In-Silico Analysis of Natural Products that Modulates Enzymes of Diabetic Target

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Specifications Table

Subject	**Pharmaceutical Science**
Specific subject area	Interdisciplinary field includes organic chemistry, biochemistry, and biology. Drug design and discovery from plant sources.
Type of data	Tables Figures
How data were acquired	MOE 2009 and GOLD V 4.51
Data format	Raw and Analysed
Parameters for data collection	Gold Fitness score, energetic values and interactions of protein with the ligand.
Description of data collection	The Proteins were collected from RCSB protein bank. The secondary metabolites structures were obtained from Pubchem online database. The docking was done using GOLD software.
Data source location	https://www.rcsb.org/ https://pubchem.ncbi.nlm.nih.gov/
Data accessibility	PDB files of the chosen enzyme targets are publically available at https://www.rcsb.org/ Tables and Figures of the docking are accessible in the article.

Value of the Data

- The screening procedure enable the researchers to rapidly identify active natural compounds which can modulate a particular biochemical pathway.
- The screening results help to study the interaction/role of active metabolites in a particular biochemical process at cellular level and provide preliminary ideas for drug design development
- By using this *in-silico* docking data, novel synthetic analogues with improved bioactivity and minimized side effects can be developed against these targets and research time can be minimized considerably.
- We select these 23 metabolites because these are abundant in nature and well explored. Among these metabolites, the compounds which show best affinity for various targets are shortlisted.
- The data is also useful for research scholars who does not have the sufficient software and hardware requirements which not affordable by them.
- Research scholars, researchers in pharmaceutical chemistry, Medicinal Chemistry, Drug Design Industry can be benefit from the data.

Table 1S. List of Targets showing the PDB ID, resolution and description of the proteins selected for docking with complexed inhibitor.

S.No	PDB ID	Resolution (Å)	Description
1	1LPB	2.46	Structure of pancreatic lipase -colipase complex [1]
2	1US0	0.66	Human Aldose Reductase in complex with NADP+ and the inhibitor IDD594 [2]
3	5U3A	0.95	The crystal structure of Human pancreatic alpha amylase [3]
4	5NN8	2.45	Crystal structure of Human lysosomal acid-alpa-glusosidase complex with Acarbose [4]

Table 2S. Inhibition of lipase by secondary metabolites

Natural Source	Secondary metabolite	IC_{50} (μM)	Reference
Penicillium purpurogenum IMM 003	Purpurolide F	1.22	[1]
	Purpurolide D	6.5	
	Purpurolide E	7.88	
Xestospongia testudinaria (sponges)	Methyl xestospongic ester	3.11	[2]
Caralluma hexagona Lavranos(aerial part)	12,20-di-O-benzoyl-3β,8β,12β,14β,20-pentahydroxy-(20R)-pregn-5-ene-3-O-β-D-glucopyranosyl-(1→4)β-D-digitalosiden	23.59	[3]
Polygonum aviculare L. whole	Quercetin (competitive inhibition)	53.05	[4]
	Kaempferol (competitive inhibition)	79.38	
	Myricitrin (non-competitive or mixed)	92.85	
	Quercitrin (non-competitive or mixed)	100.56	
	Avicularin (non-competitive or mixed)	141.84	
Trigonella foenum-graecum (seeds)	Schaftoside	230.29	[5]
	Vicenin-1	336.7	
	Isoschaftoside	584.59	

Current medication: Sorbinil, Fidarestat, Alrestatin, Epalrestat, Tolrestat, Zenarestat.
Note: Some IC_{50} values are adjusted in terms of molarity to make the comparison convenient.

