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In Silico evaluation of alpha glucosidase and alpha amylase inhibitory activity of chemical constituents from Psoralea corylifolia

Kona Latha Sai Mounika*

Department of Biotechnology, GITAM Institute of Science, GITAM University, Visakhapatnam, India

Abstract: The current study is about the evaluation of chemical constituents of Psoralea corylifolia for the inhibitory activity of alpha glucosidase and alpha amylase. In this perspective, 46 constituents of Psoralea corylifolia were selected. Acarbose, a known alpha glucosidase and alpha amylase inhibitor, was used as standard. For alpha glucosidase, docking results showed that all the selected constituents of Psoralea corylifolia had binding energy ranging between -190.438 Kcal/mol to -98.969 Kcal/mol and for alpha amylase, between -152.01 to -84.063 Kcal/mol. Bavachalcone, bisbakuchiol A, bisbakuchiol B, daucosterol psoralidin, astragalin, isopsoralenoside and isobavachalcone contributed better alpha glucosidase and alpha amylase inhibitory activity because of its structural parameters. Further studies are required to develop potent alpha glucosidase inhibitors for the treatment of diabetes.
Keywords: Docking studies; Binding energy; Molegro virtual docker; Psoralea corylifolia and diabetes mellitus.

1. Introduction:

Psoralea corylifolia L.,(Fabaceae) commonly known Babchi in Hindi and Bakuchi in Sanskrit is a well known annual herb which is widely used in traditional Chinese medicine and Ayurvedic medicine in India[1]. It is found throughout Indian plains, China, SriLanka, Burma and some southern states of United states [2,3]. The plant has been widely used in Ayurvedic and Chinese medicine system as a vasodilator, pigmentor, cytotoxic, antibacterial, antitumor, antihelmenthic and cardiac tonic[4-6]. The important bioactive components include coumarins, alkaloids, flavones, monoterpinoid phenols and chalcones.

Diabetes mellitus (DM) chronic metabolic disorder and is characterized by abnormal insulin secretion or insulin receptor or post receptor events affecting metabolism involving carbohydrates, proteins and fats in addition to damaging liver, kidney and β cells of pancreas[7].

The Insulin dependent diabetes mellitus (IDDM) is characterized by elevation of both fasting and post-prandial blood sugar levels and is observed in both adults and children. Chronic hyperglycemia during diabetes causes glycation of body proteins that in turn leads to secondary complications affecting eyes, kidneys, nerves and arteries[8]. These may be delayed, lessened or prevented by maintaining blood glucose values close to normal. For the treatment of IDDM, approaches for the control of hyperglycemia include insulin therapy, use of amylin analogues, inhibitors of intestinal alpha glucosidases like acarbose, miglitol and voglibose which delay

postprandial hyperglycemia are used. Moreover, these therapies only partially compensate for metabolic derangements seen in diabetics and do not necessarily correct the fundamental biochemical lesion [9].

2. Materials and Methods

2.1 Ligand dataset and its preparation

Ligand dataset comprised of 46 constituents of P.corylifolia and Acarbose (CID 41774) and their respective 2D structure (wherever available 3D) retrieved from NCBI PubChem in structure data format (SDF)[19]. The structures which were not available in PubChem were retrieved from respective articles as mentioned in Table. 1. The structures were drawn in Chem draw 2004 and were 3D optimized using Chem ultra 3D and were saved in .mol format. The alpha glucosidase protein complexed with Acarbose (PDB ID: 2QMJ) while the alpha amylase complexed with Acarviostatin (PDB ID: 3OLD) were chosen for targets.

