IN-SILICO ANTIDIABETIC ACTION OF PHYTOCOMPONENTS FROM SIDDHA FORMULATION MARUTHAMPATTAI KUDINEER (MPK) AGAINST TARGET ENZYME ALPHA-GLUCOSIDASE

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Abstract

In recent days, herbal medicines and its bioactive compounds have gained global attention owing to its lesser side effects, lower cost and easy availability. Diabetes mellitus is a chronic metabolic disorder with multi-factorial complications affecting the quality of life. Though there are numerous medications on the market for the treatment of diabetes, they are not free from its side effects, drug dependency and poses high economic burden.The focus of this research is to conduct an in-silico computational analysis of phytochemicals in the traditional Siddha formulation *Maruthampattai Kudineer* (MPK), which is extensively used to treat diabetes. AutoDockTools were used to prepare and optimize the ligand structures. All of the compounds were docked using Autodock Vina. The formation of a hydrogen bond between phytocomponents and the target's core amino acids (Asp568, Tyr709, Glu771, Asp392, and Arg428) will inhibit the action of the target protein enzyme alpha-glucosidase (PDB ID:4J5T), which is involved in the breakdown of starch to release sugar moieties that induce blood glucose. As a result, phytocomponents that inhibit the target enzyme alpha-glucosidase could be used as a possible targets for diabetes management.The bio-active compounds found in the Siddha formulation MPK have considerable binding to the target alpha-glucosidase (PDB ID: 4J5T), according to the results of the computational research.

Keywords: Madhumegam, Diabetic neuropathy, Anti-oxidants, Polyuria, Type 2 Diabetes, Indian Traditional Medicine, Neerizhivu.

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1. INTRODUCTION

Diabetes mellitus (DM) has afflicted people of all ages without regard for their age [1]. The International Diabetes Federation estimates that 537 million individuals would have diabetes in 2021, with that figure expected to increase to 783 million by 2045[2]. Type 1(Insulin-dependent diabetes) and type 2 (Non-insulin dependent diabetes) are the two most common varieties of diabetes. From a long-term perspective, the diabetic population is proned to cardiovascular and renal diseases, retinopathy, neuropathy, and decreased blood flow. It is a well-established truth that controlling diabetes is a complicated and challenging endeavor and as a result, over the last several decades, the development of various newer anti-diabetic medications has developed to combat this fast-emerging disorder. However, most of these adverse effects were related to central nervous system such as tingling sensation of hands and feet, dizziness, drowsiness and symptoms of hypoglycemia.[3]
Siddha medicines are used to treat illnesses and disorders because they have fewer adverse effects, and are less expensive. Several bioactive components were extracted from traditional Siddha preparation MPK and used in the screening process. We selected 18 phyto-compounds from MPK, a poly-herbal formulation indicated in Siddha medicine for the control of diabetes, in our investigation. As a result, the current work analyzes 18 phytocompounds from MPK against the alpha-glucosidase enzyme using structure-based in silico molecular docking to discover potent anti-diabetic bioactive molecules.

Maruthampattai Kudineer is a traditional Siddha formulation for *Madhumegam* (Diabetes mellitus), as stated in the Siddha book Agathiyar 1200. There are eleven distinct constituents in this polyherbal medicine, including *Maruthampattai, Naaval, Karuvellampattai, Athipattai, Avaraithol, Kadalalinjilpattai, Thetrankottai. Thandrikkaithol, Kalipakku, Kadukkai thol, and Nelli vatral.* These eleven components have long been utilized in Siddha medicine to treat fatty liver, liver disorders, diabetes, and diabetic complications.

Alpha -glucosidase
Alpha-glucosidase, a brush border enzyme that hydrolyzes starch and disaccharides to release glucose for absorption into the enterocyte.[4] In conventional therapies, alpha-glucosidase inhibitors (AGIs; acarbose, miglitol, voglibose) are widely used in the treatment of patients with type 2 diabetes. [5] Alpha-glucosidase inhibitors which inhibit the digestion of carbohydrates are used to establish greater glycemic control over hyperglycemia in diabetes mellitus type 2, particularly in postprandial hyperglycemia [6]. However, several unexpected adverse effects such as flatulence, diarrhea, and stomach pain have been reported in their clinical use.[7] In consideration of this, several efforts have been done to develop novel alpha-glucosidase inhibitors from a wide range of sources, including natural products and chemically synthesized molecules [7].

In ethnomedicine, over 1200 plant plants have been described to treat diabetes, offering them a rich and hopeful source for the invention of novel anti-diabetic molecules [4]. Many of the isolated herbal extracts have a potent alpha-glucosidase inhibitory activity such as Alkaloids, stilbenoids (polyphenol), triterpene, acids (chlorogenic acid, betulinic acid, syringic acid, vanillic acid, bartogenic acid, oleanolic acid, dehydrotrametenolic acid, corosolic acid, ellagic acid, ursolic acid, gallic acid), phytosterol, myoinositol, flavonoids, Flavonolignans, anthraquinones, anthrones, and xanthones, Feruloylglucosides, flavanone glucosides, acetophenone glucosides, glucopyranoside derivatives, genine derivatives, flavonol, anthocyanin and others[5].

2. MATERIALS AND METHODS

Test Drug MPK
Maruthampattai Kudineer is a polyherbal Siddha formulation with active components that are used to treat *Mathumegam* which is an analog with Diabetes. The following Siddha medicinal herbs are included in this *Maruthampattai Kudineer* preparation (Table 1).

Table 1: Ingredients of *Maruthamapattai Kudineer* with its botanical name and phytocomponents selected for docking

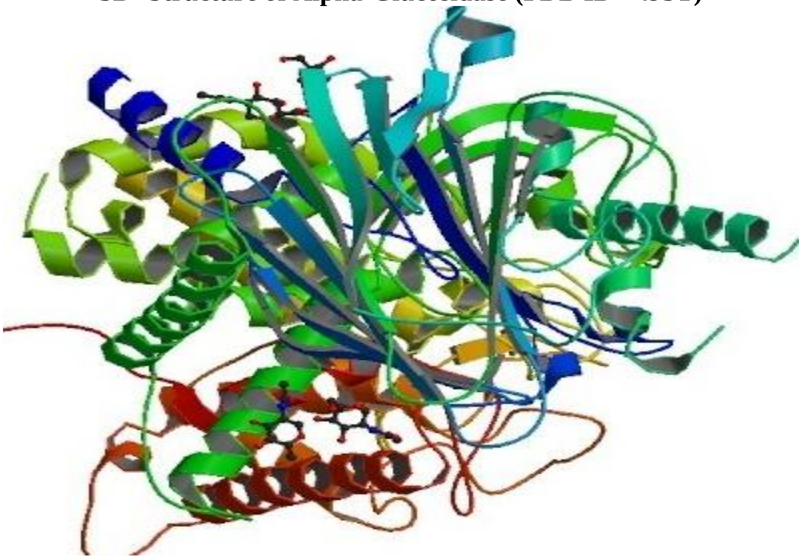
S.No	Vernacular Name	Botanical Name	Phyto components
1	*Maruthampattai*	*Terminalia arjuna*	Arjunic acid [8]
2	*Naaval*	*Syzygium cumini*	Ellagic acid [9] Kaempferol
3	*Karuvellampattai*	*Acacia nilotica*	Arabinose Catechol [10]

