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Virtual Screening, Molecular Docking and Pharmacophore Modeling of Phytoconstituents of *Flavones as* Aldose Reductase Inhibitors

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Flavones are an important class of naturally occurring heterocycles possessing various pharmacological activities. An *in silico* approach was carried out where 506 compounds containing flavone ring were utilised as ligand against the target aldose reductase enzyme. Aldose reductase is the rate-limiting enzyme in the polyol pathway, which indirectly causes diabetic complications like diabetic nephropathy and diabetic retinopathy. The flavone containing compounds retrieved from the PubChem were investigated by HTVS (high throughput virtual screening) followed by molecular docking using glide SP and XP docking module in Maestro of Schrodinger software. Among them, the best fifteen compounds were selected for further studies. The binding energy calculation was done using the Prime MM-GBSA module. PASS online prediction tools were used for predicting the antidiabetic activity of the compounds. Also, a pharmacophore model was generated for best interacted fifteen compounds by Phase, which can be used for evaluation of the characteristic features essential for this specific biological activity. The ADMET properties of the compounds were determined using the Qikprop module in the Schrodinger software.

Keywords: Flavones; aldose reductase; molecular docking; pharmacophore modeling.

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1. INTRODUCTION

An alarming increase in diabetic cases significantly impacted the spike of both mortality and morbidity rates worldwide. In 2016, WHO reported an enormous increase in diabetic patients from 108 million to 422 million in the past decade [1]. Thus, it is essential to develop a better therapeutic portofolio for diabetes management. Moreover, diabetic complications are some the worst part which has to be controlled.

Aldose reductase plays a vital role in polyol pathway, as it is involved in rate limiting step [2]. The hexokinase pathway is used for the metabolism of sugar in average conditions. During hyperglycemia, excess glucose saturates the latter and activates aldose reductase leading to the conversion of glucose into sorbitols or other sugar alcohols [3]. This fact (pathways/ transformation) indirectly causes diabetic complications like diabetic nephropathy and diabetic retinopathy [4]. Hence, aldose reductase inhibitors will reduce the glucose flux and plays a crucial role in the management of diabetes which is scarcely available. Alrestatin, benurestat, epalrestat, fidarestat, imirestat, lidorestat, minalrestat, ponalrestat, ranirestat, risarestat, sorbinil, tolrestat, zenarestat, and zopolrestat were some of the aldose reductase inhibitors which were withdrawn during clinical trials due to various adverse effects [5]. Fever, nausea, diarrhea, increases in liver enzymes, skin rashes, including toxic epidermal necrolysis and Stevens-Johnson syndrome, marked thrombocytopenia, lymphadenopathy, splenomegaly, and adult respiratory distress syndrome were some of the main adverse effects [6].Tolrestat was withdrawn because of deaths from fatal hepatic necrosis [7].

Flavones are an essential class of oxygen-containing heterocyclic systems. The benzopyran ring system in the flavones occurs as secondary metabolites in the plant kingdom [8]. Generally, the term 'Flavonoids' are used, which possess C6–C3–C6 carbon framework having a phenylbenzopyran skeleton. Further divided into the flavonoids, the isoflavonoids and the neoflavonoids based on the position of phenyl ring linkage to the benzopyran moiety [9]. Flavones are derived from chalcones through a biosynthetic pathway utilising malonyl coA and *p*-coumaroyl CoA [10].

Molecular docking is efficient *in silico* drug design approach to predict the possible binding site of the target protein for a ligand [11]. It is a virtual screening technique where many compounds are reduced to a minimum subset of compounds having a high binding affinity towards the receptors [12].The docking procedure involves the computational method to search for an appropriate ligand into the binding pockets with minimised energy conformation [13]. By applying such computational tools, we have performed the anticancer action of flavonoids [14], COX inhibitory actions of synthetic compounds [15] and in continuation of the *in silico* studies, this study focuses on developing flavones as leads as aldose reductase inhibitors.

2. MATERIALS AND METHODS

The flavones were retrieved from PubChem obeying Rule of Five properties, and 506 compounds were chosen. The target protein aldose reductase was selected as 3RX2 from protein data bank for the specified study.

2.1 Ligand Preparation

The ligands were imported to LigPrep and preparation and minimization was done by using the Ligprep module [16,17].

2.2 Protein Preparationand Receptor Grid Generation

Aldose reductase preparation was realized using the wizard of the Schrodinger software for the molecular docking studies. The three-dimensional structure of the target proteins was obtained from the RCBS (PDB ID:3RX2) [18]. Preprocess was done by assigning hydrogen orders. The optimization was also carried out by hydrogens assignment and water removal. Then minimization was carried out to ease the docking process. Grid generation is an essential feature in molecular docking. The active site was determined, and grid generation was done [19].

