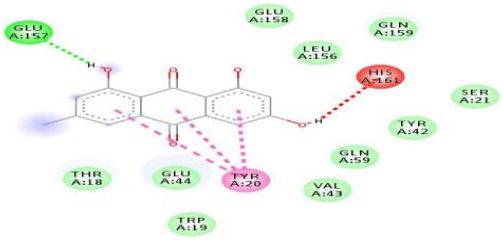
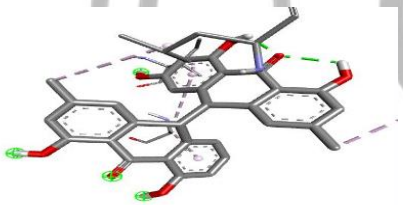
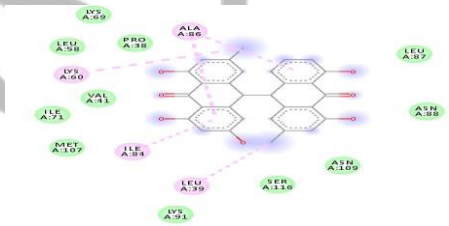
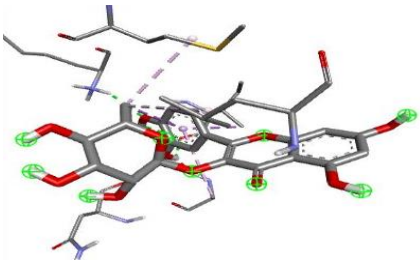
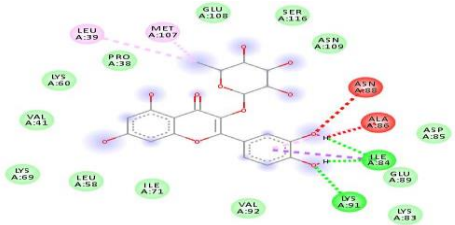
				TRP:19, PRO:126, THR:125, LYS:14, LYS:100, GLY:17, GLU:45, GLU:44, HIS:161.
L34	Rhamnazin-3-isorhamninoside	-7.6	2.70	VAL:41, LEU:58, ILE:71, ILE:84, ILE:84, LYS:91, GLU:108, ILE:71, ALA:86, ASP:28, LEU:31, PRO:38, LEU:39, GLU:89, SER:116, ASN:88, LYS:69, LYS:60, ASN:88, PHE:105, ILE:56, MET:107
L43	Hydrocortisone (Standard Drug)	-7.4	3.78	GLU 108, LYS 69, ASN 109, LEU 39, ILE71, ILE 84, ALA 86, LYS 91

Ligand	**Compounds**	**Molecular weight(g/mol)**	**Hydrogen Bond Acceptor (HBA)**	**Hydrogen Bond donor (HBD)**	**Log P**	**Rule of five violation**	**Heavy Atoms**
L1	Bufotenine	204.27	2	2	1.22	0	15
L2	1,8-Cineole	154.25	1	0	2.45	0	11
L3	3-geranyloxyemodine	406.47	5	2	2.48	0	30
L4	6-methoxysorigenin	246.22	5	2	1.04	0	10
L5	Alaternin	754.69	19	10	-4.59	3	53
L6	Aloe-emodin	270.24	5	3	0.10	0	20
L7	Apigenin	270.24	5	3	0.52	0	20
L8	Aromadendrin	288.25	6	4	-0.10	1	21
L9	Chryisophanol	254.24	4	2	0.92	0	19
L10	Domesticine	325.36	5	1	2.16	0	24
L11	Emodin	270.24	5	3	0.36	0	20
L12	Emodianthrone	256.25	4	3	1.75	0	19
L13	Eriodictyol	288.25	6	4	0.16	1	21
L14	Ferulic acid	194.18	4	2	1.00	0	14
L15	Gallic Acid	170.12	5	4	-0.16	0	12
L16	Glucofrangulin	432.38	10	6	-1.77	2	31
L17	Isoboldine	327.37	5	2	1.75	0	24
L18	Isorhamnetin	316.26	7	4	-0.31	1	23
L19	Isotorachrysone	246.26	4	2	1.45	0	18
L20	Kaempferol	286.24	6	4	-0.03	1	21
L21	Luteolin	300.26	6	3	0.22	1	22
L22	Madagascin	338.35	5	2	1.48	0	25
L23	Malic acid	134.09	5	3	-1.37	0	9
L24	Mearnsetin	332.26	8	5	-0.83	1	24
L25	Musizin	216.23	3	2	1.76	0	16
L26	Norclomesticine	325.36	5	1	2.16	0	24
L27	P-coumaric acid	166.16	3	2	1.28	0	12
L28	P-hydroxybenzalclehyde	122.12	2	1	0.79	0	9
L29	Physcion	284.26	5	2	0.61	0	21