4	*Athipattai*	*Ficus racemosa*	Amyrin Lupeol [11]
5	*Avaraithol*	*Cassia auriculata*	Beta-Sitosterol [12]
6	*Kadalalinjilpattai*	*Salacia reticulata*	Salacinol Mangiferin [13]
7	*Thetrankottai*	*Stryhcnous potatorum*	Diaboline Brucine [14]
8	*Kalipakku*	*Areca catechu*	Arecaine [15]
9	*Kadukkai thol*	*Terminalia chebula*	Gallic acid [16] Maslinic acid
10	*Nelli vatral*	*Phyllanthus emblica*	Ascorbic acid [17]
11	*Thandrikkaithol*	*Terminalia bellerica*	Quinic acid Epicatechin [18]

Target protein retrieval

Binding of phytocomponents with the core amino acids (Asp568, Tyr709, Glu771, Asp392, and Arg428) of the target by forming a hydrogen bond will hinder the function of the target protein enzyme alpha-glucosidase (PDB)-4J5T which is involved in the hydrolysis of starch to release sugar moieties that trigger blood glucose. Thereby phytocomponents that inhibit the target enzyme alpha-glucosidase may act as a potential therapeutic agent for the management of diabetes. The crystalline structure of the target protein alpha-Glucosidase (4J5T) was retrieved from the protein data bank and the protein clean-up process was done and essential missing hydrogen atoms were been added. Different orientation of the lead molecules concerning the target protein was evaluated by the Autodock program and the best dock pose was selected based on the interaction study analysis.

3D- Structure of Alpha-Glucosidase (PDB ID - 4J5T)



Ligand preparation

Ellagic acid, Catechol, Amyrin, Lupeol, Beta-Sitosterol, Salacinol, Diaboline, Maslinic acid, Epicatechin, Arjunic acid, Kaempferol, Mangiferin, Brucine, Arecaine, Gallic acid, Ascorbic acid, and Quinic acid were reported as bioactive phyto components in the Siddha formulation *Maruthampattai kudineer*. For docking investigations, the 3D structural coordinates of these 18 bioactive phytochemicals acquired from PubChem were used. Using AutoDockToolsv1.5.6, these ligand structures were further optimized and prepared [19].

Protein-ligand docking

The crystal structure of the alpha-glucosidase enzyme protein-ligand complex (PDB ID: 4J5T) was obtained from RSCB Protein Data Bank. The 3D protein structures were optimized and prepared using AutoDockTools v1.5.6. [20]

Molecular Docking Methodology

Docking calculations were carried out for retrieved phytocomponents against the target enzyme alpha-Glucosidase. Essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were added with the aid of AutoDock tools. Affinity (grid) maps of ×× Å grid points and 0.375 Å spacing were generated using the Autogrid program [21]. AutoDock parameter set- and distance-dependent dielectric functions were used in the calculation of the van der Waals and the electrostatic terms, respectively. Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method [22][23] The initial position, orientation, and torsions of the ligand molecules were set randomly. All rotatable torsions were released during docking. Each docking experiment was derived from 2 different runs that were set to terminate after a maximum of 250000 energy evaluations. The population size was set to 150. During the search, a translational step of 0.2 Å, and quaternion and torsion steps of 5 were applied.

3. RESULTS AND DISCUSSION

α-Glucosidase (α-d-glucoside glucohydrolase) is an exo-type carbohydrase which catalyzes the liberation of α-glucose from the non reducing end of the substrate. Inhibiting this enzyme slows the elevation of blood sugar following a carbohydrate meal[24] .In the present docking study 18 bioactive phyto components in the Siddha formulation *Maruthampattai kudineer* acquired from PubChem were used using AutoDockTools and protein-ligand docking was performed with crystal structure of the alpha-glucosidase enzyme protein-ligand complex (PDB ID: 4J5T).

Marutham Pattai Kudineer is a siddha formulation of 11 medicinal herbs which is noted to have individual medical significance. The pharmacological activities of each ingredient are listed in the Table 2. A total of 18 bioactive lead compounds (**Table 2**) were retrieved from the herbs present in the Siddha formulation MPK. Docking analysis revealed that Salacinol had the lowest binding affinity of -10.45 kcal/mol among all the ligands within MPK (**Table 3**). Salicinol interacts with 392 ASP, 428 ARG, 568 ASP, 709 TYR, 771 GLU of target. This aligns with the proposed catalytic regions 568 ASP and 771 GLU within the targeted protein in humans [25] Other than Salacinol, ligands with interactions with these catalytic regions include, Ellagic acid, Catechol, Amyrin, Lupeol, Diaboline, Maslinic acid and Epicatechin (**Table 4**). The phytochemicals such as Ellagic acid, Catechol, Amyrin, Lupeol, Beta-Sitosterol, Salacinol, Diaboline, Maslinic acid, and Epicatechin reveal a maximum of 4-5 interactions (80-100% affinity) with the core active amino acid residues present on the target protein enzyme alpha-Glucosidase. Followed by compounds such as Arjunic acid, Kaempferol, Mangiferin, Brucine, Arecaine, Gallic acid, Ascorbic acid, and Quinic acid ranked second with a maximum of 2-3 interactions (40-60% affinity) with the active site of the target enzyme alpha-Glucosidase. 15 of the 18 ligands were seen interacting with 428 ARG residue. Previous studies found that MPK had hypoglycemic/anti-diabetic effects in rats. The study found that the decoction significantly reduced blood glucose levels and improved glucose tolerance in rats with diabetes [26] [27] Also, it has been linked to antihyperglycemic and hypolipidemic effects in diabetic individuals [28] with improved glucose tolerance noted in patients with type 2 diabetes [29]