Table 3S. Inhibition of aldose reductase by secondary metabolites

Enzyme	*Natural Source*	*Secondary metabolite*	**IC_{50} (μM)**	*Reference*
Rat lens aldose reductase	*Cuminum cyminum* (seeds)	Cuminaldehyde	5.37	[6]
Rat lens aldose reductase	*Melastoma sanguineum*	2,″4″-O-diacetylquercitrin	0.077	[7]
Rat lens aldose reductase	*Artemisia montana* (whole plant)	Luteolin	0.19	[8]
		Hyperoside	1.85	
		Chlorogenic acid	4.36	
		3,5-Di-O-caffeoylquinic acid	5.37	
Rat lens aldose reductase (RLAR)	*Xanthium strumarium* (fruit)	Methyl-3,5-di-O-Caffeoylquinate	0.3	[9]
Human recombinant aldose reductase(rhAR)			0.67	
Rat lens aldose reductase Human recombinant aldose reductase	*Sophora flavescens* (roots)	Desmethylanhydroicaritin	0.45	[10]
			0.95	
		8-lavandulylkaempferol	0.79	
Recombinant human aldose reductase	*Rhus verniciflua*	Butein	3.8 0.5	[11]
Rat lens aldose reductase	*Smilax china L.* (stems)	Quercitrin	0.56	[12]
		3-O-Caffeoylquinic acid	0.6	
		Isoscutellarein-8-O-rhamnoside	17	
		4-O-Caffeoylquinic acid	20.1	
Rat lens aldose reductase	*Belamcanda chinensis* (rhizomes)	Tectorigenin	1.08	[13]
		Tectoridin	1.12	
Rat lens aldose reductase	*Abeliophyllum distichum* (leaves)	Acteoside	1.39	[14]
Rat lens aldose reductase	*Chrysanthemum indicum*	(2R)-eriodictyol 7-O-β -D-glucopyranosiduronic acids	1.5	[15]
		(2S)-eriodictyol 7-O-β -D-glucopyranosiduronic acids	2.1	
Rat lens aldose	*Colocasia esculenta*	Orientin	1.65	[16]

reductase		Isoorientin	1.92	
Rat lens aldose reductase	*Artemisia princeps* (Aerial part)	1,3,5-tri-O-caffeoylquinic acid	1.78	[17]
		3,4,5-tri-O-caffeoylqunic acid	1.95	
		3,4-di-O-caffeoylquinic acid	2.4	
Rat lens aldose reductase	*Glycyrrhiza uralensis* (roots)	Semilicoisoflavone B	1.8 10.6	[18]
Bovine lens aldose reductase	*Ocimum basilicum* (Aerial)	7-(3-hydroxypropyl)-3-methyl-8-β-O-d-glucoside-2H-chromen-2-one	2.095	[19]
Rat lens aldose reductase	*Maackia amurensis* (bark)	Chlorogenic acid	4.2	[20]
Rat lens aldose reductase	*Zingiber zerumbet*	Afzelin	5.54	[21]
Rat lens aldose reductase	*Cuminum cyminum* (seeds)	Cuminaldehyde	5.9	[6]
Recombinant human aldose reductase	*Nephelium lappaceum*	Geraniin	7.34	[22]
Rat lens aldose reductase	*Cassia tora* (seeds)	Chryso-obtusin-2-O-β -D-glucoside	8.8	[23]
		Aurantio-obtusin	13.6	
		Emodin	15.9	
Recombinant human aldose reductase	*Paulownia coreana*	Isocampneoside II	9.72	[24]
Rat lens aldose reductase	*Paeonia suffruticosa*	Palbinone	11.4	[25]
		30-norhederagenin	28.8	
Bovine lens aldose reductase	*Ganoderma lucidum* (fruiting body)	Lucidumol A	19.1	[26]

Current medication: Sorbinil, Fidarestat, Alrestatin, Epalrestat, Tolrestat, Zenarestat.
Note: Some IC_{50} values are adjusted in terms of molarity to make the comparison convenient.