2.2 Molecular Docking

Alpha glucosidase structure complexed with Acarbose (PDB ID: 2QMJ) as protein target using Molegro Virtual Docker[20] to study its interaction with constituents of P.corylifolia. Cavities were first predicted using "Detect cavities" module of Molegro with expanded vander waals radii to find accessible region. The maximum number of cavities was set to 5 with probe size of 1.20 Å. the minimum and maximum cavity volume was set to 10 Å and 10000 Å respectively, with a grid resolution of 0.80. This module utilizes simple grid-based cavity prediction dependent on molecular surface and/or Van der Waals radii to detect regions of accessibility. Using the "Protein Preparation" module the protein dataset was imported with its settings: atomic charges assignment, hybridization assignment and explicit hydrogen inclusion. Ligand dataset was introduced using the module "Prepare Molecules". Subsequently, for the docking process "Docking Wizard" module was used. "MolDock Score" scoring function was selected with the depiction of grid box (radius = 15 Å) centered to co-crystallized occupied cavity. The search algorithm was constrained to "MolDock Optimizer" with the following settings: population size of 50, maximum number of iterations to 2000 and cross-over rate of 0.90.

3. Results and Discussion

The constituents like Psoralen, isopsoralen, corylifolin, corylin and psoralidin have been isolated from the petroleum ether and chloroform extract of the whole plant [10]. A new isoflavone, Psoralenol[11], a monoterpene phenol, Bakuchiol [12], two novel dimeric monoterpenoids Bisbakuchiols A and B[13] have been isolated from the seeds of P.Corylifolia. The ethereal seed extract showed the presence of isoneobavachalcone[14] and Corylinal[15]. High-speed counter current chromatography showed the presence of constituents like Psoralen and isopsoralen[16]. Four flavonoids bavachin, isobavachin bavachinin and isobavachalcone were isolated from the seeds of P. corylifolia[17]. Sophoracoumestan A, neobavaisoflavone, daidzein and uracil, have been reported from the dried fruits of P. corylifolia[18].

Among the 46 constituents of P.corylifolia, Bavachalcone (Figure 1), Bisbakuchiol A(Figure 2a), Bisbakuchiol B, Daucosterol, Psoralidin, Isobavachalcone, Corylifol A, Corylifol C and Brosimacutin G showed more binding affinity than the standard, Acarbose (figure 3a) for alpha glucosidasde (Table 1). For alpha amylase, more binding affinity was showed by Bisbakuchiol A(Figure 2b), Bisbakuchiol B, Daucosterol, Astragalin and Isopsoralenoside than Acarbose (Figure 3b) (Table 1).

Bavachalcone showed hydrogen bonding with Gly 457 and Bavachalcone also had interactions with Cys 458, Ser 458, Val 455, Val 451 and Ser 456(Figure 4). Hence, Bavachalcone has more binding affinity and more inhibition towards alpha glucosidase. The schematic interaction diagram between N-terminal catalytic domain of maltase - glucoamylase was depicted in Figure 5.

Table 1. Table containing the binding affinities of 46 constituents of P.Corylifolia for alpha glucosidase with PDB ID- 2QMJ and for alpha amylase with PDB ID-3OLD