Since α-Glucosidase is the key enzyme catalyzing the final step in the digestive process of carbohydrates,α-glucosidase inhibitors can retard the liberation of d-glucose from dietary complex carbohydrates and delay glucose absorption, resulting in reduced postprandial plasma glucose levels and suppression of postprandial hyperglycemia.[30]

Report suggests that isolated postprandial hyperglycemia (2-hour postprandial glucose level >140 mg/dL [>7.8 mmol/L]) in the face of normal fasting plasma glucose (<110 mg/dL [<6.1 mmol/L]) and normal hemoglobin A_{1c} (<6.1%) values is associated with a 2-fold increased risk of death from cardiovascular disease. Hence from these observations more strict glycemic control is required to prevent macrovascular disease than microvascular disease.Therefore, therapeutic approaches based on natural medicines from traditional formulations would be precise need of the hour to treat this disorder. Further scientific validation to confirm the safety and efficacy is warranted to confirm the anti-diabetic effects as indicated in Siddha text.

Table 2: ligand properties of the compounds selected for docking analysis

S. No	**Compound**	**Molar weight g/mol**	**Molecular Formula**	**H Bond Donor**	**H Bond Acceptor**	**Rotatable bonds**
1	Arjunic acid	488.7 g/mol	$C_{30}H_{48}O_5$	4	5	1
2	Ellagic acid	302.194 g/mol	$C_{14}H_6O_8$	4	8	0
3	Kaempferol	286.24 g/mol	$C_{15}H_{10}O_6$	4	6	1
4	Arabinose	150.13 g/mol	$C_5H_{10}O_5$	4	5	0
5	Catechol	110.11 g/mol	$C_6H_6O_2$	2	2	0
6	Amyrin	426.7 g/mol	$C_{30}H_{50}O$	1	1	0
7	Lupeol	426.7 g/mol	$C_{30}H_{50}O$	1	1	1
8	Beta-Sitosterol	414.7g/mol	$C_{29}H_{50}O$	1	1	6
9	Salacinol	334.354 g/mol	$C_9H_{18}O_9S_2$	5	9	6
10	Mangiferin	422.342 g/mol	$C_{19}H_{18}O_{11}$	8	11	2
11	Diaboline	352.4 g/mol	$C_{21}H_{24}N_2O_3$	1	4	0
12	Brucine	394.5 g/mol	$C_{23}H_{26}N_2O_4$	0	5	2
13	Arecaine	141.17 g/mol	$C_7H_{11}NO_2$	1	3	1
14	Gallic acid	170.12 g/mol	$C_7H_6O_5$	4	5	1
15	Maslinic acid	472.7 g/mol	$C_{30}H_{48}O_4$	3	4	1
16	Ascorbic acid	176.12 g/mol	$C_6H_8O_6$	4	6	2
17	Quinic acid	192.17 g/mol	$C_7H_{12}O_6$	5	6	1
18	Epicatechin	290.271 g/mol	$C_{15}H_{14}O_6$	5	6	1

Table 3: Summary of the molecular docking studies of compounds against Alpha-Glucosidase (PDB) - 4J5T

S.No	Compound	Est. Free Energy of Binding	Est. Inhibition Constant, Ki	Electrostatic Energy	Total Intermolec. Energy	Interact. Surface
1	Arjunic acid	-6.35 kcal/mol	22.21 uM	-1.41 kcal/mol	-7.83 kcal/mol	906.773
2	Ellagic acid	-5.65 kcal/mol	72.55 uM	-0.83 kcal/mol	-5.34 kcal/mol	563.605
3	Kaempferol	-4.77 kcal/mol	320.79 uM	-0.53 kcal/mol	-5.70 kcal/mol	634.794
4	Arabinose	-6.80 kcal/mol	10.29 uM	-0.57 kcal/mol	-4.91 kcal/mol	396.847
5	Catechol	-6.34 kcal/mol	22.38 uM	-0.59 kcal/mol	-6.50 kcal/mol	598.158
6	Amyrin	-7.11 kcal/mol	6.14 uM	-0.00 kcal/mol	-7.41 kcal/mol	949.672
7	Lupeol	-7.25 kcal/mol	4.81 uM	-0.02 kcal/mol	-7.90 kcal/mol	904.039

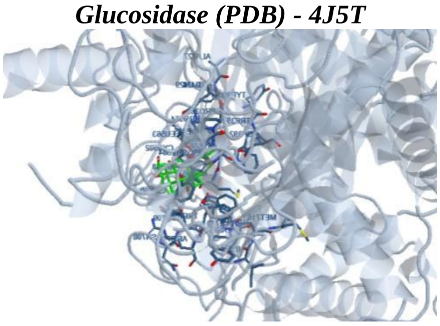
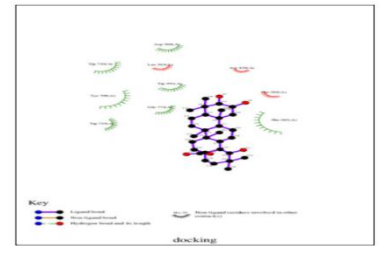
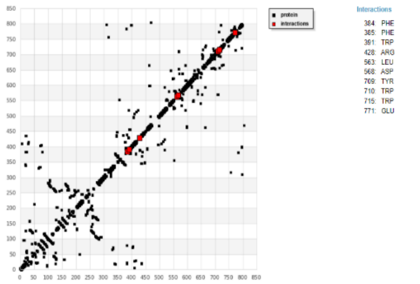
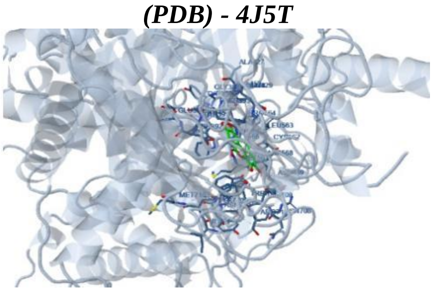
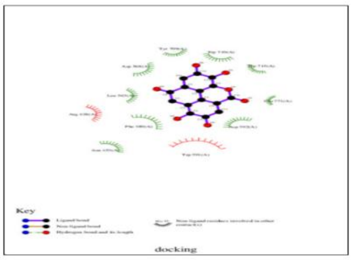
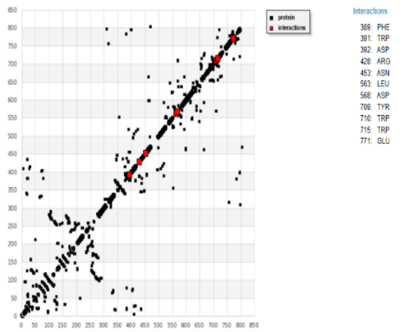
8	Beta-Sitosterol	-9.12 kcal/mol	207.90 nM	-0.08 kcal/mol	-10.70 kcal/mol	881.527
9	Salacinol	-10.45 kcal/mol	21.87 nM	-1.77 kcal/mol	-7.72 kcal/mol	576.031
10	Mangiferin	-5.92 kcal/mol	45.61 uM	-1.66 kcal/mol	-4.73 kcal/mol	722.519
11	Diaboline	-8.49 kcal/mol	598.90 nM	-2.05 kcal/mol	-8.79 kcal/mol	721.954
12	Brucine	-8.81 kcal/mol	346.21 nM	-1.48 kcal/mol	-9.32 kcal/mol	797.372
13	Arecaine	-4.78 kcal/mol	312.89 uM	-1.49 kcal/mol	-5.08 kcal/mol	395.935
14	Gallic acid	-3.91 kcal/mol	1.36 mM	-0.23 kcal/mol	-3.68 kcal/mol	396.561
15	Maslinic acid	-5.64 kcal/mol	73.44 uM	-1.33 kcal/mol	-6.70 kcal/mol	927.819
16	Ascorbic acid	-5.29 kcal/mol	132.37 uM	-0.43 kcal/mol	-5.47 kcal/mol	633.929
17	Quinic acid	-4.83 kcal/mol	289.75 uM	-0.70 kcal/mol	-4.40 kcal/mol	431.06
18	Epicatechin	-6.25 kcal/mol	26.20 uM	-0.83 kcal/mol	-6.97 kcal/mol	650.414