Table 4S: Inhibition of α-amylase by secondary metabolites

Natural Source	Secondary metabolite	IC_{50} value (μM)	Reference
Ficus deltoidea	Vitexin	0.046	[27]
	Isovitexin	0.138	
Solenostemma argel	Kaempferol-3-O-neohesperidoside	0.08	[28]
Olea europaea	Oleanolic acid	0.219	[29]
Eruca vesicaria	Erucin	0.315	[30]
Ruellia tuberosa	Betulin	0.316	[31]
Citrus paradise	Pectin	2.11	[32]
Abelmoschus esculentus	Proanthocyanidins	3.88	[33]
Phyllanthus amarus	Oleanolic acid+ Ursolic acid	4.4	[34]
Vitex glabrata	ß amyrin	32.33	[35]
Rheum turkestanicum	Daucosterol	46.4	[36]
Himatanthus drasticus	Plumieride	71.69	[37]
Vaccinium arctostaphylos (Ericaceae)	Malvidin-3-O-beta-glucoside	329	[38]
Setosphaeria rostrata	Rostratazine B	578	[39]
Psidium guajava Linn. (Myrtaceae)	Myricetin	4300	[40]
	Kaempferol	5300	

Current medication: Acarbose, biguanides, miglitol, voglibose, and 1-deoxynojirimycin.
Note: Some IC_{50} values are adjusted in terms of molarity to make the comparison convenient.

Table 5S: Inhibition of α-glucosidase by secondary metabolites

Natural Source	Secondary metabolite	IC_{50} (μM)	Reference
Salacia hainanensis Chun	2,3-seco-lup-20(29)en-2,3-dioic acid	0.01	[41]
	Lup-20(29)-en-3,21-dione	0.07	
	30-hydroxy-friedelan-3one	0.08	
	3α-hydroxy-lup-20(29)-en-2-one	0.09	
Salvia miltiorrhiza Bge	Isosalvianolic acid C methyl ester	111.9 $x10^{-3}$	[42]
	Dihydrotanshinone	320.1 $x10^{-3}$	
	Isocryptotanshinone	452.1 $x10^{-3}$	
Polygonum hyrcanicum	N-trans-Caffeoyl-tyramine	0.3	[43]
	Myricitrin	0.6	
	(-) Gallocatechin	1	
Harungana madagascariensis	Kenganthranols B	6.3	[44]
	Kenganthranols C	21.9	
Punica granatum	Punicatannins A	7.15 ± 0.27	[45]

	Punicatannins B	12.39 ± 0.05	
Quercus gilva	Tiliroside	28.36	[46]
*Euonymus alatus (*Twig*)*	Betulinic acid	83.6	[47]
	Hederagenin	85.3	
	Naringenin	96.8	
	Kaempferol	107.8	
Dryopteris cycadina	3, 5, 7-trihydroxy-2-(*p*-tolyl) chorman-4-one	133	[48]
	β-Sitosterol	143	
	5,7,4/-Trihydroxyflavon-3-glucopyranoid	146	
Brickellia cavanillesii	Calein C	280	[49]
	6-hydroxyacetyl-5-hydroxy-2,2-dimethyl-2H-chromene	420	
Aspergillus aculeatus	Aspergillusol A	465	[50]
Uncaria cordata	Querecetin	1840.82	[51]
	2,4-Hydroxybenzoic acid	3652.16	
Ligusticum porter	3-(Z)-butylidenephthalide	2350	[52]

Current medication: Acarbose, miglitol, Voglibose, genistein, quercitrin, and 1-deoxynojirinmycin
Note: Some IC_{50} values are adjusted in terms of molarity to make the comparison convenient

Table 6S. Prediction of toxicity of secondary metabolites inhibiting metabolic enzymes using ProTox-II