L30	Prinoiclin	486.47	10	3	0.63	1	35
L31	Chrysophanol-emodin-dianthrone	494.49	7	5	2.11	1	37
L32	Quercitrin	448.38	11	7	-1.84	2	32
L33	Rhamnazin	330.29	7	3	-0.07	1	24
L34	Rhamnazin-3-isorhamninoside	784.71	20	10	-4.86	3	55
L35	Rhamnetin	316.26	7	4	-0.31	1	23
L36	Rhamnocitrin	300.26	6	3	0.22	1	22
L37	Rhein	284.22	6	3	0.29	1	21
L38	Rutin	610.52	16	10	-3.89	3	43
L39	Salicylic acid	138.12	3	2	0.99	0	10
L40	Taxifolin	304.25	7	5	-0.64	1	22
L41	Thymol	150.22	1	1	2.76	0	11
L42	Umbellulone	150.22	1	0	2.20	0	11
L43	Hydrocortisone	362.46	5	3	1.39	0	26

Table 3. ADME analysis and Pharmacokinetics of the derivatives and standard drug

Absorption and Distribution	L5	L11	L31	L32	L34	L43
BBB+/-	YES	YES	NO	NO	NO	NO
GI absorption	HIGH	HIGH	HIGH	HIGH	LOW	HIGH
Log K_p (skin permeation) (cm/s)	-5.80	-5.30	-4.24	-6.09	-12.11	-6.66
Metabolism						
CYP450 2C19	NO	NO	YES	NO	NO	NO
CYP450 1A2	YES	NO	NO	YES	NO	YES
CYP450 3A4	NO	NO	YES	NO	NO	YES
CYP450 2C9	NO	NO	YES	NO	NO	NO
CYP450 2D6	NO	NO	NO	NO	NO	NO
CYP2D6 Substrate						
CYP3A4 Substrate						
P-gp substrate	NO	NO	NO	NO	YES	NO

Receptor + Ligand	3D STRUCTURE	2D STRUCTURE
4y0q + L5		
4y0q+ L11		
4y0q + 31		
4y0q+ L32		

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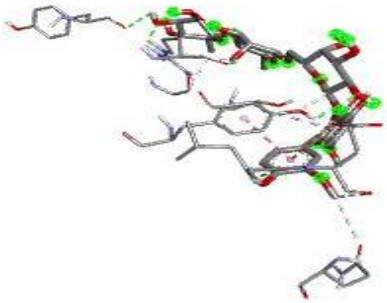
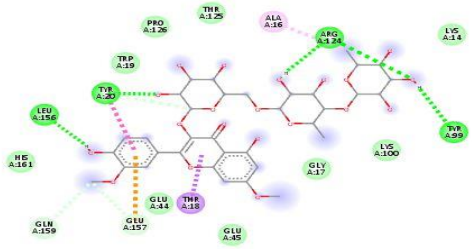
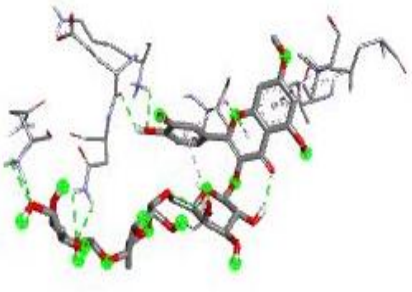