2.3 High Throughput Virtual Screening (HTVS)

The 506 ligands retrieved from PubChem were undergone HTVSfor the enzyme aldose reductase, where 339 compounds interacted with it.HTVS reduces the number of intermediate conformation throughout the docking funnel and reduces the thoroughness of the final torsional refinement. Hence, HTVS aids in identifying specific molecules of interest from the rest of the

testing set molecules. However, the XP docking was also carried out only for the compounds showing the least G.score from virtual screening to produce a more sophisticated scoring function than HTVS [17,20].

2.4 Molecular Docking

Molecular docking is used to determine the interaction between the ligand and the target protein. 339 compounds were performed for glide SP docking followed by glide XP docking. In the GLIDE ligand docking module, the corresponding generated grid of the receptor and ligprep files were inserted, anddocking was performed [17,21].The ligands which interacted with 3RX2 by XP docking method were listed in Table 1.

2.5 Pharmacophore Modeling

A pharmacophore model was generated for best-interacted compounds by PHASE [17]. It can investigate the characteristic features essential for biological activity. The generated five featured pharmacophores in this study showed three main elements: hydrogen bond acceptors (HBAs), hydrogen bond donors (HBDs) and aromatic rings (AR). HBDs are shown in blue, HBAs in pink and ARs in orange. The three and four featured pharmacophore hypotheses were rejected due to the low value of survival score. They were unable to define the entire binding space of the selected molecules. Five featured pharmacophore hypotheses were established and subjected to rigorous scoring function analysis. Common pharmacophore hypotheses (CPH) were searched, which included at least five sites common-to-all molecules. Further, the best CPH was selected depending on the survival score until at least one hypothesis was found and scored successfully. Pharmacophore-matching tolerance was set to 2 A°. The highest survival score for the common pharmacophore hypothesis gives the best alignment of the active ligands to this hypothesis. This alignment provides fitness to all of the inhibitors [22].

2.6 Physicochemical and ADMET Studies

The physicochemical and ADMET properties of the compounds were determined by using the Qikprop module in the Schrodinger software [17,23-24]. ADME properties prediction before expensive experimental processes can eliminate unnecessary testing on compounds that will probably fail in clinical trials.

2.7 Antidiabetic Activity Prediction in PASS Online

Prediction of antidiabetic activity for the selected 15 flavones wasmade with the help of the computer program PASS (Prediction of activity spectra for substances) [25]. PASS is a computer-based program used to predict different pharmacological activities for other substances, including phytoconstituents. Prediction of this spectrum by PASS is based on structural activity relationship (SAR) analysis of the training set containing more than 205,000 compounds exhibiting more than 3750 kinds of biological activities. The predicted activity spectrum of a compound is estimated as probable activity (Pa) and probable inactivity (Pi). The compounds showing more Pa value than Pi are the only constituents considered as possible for a particular pharmacological activity.

3. RESULTS

3.1 Virtual Screening and Molecular Docking

Among the 506 selected compounds, the high throughput virtual screening produced 339 compounds against aldose reductase enzymes. The docking scores and interactions are given in Table 2 and Fig. 1(a-b), 2(a-b).

3.2 Pharmacophore Hypothesis Generation and Modeling

The results of all featured pharmacophore hypotheses are presented in Table 3. The first hypothesis, AADRR_1, is the best hypothesis in this study, characterised by the highest survival score (4.8906), which consists of two hydrogen bond acceptors (A), one hydrogen bond donors (D), and two aromatic rings (R) (Fig. 2). The distances between the sites in the common pharmacophore hypothesis AADRR_1 are given in Figs. 3(a-c) and Table 4 and 5.

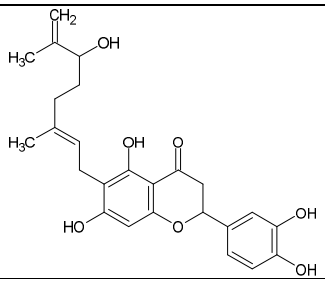
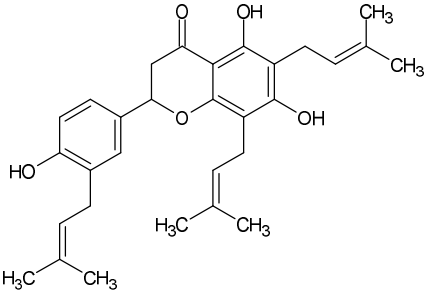
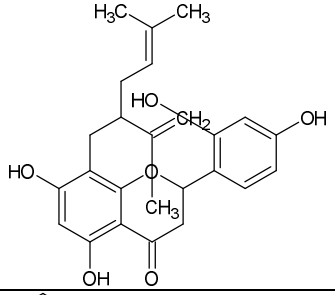
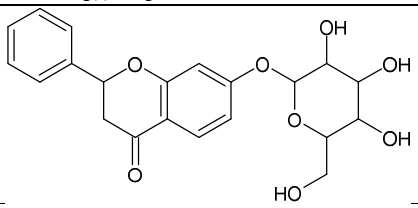
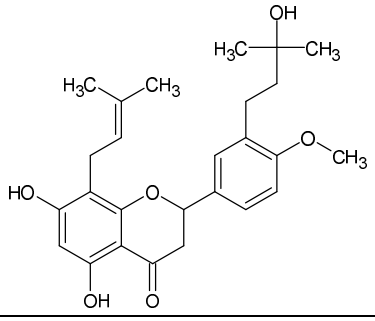
3.3 ADMET and Physicochemical Properties