Compound	LD50mg/Kg	Toxicity class	Active target	Probability
(-) gallocatechin	10000	6	-	-
(2R)-eriodictyol 7-O-β -D-glucopyranosiduronic acids	2300	5	Immunotoxicity	0.84
(2S)-eriodictyol 7-O-β -D-glucopyranosiduronic acids	2300	5	Immunotoxicity	0.84
1,3,5-Tricaffeoylquinic acid	5000	5	Immunotoxicity	0.97
1,7-bis(4-hydroxyphenyl)-3,5-diol	1600	4	-	-
2-(4-hydroxyphenyl)-ethyl-3,4,5-trihydroxybenzoate	1700	4	Estrogen Receptor Ligand Binding Domain	0.7
2,″4″-O-diacetylquercitrin	5000	5	Immunotoxicity	0.98
2,3-seco-lup-20(29)en-2,3-dioic acid	2500	5	-	-
2,4-hydroxybenzoic acid	2000	4	Carcinogenicity	0.72
3-oxolupenal	5000	5	-	-
3,4,5-tri-O-caffeoylqunic acid	5000	5	Immunotoxicity	0.98
3,4-di-O-caffeoylquinic acid	5000	5	Immunotoxicity	0.99
3,5,7-trihydroxy-2-(p-yolyl)chroman-4-one	2000	4	Aryl hydrocarbon Receptor	0.98
			Aromatase	0.79
			Estrogen Receptor Alpha	0.95
			Estrogen Receptor Ligand Binding Domain	0.88
			Mitochondrial Membrane Potential	0.98
3α-hydroxy-lup-20(29)-en-2-one	2500	5	-	-
3,5-Di-O-caffeoylquinic acid	5000	5	Immunotoxicity	0.99
3-(z)-butylidenepthalide	1850	4	-	-
4-O-Caffeoylquinic acid	5000	5	Immunotoxicity	0.99
5,7,4-trihydroxyflavon-3-glucopyranoid	5000	5	Immunotoxicity	0.98
6-gingerol	250	3	Immunotoxicity	0.96
6-hydroxyaceyl-5-2,2-dimethyl-2H-chromene	500	4	Immunotoxicity	0.9
12,20-di-O-benzoyl-3β,8β,12β,14β,20-pentahydroxy-(20R)-pregn-5-ene-3-O-β-D-glucopyranosyl-(1→4)β-D-digitaloside	650	4	Immunotoxicity	0.99
(20R)-pregn-5-ene-3-O-β-D-glucopyranosyl-(1→4)β-D-digitaloside				
30-hydroxy-friedelan-3-one	3265	5	Immunotoxicity	0.84
30-N0rhederagenin	2000	4	Immunotoxicity	0.72
Acarbose (commercial drugs for diabetes)	24000	6	Immunotoxicity	0.9
Acteoside	5000	5	Immunotoxicity	0.99
Afzelin	5000	5	Immunotoxicity	0.92
Aspergillusol A	5000	5	-	-

Aurantio-obtusin	5000	5	Immunotoxicity	0.87
			Mitochondrial Membrane Potential (MMP)	0.85
Avicularin	5000	5	-	-
Azadiradione	600	4	Immunotoxicity	0.85
B2-3'-O-gallate	1000	4	Immunotoxicity	0.98
B- amyrin	7000	6	Immunotoxicity	0.93
β-sitosterol	890	4	Immunotoxicity	0.99
Betulin	2000	4	-	-
Butein	1000	4	Immunotoxicity	0.95
			Aryl hydrocarbon Receptor(ArH)	0.72 0.96
			Estrogen Receptor Alpha (ER)	0.91 0.97
			Estrogen Receptor Ligand Binding Domain	
			Mitochondrial Membrane potential	
Calein C	7	2	Immunotoxicity	0.99
Chlorogenic acid	5000	5	Immunotoxicity	0.99
chryso-obtusin-2-O-β -D-glucoside	3000	5	Immunotoxicity	0.99
Cuminaldehyde	1320	4	-	-
Daucosterol	8000	6	Immunotoxicity	0.99
Desmethylanhydroicaritin	3919	5	Mitochondrial Membranz Potential (MMP)	0.77
Dihydrotanshinone	260	3	Immunotoxicity	0.98
Emodin	5000	5	Mutagenicity	0.93
			Aryl hydrocarbon Receptor	1
			Estrogen Receptor Alpha	1
			Estrogen Receptor Ligand Binding Domain	1
			Mitochondrial Membrane Potential	0.99
			Phosphoprotein (Tumor Supressor) p53	1
Epalrestat (Commercial drugs for aldol reductase)	5	2	ATPase family AAA domain-containing protein 5	0.98
Erucin	39800	6	No	-
Ganomycin I	2000	4	No	-
Gedunin	2744	3	Immunotoxicity	0.99
Geraniin	122	3	Mutagenicity	0.98
Hederagenin	2000	4	-	-
Hyperoside	5000	5	-	-
Isocampneoside II	5000	5	Immunotoxicity	0.99