S N.	Name	PubChem ID or reference article	MolDock Score for PDB ID- 2QMJ (alpha glucosidase with acarbose)	MolDock Score for PDB ID- 3OLD (Alpha amylase with Acarviostatin)
1.	Bavachalcone	CID 5321765	-190.438	-137.25
2.	Bisbakuchiol A	13	-181.093	-152.071
3.	Bisbakuchiol B	13	-177.842	-144.293
4.	Daucosterol	CID 5742590	-170.85	-151.293
5.	Psoralidin	CID 5281806	-167.531	-126.735
6.	Isobavachalcone	CID 5281255	-166.162	-120.944
7.	Corylifol C	21	-165.476	-132.806
8.	Corylifol A	21	-165.471	-141.465
9.	Brosimacutin G	CID 11325738	-162.686	-135.886
10.	Acarbose	CID 41774	**-158.675**	**-142.064**
11.	Isobavachin	CID 11609510	-156.734	-117.192
12.	Isopsoralenoside	21	-155.207	-150.045
13.	Isoneobavachalcone	CID 5318608	-153.64	-114.396
14.	Astragalin	CID 5282102	-152.779	-150.716
15.	Neobavachalcone	CID 5320052	-151.453	-115.312
16.	Bavachromene	CID 5321800	-150.822	-123.945
17.	Bakuchalcone	CID 6476086	-148.799	-126.049
18.	Bavachromanol	CID 5321790	-146.729	-122.755
19.	Stigmasterol	CID 5280794	-145.153	-134.128
20.	Bavachinin	CID 122835	-139.782	-131.824
21.	Bavachin	CID 5321775	-139.713	-124.023
22.	8-prenyldiadzein	21	-136.513	-111.58
23.	sophoracoumestan A	CID 14630492	-134.626	-119.519
24.	Corylinal	CID 44257227	-134.152	-112.49
25.	Bakuchiol	CID 5468522	-133.284	-107.948
26.	Corylifonol	22	-130.203	-105.203
27.	(+)-Bakuchiol	CID 5321439	-129.921	-106.581
28.	Corylidin	CID 5316096	-127.958	-112.897
29.	Psoracorylifol B	21	-127.522	-93.9434
30.	4-methoxy flavone	23	-126.031	-98.8406
31.	Isocorynifolol	21	-125.251	-95.5546
32.	Triacontane	CID 12535	-123.764	-133.423
33.	Corylin	CID 5316097	-122.887	-111.179
34.	Psoralenoside	21	-120.793	-129.079
35.	Biochanin A	CID 5280373	-120.153	-110.904
36.	Psoralenol	CID 5320772	-118.022	-103.532
37.	Psoracorylifol C	21	-116.839	-94.9724
38.	Genistein	CID 5280961	-116.124	-103.46
39.	Daidzein	CID 5281708	-115.575	-103.663
40.	Psoralen	CID 6199	-114.445	-84.7463
41.	Psoracorylifol A	21	-112.294	-119.559
42.	Erythrinin A	21	-110.042	-96.0089
43.	Corylifolin	CID 5470819	-107.987	-87.9668
44.	Isopsoralen	CID 10658	-105.569	-87.8547
45.	8-methoxy psoralen	CID 4114	-103.902	-92.719
46.	β- caryophyllene	CID 5281515	-99.1328	-84.0603
47.	Bakuchicin	CID 3083848	-98.969	-89.478

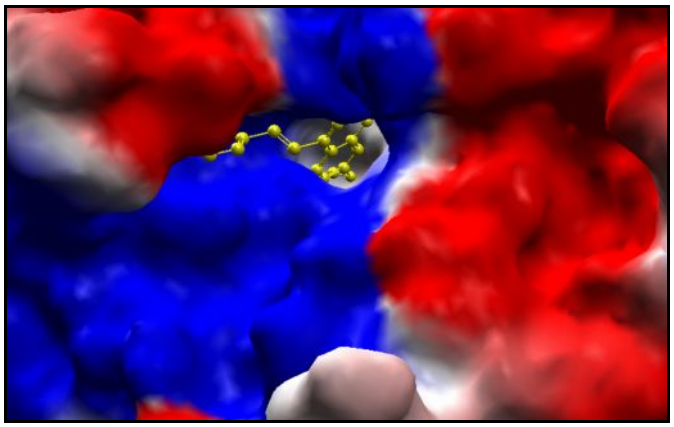


Figure 1: Docking position of Bavachalcone with alpha glucosidase

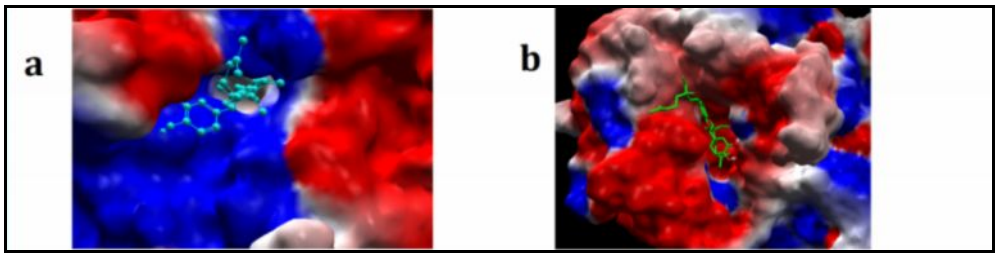


Figure 2: Docking position of a) Bisbakuchiol A with alpha glucosidase b) Bisbakuchiol A with alpha amylase