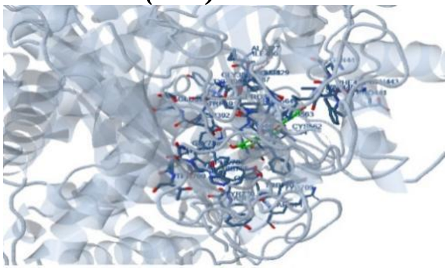
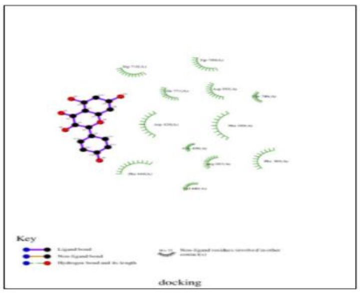
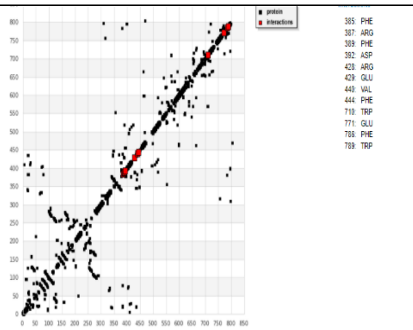
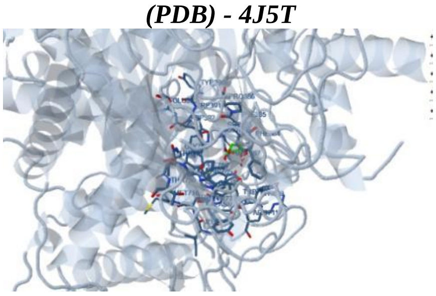
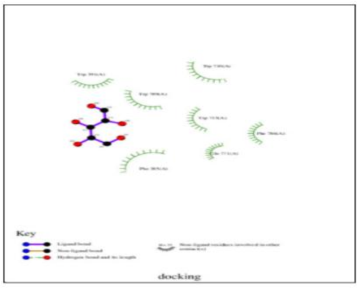
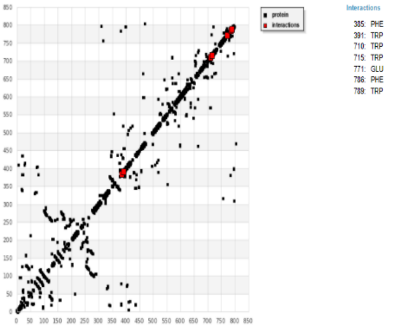
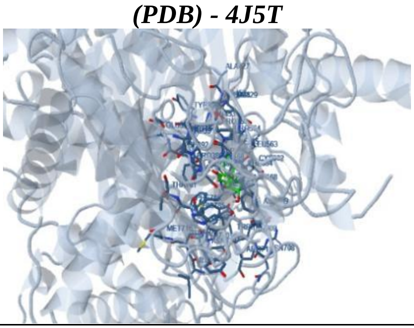
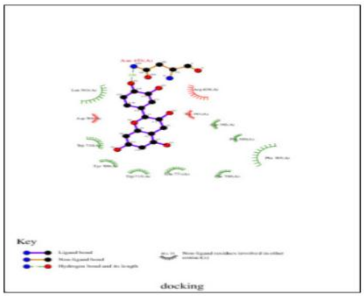
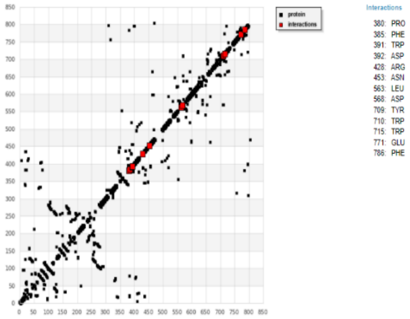
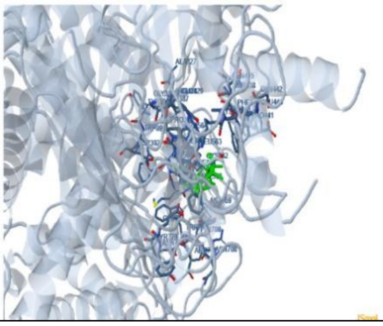
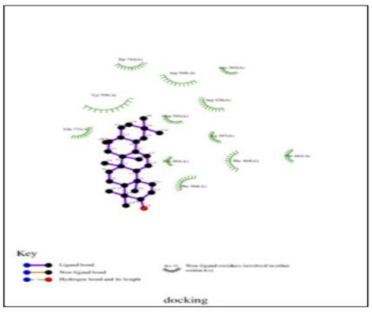
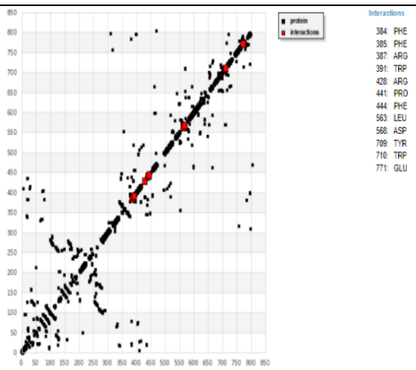
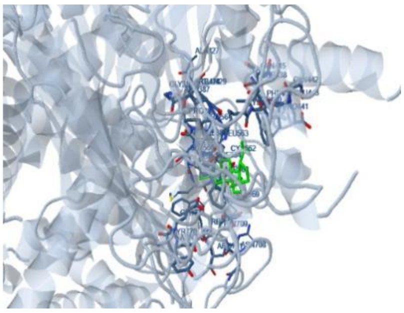
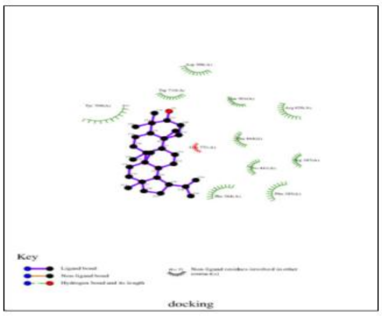
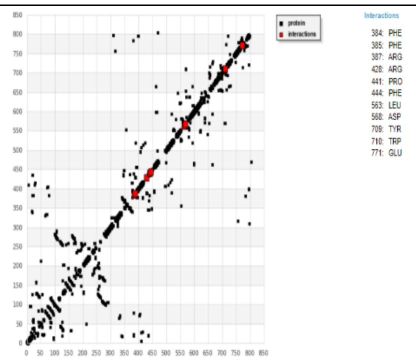
Table 4: Amino acid Residue Interaction of Lead against Alpha-Glucosidase (PDB) - 4J5T