Isocryptotanshinone	2000	4	Immunotoxicity	0.89
Isosalvianolic acid C methyl ester	5000	5	Immunotoxicity	0.99
Isoschaftoside	536	4	-	-
Isoscutellarein-8-O-rhamnoside	5000	5	Immunotoxicity	0.86
Isovitexin	159	3	-	-
Kaempferol	3919	5	Aryl hydrocarbon receptor	1
			Aromatase	0.96
			Estrogen Receptor Alpha (ER)	1
			Estrogen Receptor Ligand Binding Domain	0.95
			Mitochondrial Membrane Potential	1
kaempferol-3-O-neohesperidoside	5000	5	Immunotoxicity	0.98
katononic acid	5000	5	-	-
kenganthranols B	5000	5	Immunotoxicity	0.97
			Mitochondrial Membrane Potential	0.8
kenganthranols C	1340	4	Immunotoxicity	0.96
Lucidumol A	1860	4	Carcinogenicity	0.72
lup-20(29)-en-3,21-dione	5000	5	-	-
Lycopene	5000	5	Androgen receptor ligand binding	1
			Estrogen receptor	1
			Alpha Estrogen receptor ligand binding domain	1
Malvidin-3-O-beta-glucoside	5000	5	Immunotoxicity	0.98
Melacolin	600	4	Aryl hydrocarbon Immunotoxicity	0.87
			Mitochondrial Membrane Potential	0.79
Methyl xestospongic ester	338	4	-	-
methyl-3,5-di-O-caffeoylquinate	5000	5	Immunotoxicity	0.99
Myricetin	159	3	Aryl hydrocarbon Receptor (AhR)	0.91
			Estrogen Receptor Alpha (ER)	0.87
			Estrogen Receptor Ligand Binding Domain	0.95,
			Mitochondrial Membrane Potential (MMP)	1
Myricitrin	159	3	Immunotoxicity	0.95
			Mitochondrial Membrane Potential	0.76
Naringenin	2000	4	Estrogen Receptor Alpha	0.74
			Mitochondrial	0.74

			Membrane Potential	
N-trans-caffeoyl-tyramine	500	4	-	-
Oleanolic acid	159	4	Immunotoxicity	0.79
			Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	0.7
			Heat shock factor response element (HSE)	0.7
Orientin	5000	5	-	-
Orlistat (commercial drugs for lipase)	1300	4	Hepatotoxicity	0.7
Papyriflavonol A	5000	5	Immunotoxicity	0.92
			Mitochondrial Membrane Potential	0.73
Palbinone	4000		Immunotoxicity	0.95
			Androgen receptor (AR)	0.75
Pectin	10000	6	-	-
Plumieride	2000	4	Immunotoxicity	0.93
Proanthocyanidins	2500	5	Immunotoxicity	0.98
punicatannins A	419	4	Immunotoxicity	0.99
purpurolide D	3220	5	-	-
purpurolide E	3220	5	-	-
purpurolide F	3220	5	-	-
Quercetin	159	3	Aryl hydrocarbon Receptor (AhR)	0.91
			Estrogen Receptor Alpha (ER)	0.87
			Estrogen Receptor Ligand Binding Domain	0.95
			Mitochondrial Membrane Potential	1
Quercitrin	5000	5	Immunotoxicity	0.97
			Immunotoxicity	0.97
Rosamarinate acid	5000	5	Immunotoxicity	0.93
Rostratazine B	3549	5	-	-
Schaftoside	2000	4	-	-
Semilicoisoflavone B	3850	5	-	-
Sinigrin	15	2	-	-
Tectoridin	5000	5	Immunotoxicity	0.95
Tectorigenin	2500	5	Immunotoxicity	0.71
			Aryl hydrocarbon Receptor (AhR)	0.97
			Estrogen Receptor Alpha (ER)	0.88
			Estrogen Receptor Ligand Binding	0.89