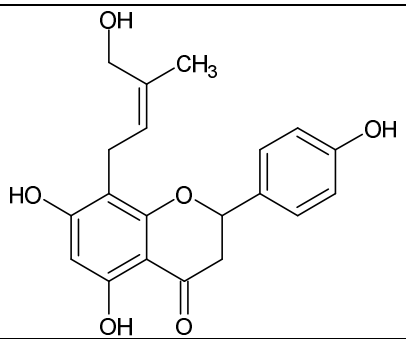
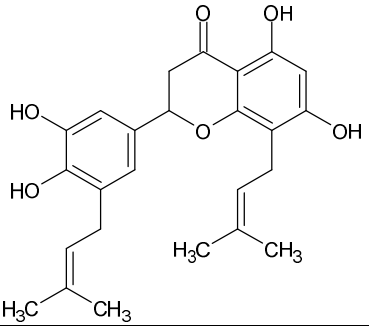
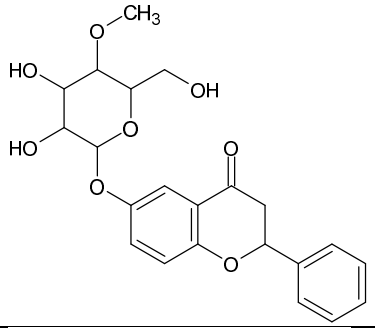
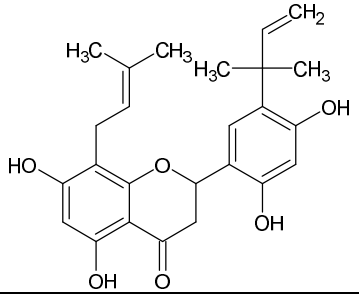
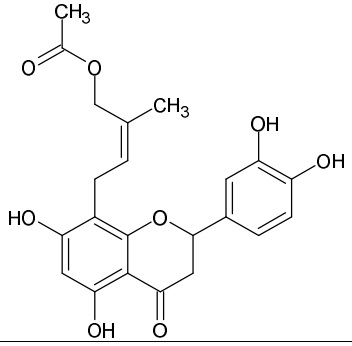
The selected flavonoids were screened for their physicochemical and ADMET properties and the results are portrayed in Tables 6. The predicted properties state that all the flavonoids, except naringin, showed values within the permissible limit, confirming that they might act as good oral bioavailable drugs.

3.4 PASS Predictions for Antidiabetic Activities

The anticancer activity spectra of myricetin and quercetin were obtained by online PASS version. These predictions were interpreted and used in a flexible manner. PASS predicted probable activity (Pa) of myricetin and quercetin for different cancer targets was predicted and reported in the given Table 7.

Table 1. List of the best ligands interacted with the protein 3RX2

Sl. No.	Ligand PubChem ID and name	Structure
1.	11247668 Tanariflavanone D	
2.	14134104 Amorilin	
3.	101670967 2',4',5,7-Tetrahydroxy-8-[(R)-2-isopropenyl-5-methyl-4-hexenyl]flavanone	
4.	440195 Flavanone 7-O-glucoside	
5.	42607958 5,7-Dihydroxy-4'-methoxy-8-C-prenyl-3'-(3-hydroxy-3-methylbutyl)flavanone	

6.	101367766 4',5,7-Trihydroxy-8-[(E)-3-methyl-4-hydroxy-2-butenyl]flavanone	
7.	480770 Gancaonin E	
8.	101843485 (2R)-6-(4-O-Methyl-beta-D-glucopyranosyloxy)flavanone	
9.	10251761 2S)-5,7,2',4'-Tetrahydroxy-8-prenyl-5'-(1,1-dimethylallyl)flavanone	
10.	42607996 Kanzonol S	