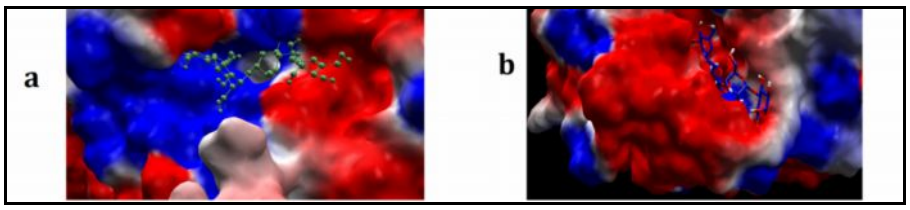


Figure 3: Docking position of a) Acarbose with alpha glucosidase b) Acarbose with alpha amylase

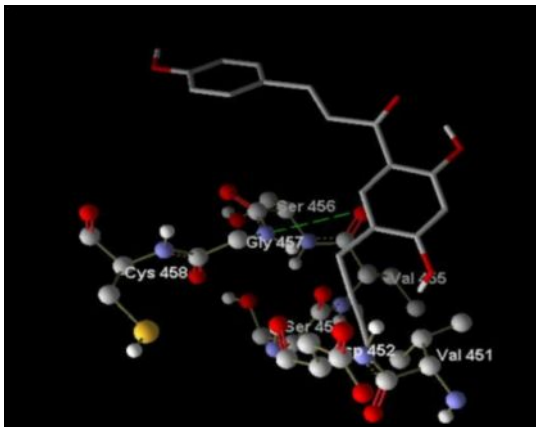


Figure 4: Bavachalcone showing hydrogen bond interactions

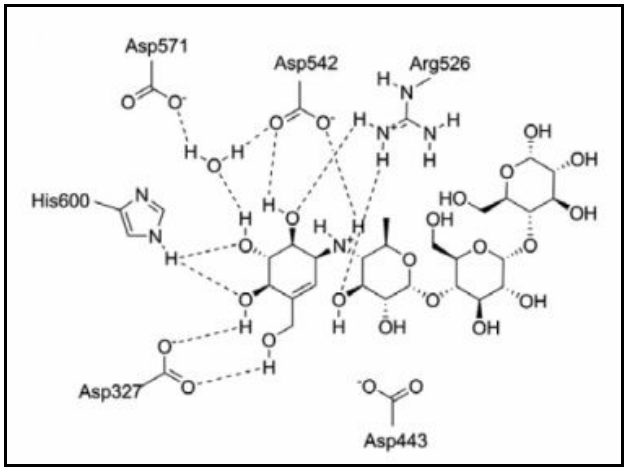
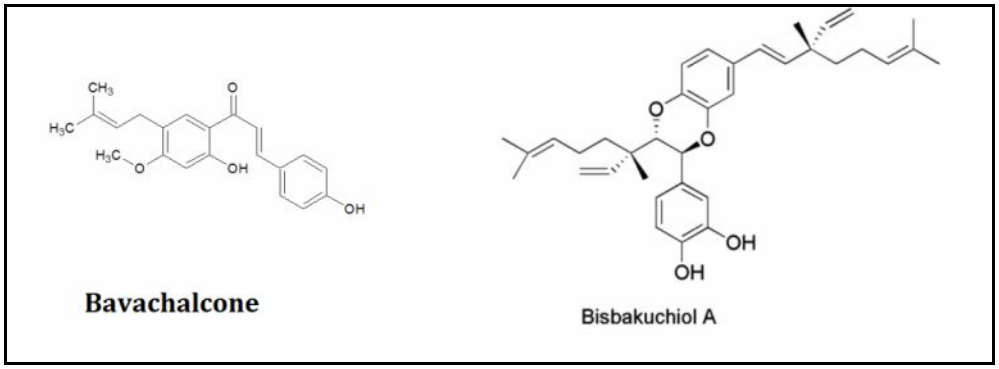
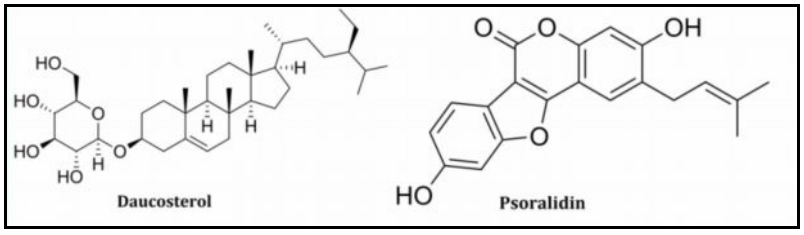