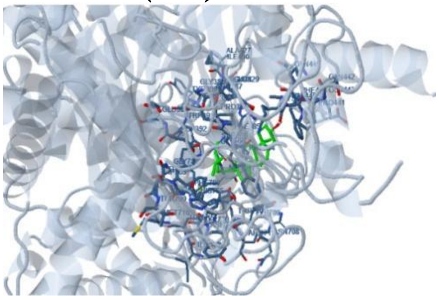
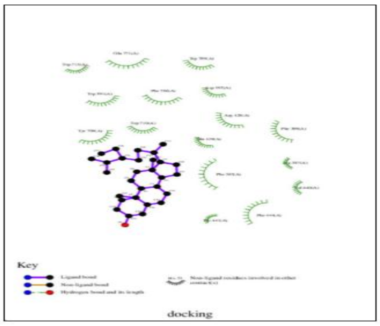
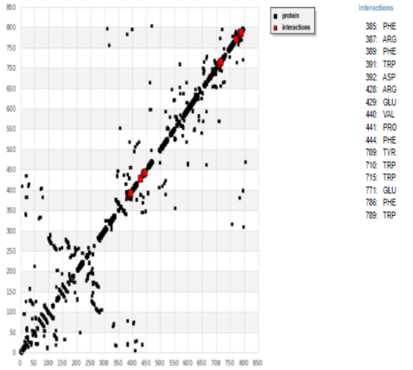
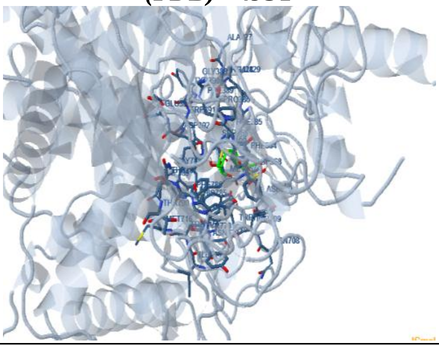
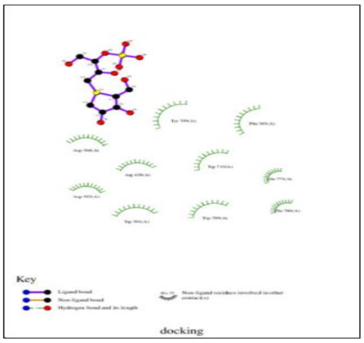
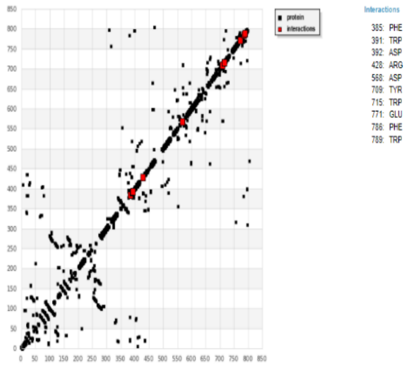
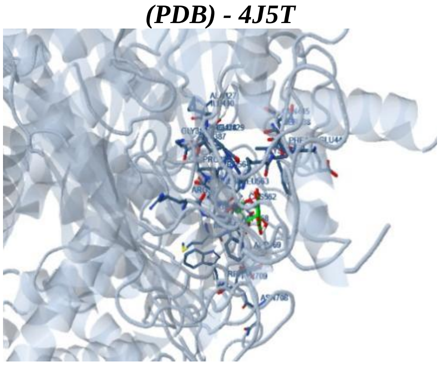
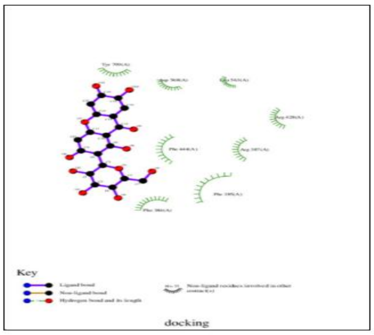
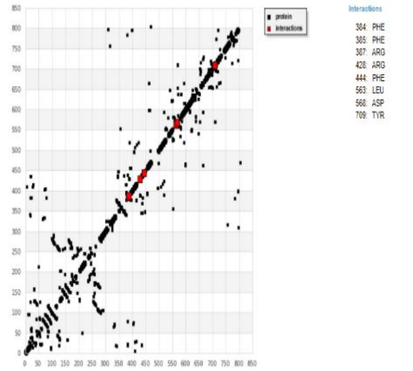
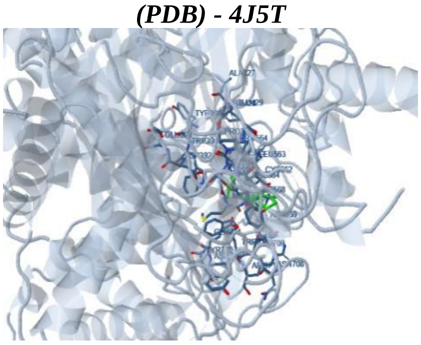
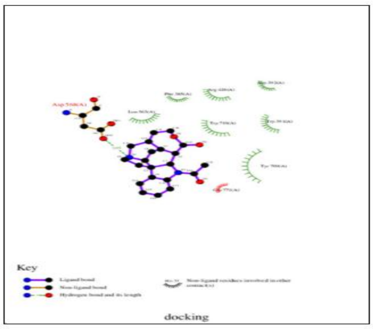
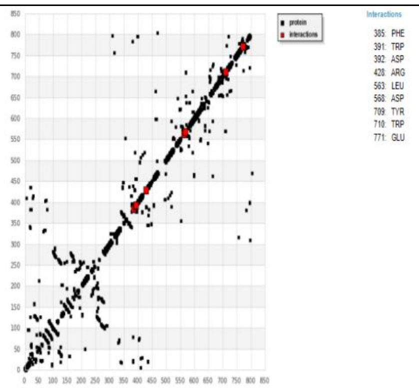
S. No	**Compounds**	**Interaction**	**Amino Acid residue**												
1	Arjunic acid	3	384 PHE	385 PHE	391 TRP	428 ARG	563 LEU	709 TYR	715 TRP	771 GLU					
2	Ellagic acid	5	389 PHE	391 TRP	392 ASP	428 ARG	453 ASN	563 LEU	568 ASP	709 TYR	710 TRP	715 TRP	771 GLU		
3	Kaempferol	3	385 PHE	387 ARG	389 PHE	392 ASP	428 ARG	429 GLU	440 VAL	444 PHE	710 TRP	771 GLU	796 PHE	789 TRP	
4	Arabinose	1	385 PHE	391 TRP	710 TRP	715 TRP	771 GLU	796 PHE	789 TRP						
5	Catechol	5	380 PRO	389 PHE	391 TRP	392 ASP	428 ARG	453 ASN	563 LEU	568 ASP	709 TYR	710 TRP	715 TRP	771 GLU	786 PHE
6	Amyrin	4	384 PHE	385 PHE	387 ARG	389 PHE	391 TRP	428 ARG	444 PHE	563 LEU	568 ASP	709 TYR	710 TRP	771 GLU	
7	Lupeol	4	384 PHE	385 PHE	387 ARG	428 ARG	441 PRO	444 PHE	563 LEU	568 ASP	709 TYR	710 TRP	771 GLU		
8	Beta-itosterol	4	385 PHE	387 ARG	389 PHE	391 TRP	392 ASP	428 ARG	440 VAL	441 PRO	444 PHE	709 TYR	710 TRP	715 TRP	771 GLU
9	Salacinol	5	385 PHE	391 TRP	392 ASP	428 ARG	568 ASP	709 TYR	715 TRP	771 GLU	786 PHE	789 TRP			