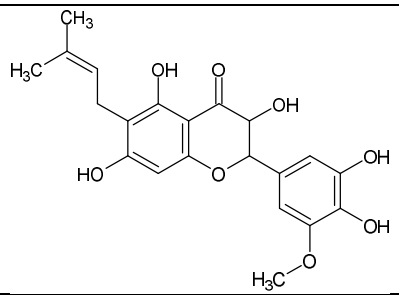
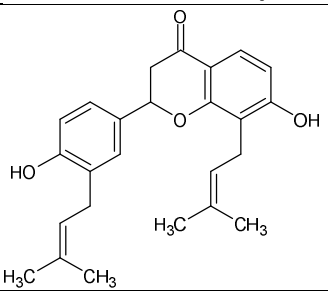
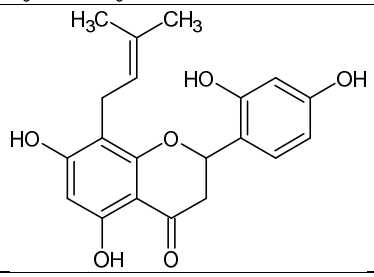
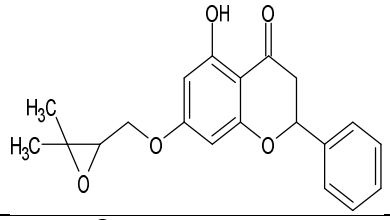
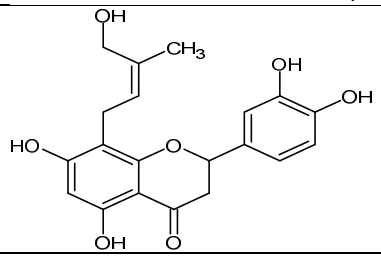
11.	74333987 3,4',5,5',7-Pentahydroxy-3'-methoxy-6-(3-methyl-2-butenyl) flavanone	
12.	480768 Glabrol	
13.	11810419 (+/-)-Leachianone G	
14.	42607867 5-Hydroxy-7-(3-methyl-2,3-epoxybutoxy)flavanone	
15.	11111496 Licoleafol	

Table 2. Docking scores and interactions of ligands with 3RX2

Sl. No.	Name	Docking scores			Docking interactions		
		XP*	SP*	HTVS*	Hydrophobic interaction	Polar interaction	Hydrogen bonding
1.	11247668 Tanariflavanone D	-14.378	-9.582	-8.026	Leu 301, Ile 260, Leu 300, Trp 79, Tyr 209, Ala 299, Cys 298, Trp 111, Trp 219, Phe 122, Val 297, Trp 20, Val 47, Tyr 48	Ser 302, Hid 110, Ser 159 Asn 160 Gln 183	Leu 301 Leu 300 Gln 183

2.	Amorilin	-14.037	-8.784	-5.679	Leu 301,Leu 300, Ala 299, Val 297, Cys 298, Tyr 209, Ile 260, Trp 20, Trp 79, Tyr 40, Val 47, Trp 111, Trp 219, Phe 122, Pro 218	Ser 302, Gln 183, Ser 159 Asn 160, Ser 210, Hid 110	Ser 302, Leu 301, Leu 300 Ala 299, Hid 110
3.	2',4',5,7-Tetrahydroxy-8-[(R)-2-isopropenyl-5-methyl-4-hexenyl]flavanone	-14.649	-8.959	-5.187	Pro 218, Trp 219, Leu 301, Leu 300, Ala 299, Val 297, Cys 298, Trp 79, Trp 111, Trp 20, Val 47, Tyr 48, Phe 122	Ser 302, Hid 110	Leu 301 Leu 300 Ser 302 Hid 110
4.	Flavanone 7-O-glucoside	-13.919	-9.222	-9.241	Val 297, Cys 298, Trp 219, Ala 299, Leu 301, Leu 300, Tyr 209, Trp 111 Phe 122, Tyr 48, Val 47, Trp 79, Trp 20	Ser 302, Hid 110, Ser 159, Asn 160, Gln 183	Val 297 Leu 300
5.	5,7-Dihydroxy-4'-methoxy-8-C-prenyl-3'-(3-hydroxy-3-methylbutyl)flavanone	-13.855	-9.144	-7.222	Trp 219, Ala 299, Leu 301, Leu 300, Cys 298, Val 47, Tyr 48, Trp 111, Tyr 209, Trp 20, Trp 79, Leu 124, Phe 122	Ser 302 Hid 110 Asn 160	Leu 301 Leu 300 Hid 110 Tyr 48
6.	4',5,7-Trihydroxy-8-[(E)-3-methyl-4-hydroxy-2-butenyl]flavanone	-12.938	-10.037	-7.657	Ala 299, Leu 301, Leu 300, Hid 110, Trp 20, Trp 219, Trp 111, Trp 79, Trp 20, Tyr 48, Val 47, Phe 122	Ser 302 Hid 110	Leu 301,Leu 300, Hid 110 Trp 20
7.	Gancaonin E	-12.922	-7.791	-7.266	Leu 301, Leu 300, Ala 299, Cys 298, Val 297, Trp 111, Tyr 209, Ile 260, Trp 219, Pro 218 , Phe 122, Trp 79, Trp 20, Tyr 48, Val 47	Ser 302 Hid 110 Ser 159 Asn 160 Gln 183	Leu 301 Leu 300 Ala 299 Ser 302 Hid 110
8.	(2R)-6-(4-O-Methyl-beta-D-glucopyranosyloxy)flavanone	-12.743	-8.915	-6.525	Leu 301, Leu 300, Ala 299, Cys 298, Val 297, Trp 111, Tyr 209, Ile 260, Trp 20, Trp 79, Tyr 48, Val 47, Phe 122, Trp 219	Ser 302 Hid 110 Ser 159 Asn 160 Gln 183	Ser 302 Leu 300 Ala 299
9.	2S)-5,7,2',4'-Tetrahydroxy-8-prenyl-5'-(1,1-dimethylallyl)flavanone	-12.662	-7.215	-7.246	Leu 301, Leu 300, Ala 299, Cys 298, Val 297, Trp 20, Tyr 209, Trp 79, Val 47, Tyr 48, Trp 111, Phe 122, Pro 218, Trp 219	Ser 302 Ser 159 Asn 160 Hid 110	Ser 302 Leu 301 Leu 300 Ala 299 Hid 110
10.	Kanzonol S	-12.487	-8.710	-6.249	Leu 301, Leu 300, Ala 299, Cys 298, Pro 218, Trp 219, Trp 79, Trp 111, Tyr 209, Trp 20, Tyr 48, Val 47, Phe 121, Phe 122	Hid 110 Asn 160 Ser 159 Gln 49 Gln183	Cys 298 Val 47 Tyr 48