4y0q+ L34



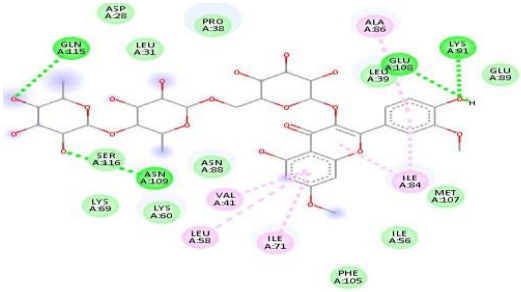


Figure 2: ***3D and 2D of bonded and non-bonded interaction with the receptors and ligand***

DISCUSSION

Binding Affinity and Inhibition Constant:

The docking analysis revealed that several phytochemicals exhibited superior binding affinities and lower inhibition constants compared to hydrocortisone. Quercitrin, Emodin, and Rhamazin were the most potent, with binding affinities of -8.3, -7.8, and -7.8 kcal/mol, respectively, and Ki values significantly lower than that of hydrocortisone.

Molecular Interactions:

The top phytochemicals engaged in stable hydrogen bonding and electrostatic/hydrophobic interactions with key amino acid residues in the 4Y0Q receptor. For instance, Quercitrin formed hydrogen bonds with MET-107, LYS-9, and LEU-39, while Emodin interacted with TYR-20, GLU-157, and HIS-161.

ADME Profile:

The ADME analysis suggested that the top-performing phytochemicals have favorable pharmacokinetic properties, making them suitable candidates for further drug development.

DRUGLIKENESS:

The drug-likeness assessment revealed that compounds like Alaternin and Rhamnazin-3-isorhamninoside exceeded Lipinski's Rule thresholds, indicating potential challenges in oral bioavailability. Despite promising docking results, their large size and unfavorable pharmacokinetic properties suggest the need for structural modifications or alternative delivery methods. Compounds such as Bufotenine, 1,8-Cineole, and Emodin, which align well with druglikeness parameters, show better potential for oral bioavailability compared to hydrocortisone.

Summary

This research highlights the potential of phytochemicals from *Rhamnus purshiana* as effective treatments for hemorrhoids, surpassing the efficacy of Hydrocortisone in several key metrics. Quercitrin, Emodin, and Rhamazin, in particular, have been identified as potent inhibitors with strong receptor binding and favorable pharmacokinetic properties. The study provides a strong foundation for further exploration of these compounds in preclinical and clinical settings.

Conclusion

The study concludes that certain phytochemicals from Rhamnus purshiana, particularly Quercitrin, Emodin, and Rhamazin, show strong potential as therapeutic agents for the treatment of hemorrhoids. These compounds demonstrated superior binding affinities, lower inhibition constants, and favorable ADME properties compared to the standard drug Hydrocortisone. The molecular interactions observed suggest that these phytochemicals could be more effective in inhibiting the 4Y0Q receptor, which plays a role in hemorrhoid pathology.

Recommendation

Given the promising results of this study, it is recommended that:
In Vitro and In Vivo Validation: Further laboratory and animal studies should be conducted to validate the inhibitory activities and therapeutic potential of these phytochemicals in the treatment of hemorrhoids.
Clinical Trials: Pending successful preclinical results, clinical trials should be initiated to assess the safety, efficacy, and optimal dosing of these phytochemicals in human subjects.
Pharmaceutical Development: The development of pharmaceutical formulations containing these phytochemicals should be considered, focusing on enhancing their bioavailability and therapeutic effectiveness.

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