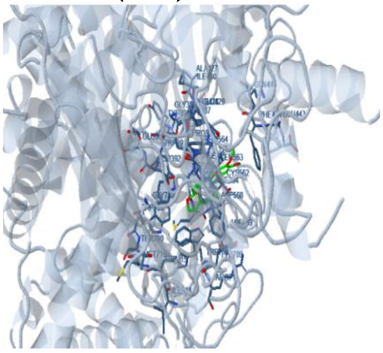
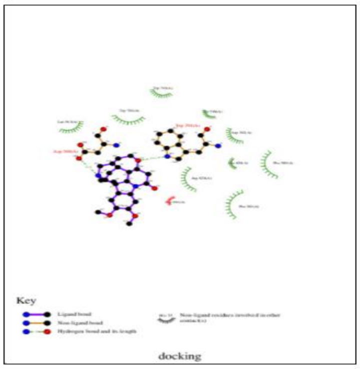
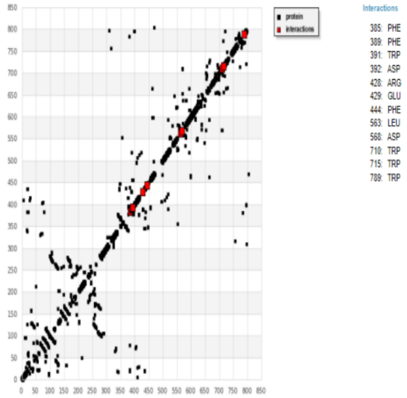
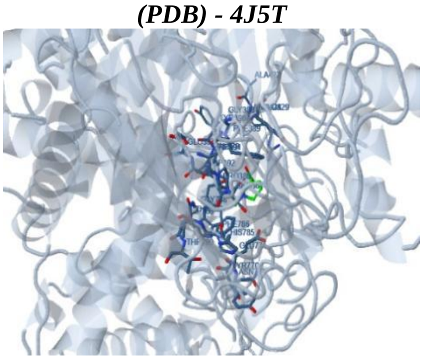
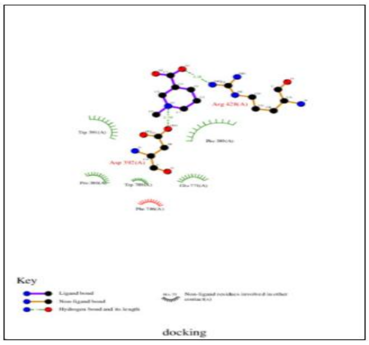
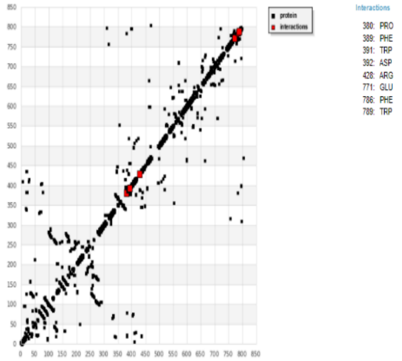
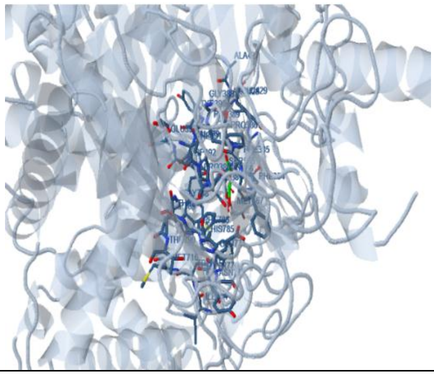
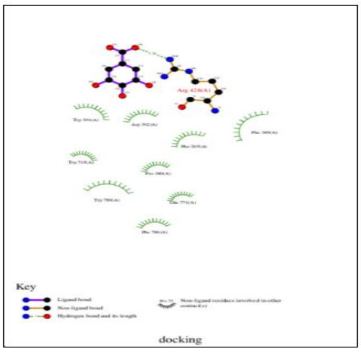
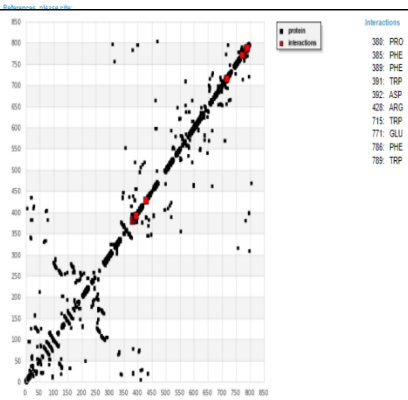
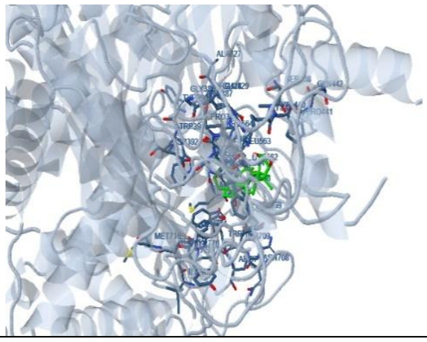
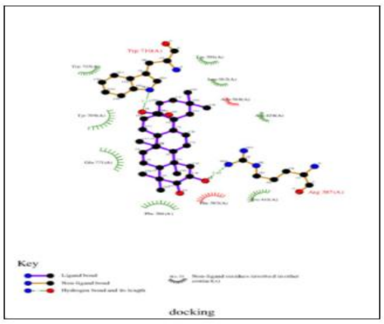
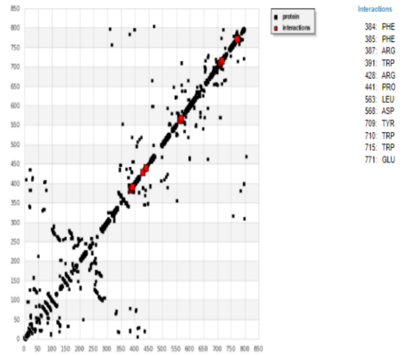
10	Mangiferin	3	384 PHE	385 PHE	387 ARG	428 ARG	444 PHE	563 LEU	563 LEU	568 ASP	709 TYR				
11	Diaboline	5	385 PHE	391 TRP	392 ASP	428 ARG	563 LEU	568 ASP	709 TYR	710 TRP	771 GLU				
12	Brucine	3	385 PHE	389 PHE	391 TRP	392 ASP	428 ARG	429 GLU	444 PHE	563 LEU	568 ASP	710 TRP	715 TRP	789 TRP	
13	Arecaine	3	380 PRO	389 PHE	391 TRP	392 ASP	428 ARG	771 GLU	786 PHE	789 TRP					
14	Gallic acid	3	380 PRO	385 PHE	389 PHE	391 TRP	392 ASP	428 ARG	715 TRP	771 GLU	786 PHE	789 TRP			
15	Maslinic acid	5	384 PHE	385 PHE	387 ARG	391 TRP	392 ASP	428 ARG	563 LEU	568 ASP	709 TYR	710 TRP	715 TRP	771 GLU	
16	Ascorbic acid	2	568 ASP	709 TYR	710 TRP	441 PRO									
17	Quinic acid	3	389 PHE	391 TRP	392 ASP	428 ARG	710 TRP	771 GLU							
18	Epicatechin	4	380 PRO	385 PHE	389 PHE	392 ASP	568 ASP	569 ASP	709 TYR	710 TRP	715 TRP	771 GLU	786 PHE	789 TRP	