11.	3,4',5,5',7-Pentahydroxy-3'-methoxy-6-(3-methyl-2-butenyl) flavanone	-12.435	-9.349	-9.131	Leu 301, Leu 300, Ala 299, Cys 298, Trp 79, Trp 20, Tyr 209, Ile 260, Trp 111, Val 47, Tyr 48, Phe 122, Trp 219	Ser 302 Ser 159 Asn 160 Ser 210 Gln 183 Hid 110	Leu 300 Asn 160 Gln 183 Hid 110
12.	Glabrol	-12.419	-8.031	-6.910	Leu 301, Leu 300, Ala 299, Cys 298, Val 297, Trp 20, Trp 111, Tyr 209, Ile 260, Trp 79, Tyr 48, Val 47, Phe 122, Pro 218, Trp 219	Ser 302 Hid 110 Asn 160 Ser 159 Gln 183 Ser 210	Leu 300 Hid 110
13.	(+/-)-Leachianone G	-12.388	-9.593	-6.555	Leu 301, Leu 300, Ala 299, Cys 298, Trp 79, Trp 111, Tyr 48, Val 47, Trp 20, Trp 219, Pro 218, Phe 122	Ser 302 Hid 110	Leu 301 Leu 300 Hid 110
14.	5-Hydroxy-7-(3-methyl-2,3-epoxybutoxy)flavanone	-12.306	-10.289	-7.705	Leu 301, Leu 300, Ala 299, Cys 298, Val 297, Trp 219, Phe 122, Tyr 48, Val 47, Trp 79, Trp 111, Tyr 209, Trp 20	Ser 302 Hid 110 Ser 159 Asn 160 Gln 183	Leu 301
15.	Licoleafol	-12.296	-7.478	-7.011	Leu 301, Leu 300, Ala 299, Cys 298, Val 297, Trp 219, Phe 122, Tyr 48, Val 47, Trp 79, Trp 111, Tyr 209, Trp 20,Leu 124	Ser 302 Hid 110 Asn 160	Ser 302 Leu 301 Leu 300

**XP – Extra precision docking mode*
**SP – Standard precision docking mode*
**HTVS – High throughput virtual screening docking mode*

Table 3. Score hypothesis

Hypothesis ID	Survival Score	Site Score	Vector Score	Volume	Selectivity
AAARR_1	4.905968	0.909404	0.944806	0.758569	1.448091
AAARR_2	4.719167	0.839363	0.925984	0.685939	1.422783
AARR_1	4.73652	0.995995	0.977851	0.771576	1.146001
AAADR_3	4.470966	0.766008	0.888087	0.596471	1.375302
AAAR_1	4.51448	0.910466	0.976616	0.719978	1.062321
AAARR_3	4.294547	0.548372	0.936455	0.491911	1.47271
AAADR_2	4.482927	0.713844	0.823981	0.684051	1.415953
AARR_5	4.469604	0.859936	0.93843	0.689076	1.137065
AAADR_4	4.46516	0.641664	0.826461	0.682667	1.46927
AAADR_5	4.454217	0.741946	0.86983	0.602395	1.394949
AAAR_2	4.488486	0.914892	0.985656	0.717451	1.025389
AAADR_1	4.525006	0.659007	0.871871	0.674386	1.474644
AAADR_6	4.450901	0.780323	0.849019	0.696145	1.280316
AARR_3	4.593529	0.910107	0.954107	0.728008	1.156209
AAADR_7	4.328644	0.657107	0.853691	0.585581	1.387167
AARR_2	4.653074	0.908201	0.971368	0.743644	1.184763
AARR_4	4.504126	0.915481	0.931649	0.684828	1.12707
AARR_6	4.457571	0.892778	0.900315	0.659987	1.159393
AAAR_4	4.318837	0.834955	0.879186	0.691333	1.068265