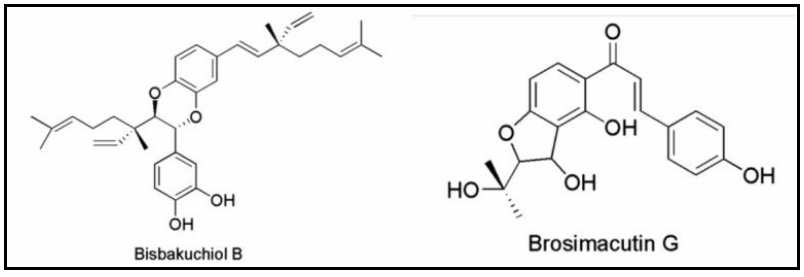
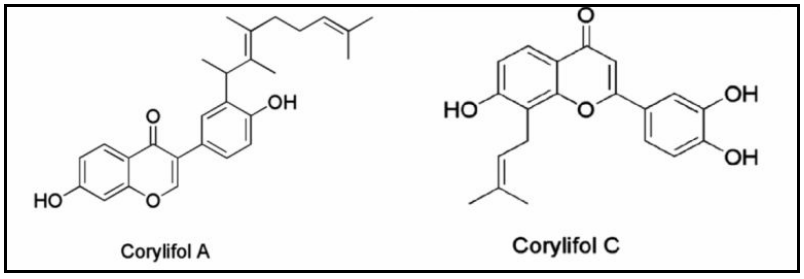


Figure 5: Schematic interaction diagram between Acarbose and N-terminal catalytic domain of maltase-glucoamylase









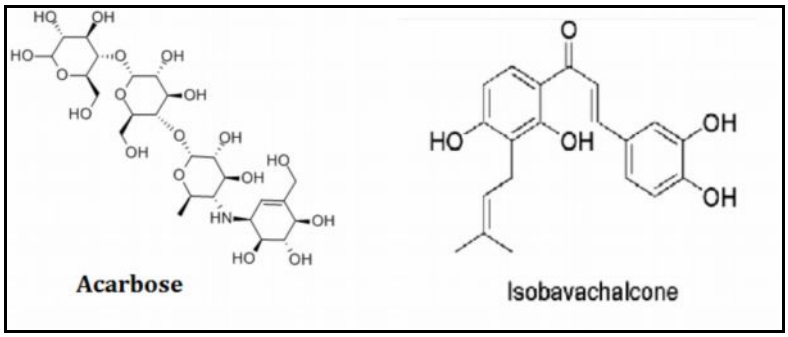


Figure 6: Structures of the constituents which showed more binding affinity towards alpha glucosidase

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