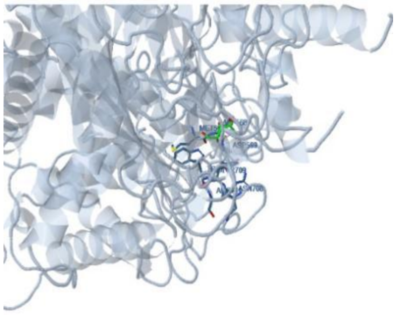
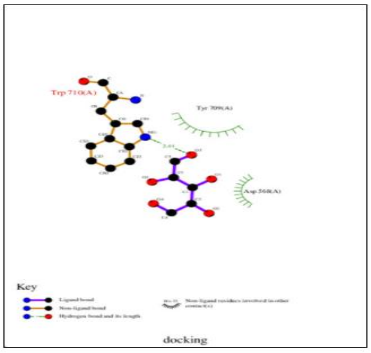
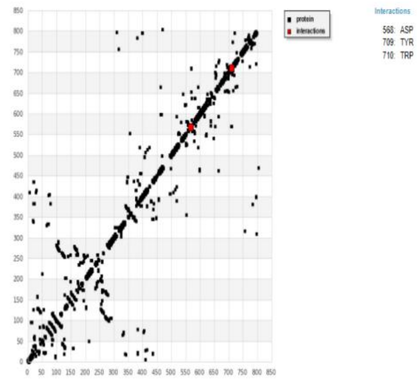
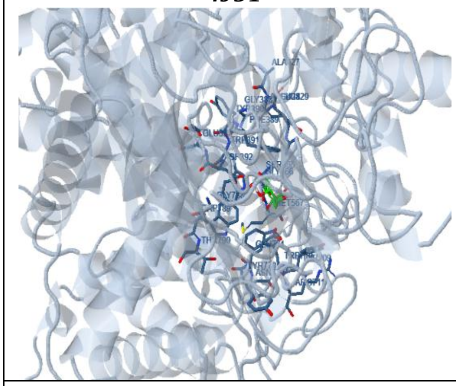
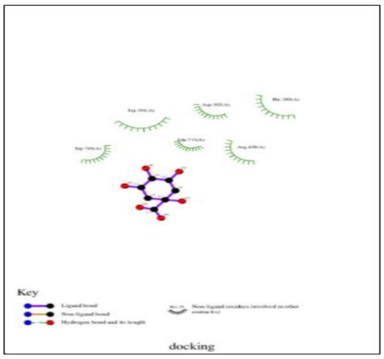
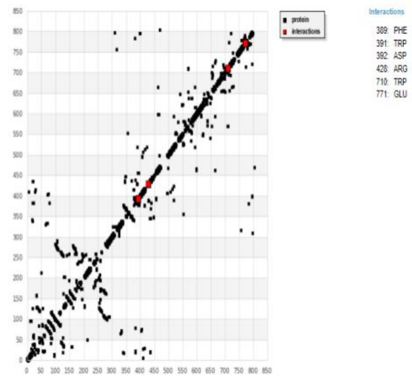
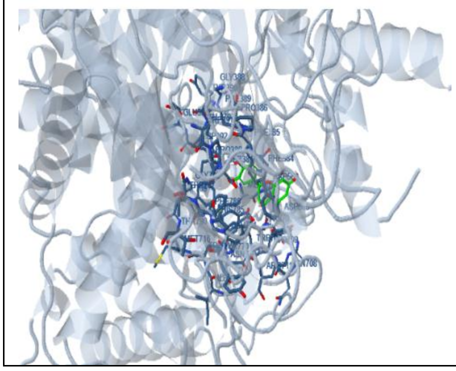
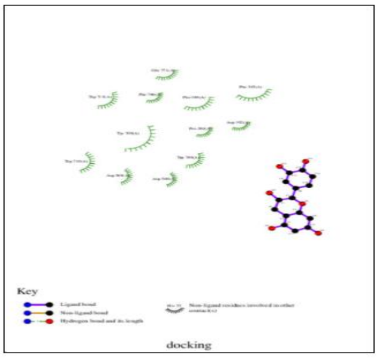
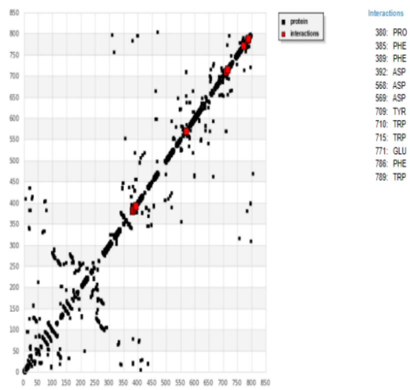
Docking Pose