Table 4. Distances between different sites of model AAARR_1 3RX2

Sl. No.	Site 1	Site 2	Distances (A^0)
1.	R15	A1	3.61
2.	R15	A2	6.11
3.	R15	R14	6.32
4.	R15	A4	8.27
5.	A1	A2	4.14
6.	A1	R14	2.76
7.	A1	A4	4.75
8.	A2	R14	3.71
9.	A2	A4	6.44
10.	A4	R14	2.78

Table 5. Angles between different sites of model AAARR_1 3RX2

Sl. No.	Site 1	Site 2	Site3	Angle (Å)
1.	R15	A1	R14	165.1
2.	R15	A2	R14	75.7
3.	R15	A1	A4	163.5
4.	R15	A2	A4	82.4
5.	R15	A1	A2	103.9
6.	R15	R14	A2	69.6
7.	R15	A4	A2	47.1
8.	R15	R14	A4	126.2
9.	R15	A2	A1	35.0
10.	R15	R14	A1	8.4
11.	R15	A4	A1	7.1
12.	R15	A4	R14	38.1
13.	A1	R15	A2	41.1
14.	A1	A2	R14	40.7
15.	A1	R14	A4	117.8
16.	A1	A4	R14	31.0
17.	A1	A4	A2	40.0
18.	A1	R15	A4	9.4
19.	A1	R14	A2	78.0
20.	A1	R15	R14	6.4
21.	A1	A2	A4	47.5
22.	A2	A1	R14	61.3
23.	A2	R14	A4	164.3
24.	A2	A1	A4	92.6
25.	A2	R15	A4	50.5
26.	A2	R15	R14	34.7
27.	A2	A4	R14	9.0
28.	R14	A2	A4	6.7
29.	R14	R15	A4	15.8
30.	R14	A1	A4	31.2

4. DISCUSSION

The selected flavones show good binding activity against aldose reductase enzymes. The first 15 compounds having good docking scores were chosen. The docking scores of the products against 3RX2 were in the range of -14.37 to -12.30 kcal/mol. Tanariflavanone D shows the highest XP docking score of -14.378 against 3RX2 (aldose reductase). The interaction studies showed that all the 15 compounds against 3RX2 showed hydrophobic interaction, polar interaction and hydrogen bonding. Tanariflavanone D interacted with the amino acids Leu 301, Ile 260, Leu 300, Trp 79,Tyr 209, Ala 299, Cys 298, Trp 111,Trp 219, Phe 122,Val 297, Trp 20, Val 47, Tyr 48 by hydrophobic interactions and with Ser 302, Hid 110, Ser 159, Asn 160, Gln 183 in polar interactions. All the flavone derivatives had hydroxy phenyl substitutions in the second

position. In contrast, an alkyl chain substitution at the C6 position showed to be effective for binding against the aldose reductase enzyme. Thus, hydroxyl phenyl substitutions in the C2 position are essential in the flavones derivatives for better binding affinity against the aldose reductase receptor proteins.