			Domain Mitochondrial Membrane Potential (MMP)	0.92
Tiliroside	5000	5	Immunotoxicity	0.97
Ursolic acid	2000	4	Immunotoxicity	0.95
			Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	0.7
			Heat shock factor response element (HSE)	0.7
Vicenin-1	536	4	-	-
Vitexin	1213	4	-	-

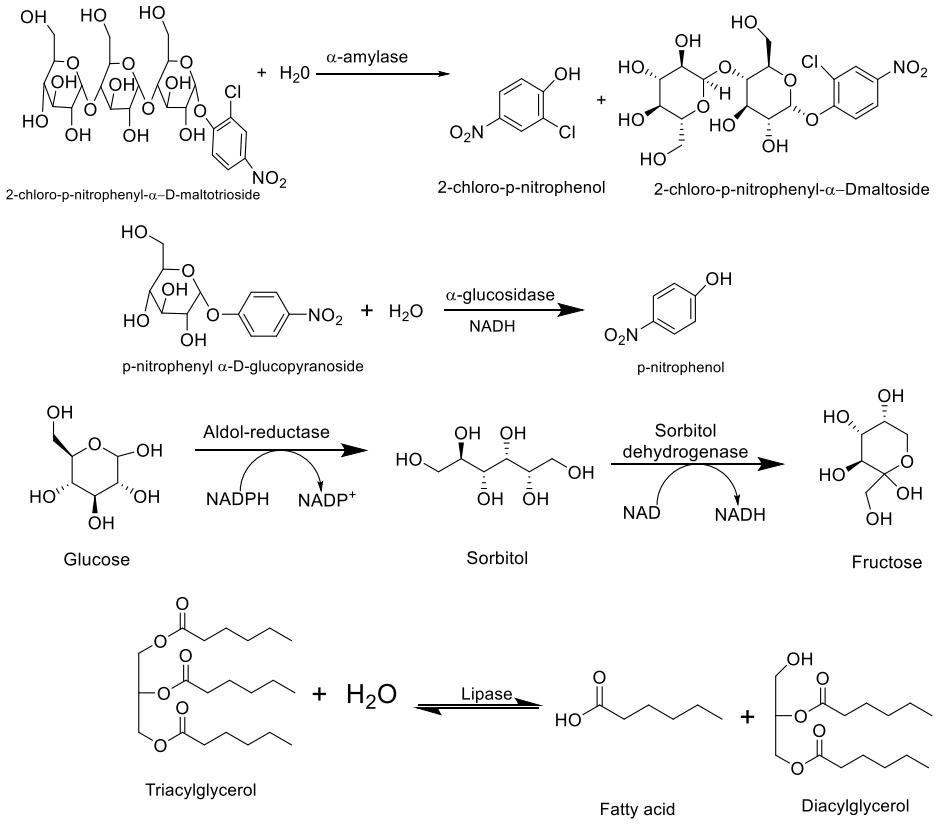

Figure 1S. Enzymatic reactions catalysed by α-amylase, α-glucosidase, aldose reductase and lipase.

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