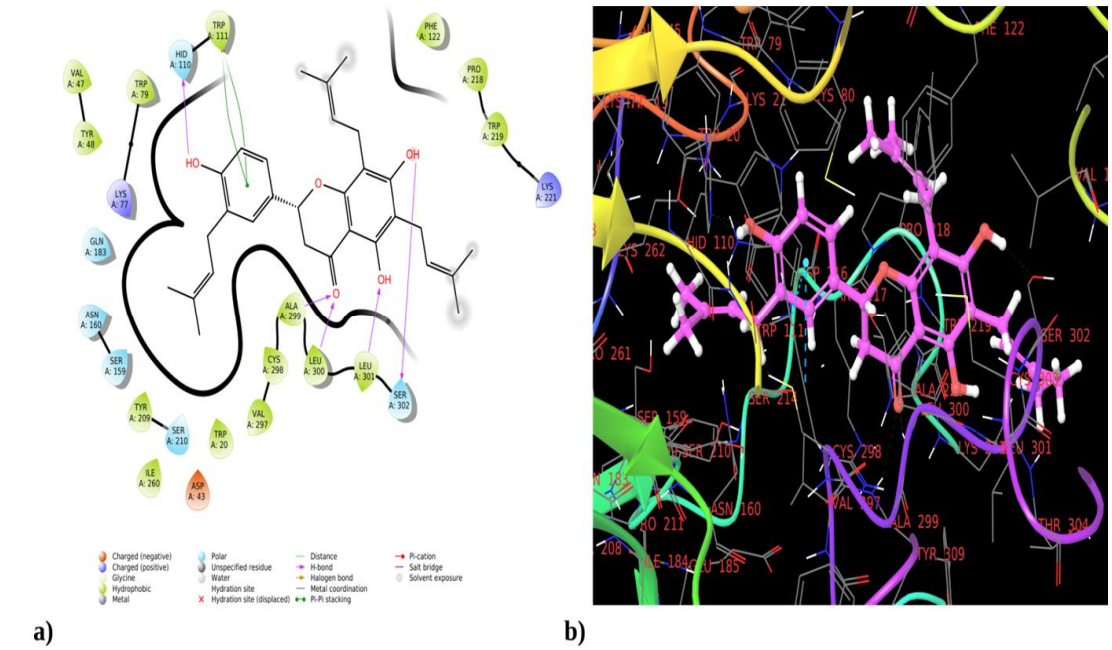


Fig. 1. (a) 2D and (b) 3D interactions of Tanariflavanone D

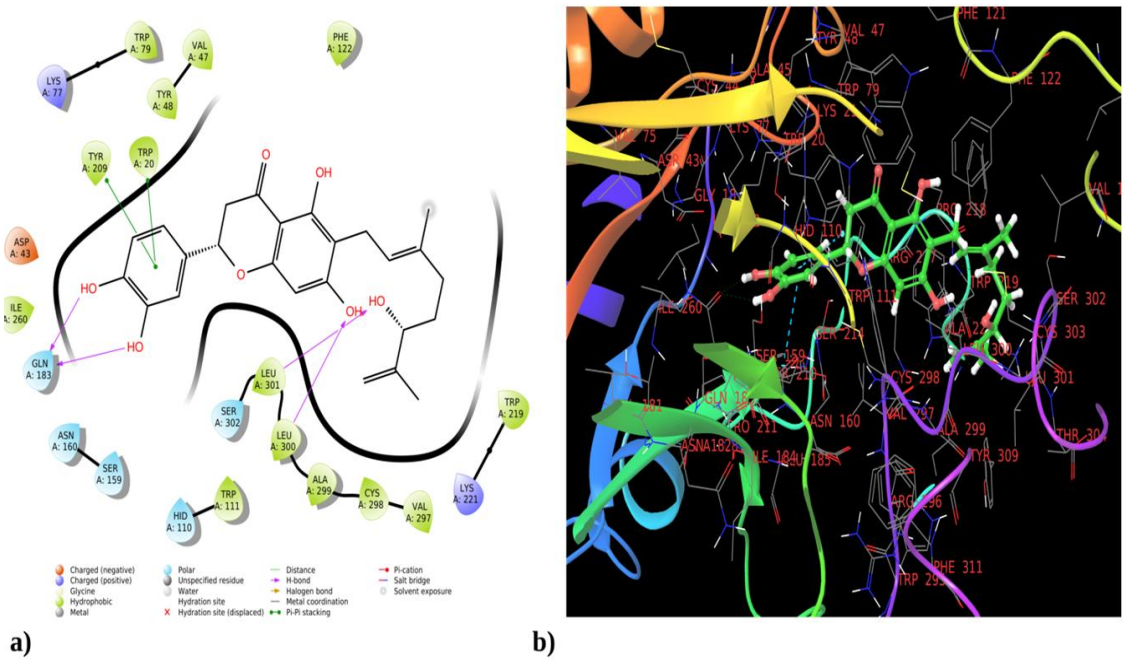


Fig. 2. (a) 2D and (b) 3D interactions of Amorilin

Table 6. Physicochemical and ADMET properties of ligands interacted with 3RX2

Sl. No.	Ligands	Physicochemical properties					ADMET properties	
		Molecular weight	PSA	Log P	H bond donor	H bond acceptor	QPPCaCo	Human oral absorption
1.	Tanariflavanone D	440.492	139.175	3.308	4.000	6.450	32.201	73.304
2.	Amorilin	476.611	90.586	6.491	2.000	4.000	358.829	100.00
3.	2',4',5,7-Tetrahydroxy-8-[(R)-2-isopropenyl-5-methyl-4-hexenyl]flavanone	424.493	109.8	4.151	3.000	4.750	168.246	91.089
4.	Flavanone 7-O-glucoside	402.400	136.720	0.472	4.000	12.000	78.280	63.600
5.	5,7-Dihydroxy-4'-methoxy-8-C-prenyl-3'-(3-hydroxy-3-methylbutyl)flavanone	440.535	101.746	5.255	2.000	4.750	224.002	86.823
6.	4',5,7-Trihydroxy-8-[(E)-3-methyl-4-hydroxy-2-butenyl]flavanone	336.324	118.781	2.172	3.000	5.700	53.771	70.636
7.	Gancaonin E	424.493	116.096	4.019	3.000	4.750	77.590	84.303
8.	(2R)-6-(4-O-Methyl-beta-D-glucopyranosyloxy)flavanone	416.427	120.954	1.215	3.000	12.000	263.522	77.387
9.	2S)-5,7,2',4'-Tetrahydroxy-8-prenyl-5'-(1,1-dimethylallyl)flavanone	424.493	112.74	3.857	3.000	4.750	113.939	86.342
10.	Kanzonol S	414.411	155.66	2.435	3.000	6.750	18.165	63.739
11.	3,4',5,5',7-Pentahydroxy-3'-methoxy-6-(3-methyl-2-butenyl) flavanone	402.400	144.682	1.908	4.000	7.200	40.391	66.869
12.	Glabrol	392.494	75.530	5.041	2.000	4.250	567.643	92.794
13.	(+/-)-Leachianone G	356.374	116.254	2.682	3.000	4.750	84.251	77.113
14.	5-Hydroxy-7-(3-methyl-2,3-epoxybutoxy)flavanone	340.375	75.877	3.559	0.000	5.250	1413.389	100.00
15.	Licoleafol	372.374	140.509	1.475	4.000	6.450	19.190	58.546

Table 7. PASS predictions for antidiabetic activities

Sl. No.	Ligands	Pa	Pi	Predicted Activity
1.	Tanariflavanone D	0.18	0.15	Antidiabetic symptomatic
2.	Amorilin	0.34	0.06	Antidiabetic
3.	2',4',5,7-Tetrahydroxy-8-[(R)-2-isopropenyl-5-methyl-4-hexenyl] flavanone	0.35	0.05	Antidiabetic
4.	Flavanone 7-O-glucoside	0.68	0.007	Antidiabetic
5.	5,7-Dihydroxy-4'-methoxy-8-C-prenyl-3'-(3-hydroxy-3-methylbutyl)flavanone	0.37	0.05	Antidiabetic
6.	4',5,7-Trihydroxy-8-[(E)-3-methyl-4-hydroxy-2-butenyl]flavanone	0.36	0.01	Antidiabetic symptomatic
7.	Gancaonin E	0.31	0.07	Antidiabetic
8.	(2R)-6-(4-O-Methyl-beta-D-glucopyranosyloxy) Flavanone	0.59	0.01	Antidiabetic
9.	2S)-5,7,2',4'-Tetrahydroxy-8-prenyl-5'-(1,1-dimethylallyl) flavanone	0.26	0.06	Antidiabetic symptomatic
10.	Kanzonol S	0.33	0.02	Antidiabetic symptomatic
11.	3,4',5,5',7-Pentahydroxy-3'-methoxy-6-(3-methyl-2-butenyl) flavanone	0.34	0.06	Antidiabetic
12.	Glabrol	0.33	0.06	Antidiabetic
13.	Leachianone G	0.36	0.05	Antidiabetic
14.	5-Hydroxy-7-(3-methyl-2,3epoxybutoxy)flavanone	0.20	0.12	Antidiabetic symptomatic
15.	Licoleafol	0.36	0.28	Antidiabetic

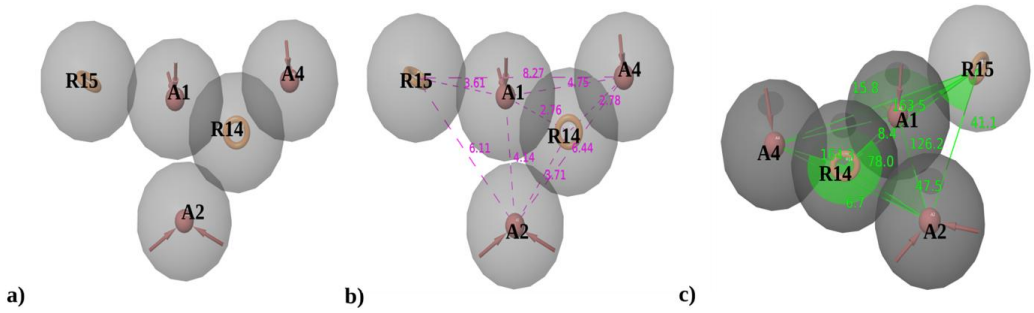


Fig. 3. (a,b,c) Distances of Pharmacophore Hypothesis AADRR_1

5. CONCLUSION

From the above, *in silico* studies proved to be a better methodology for predicting biological activity. In this study, 506 flavones were undergone virtual screening for the aldose reductase inhibitory action and found that 339 flavones interacted and on further screening fifteen ligands interacted well. Among them tanariflavanone D shows the highest XP docking score with aldose reductase. Thus, this study concludes that flavones possess antidiabetic action, which has to be further confirmed by *in vitro* and *in vivo* studies. The results can be utilised for the drug development process and aid to develop newer medicinally important moiety.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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