Q *Arjunic acid with Alpha-Glucosidase (PDB) - 4J5T*	**2D Interaction Plot Analysis**	**Hydrogen bond plotting with core amino acid Analysis**
		
Ellagic acid with Alpha-Glucosidase (PDB) - 4J5T 		

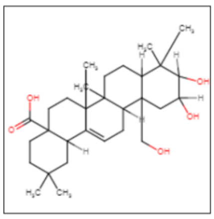
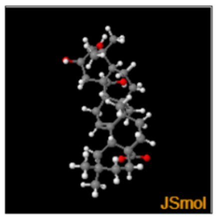
Kaempferol with Alpha-Glucosidase (PDB) - 4J5T 		
Arabinose with Alpha-Glucosidase (PDB) - 4J5T 		
Catechol with Alpha-Glucosidase (PDB) - 4J5T 		
Amyrin with Alpha-Glucosidase (PDB) - 4J5T 		
Lupeol with Alpha-Glucosidase (PDB) - 4J5T 		

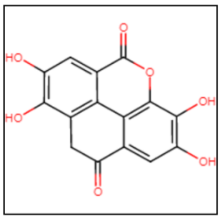
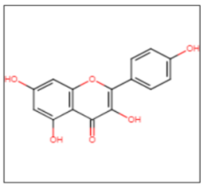
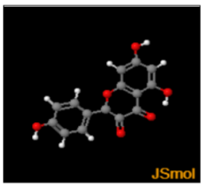
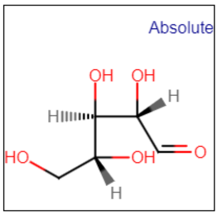
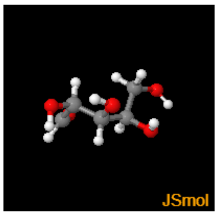
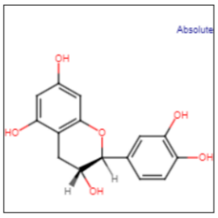
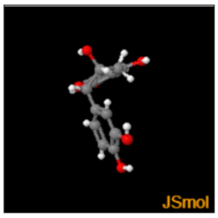
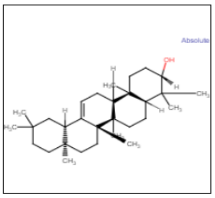
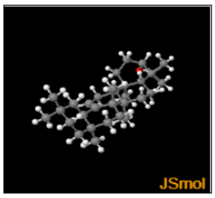
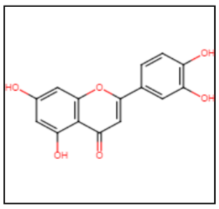
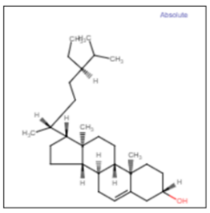
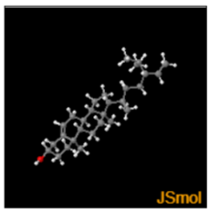
Beta-Sitosterol with Alpha-Glucosidase (PDB) - 4J5T 		
Salacinol with Alpha-Glucosidase (PDB) - 4J5T 		
Mangiferin with Alpha-Glucosidase (PDB) - 4J5T 		
Diaboline with Alpha-Glucosidase (PDB) - 4J5T 		

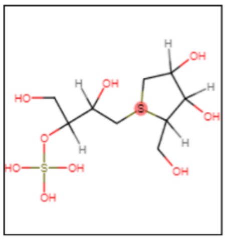
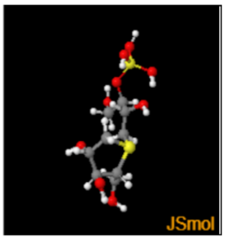
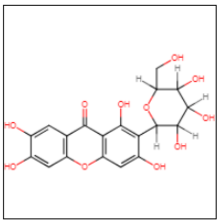
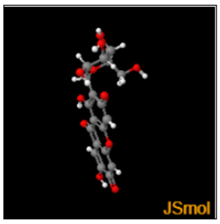
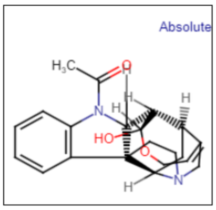
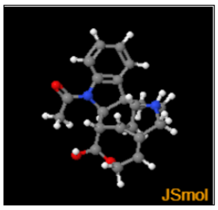
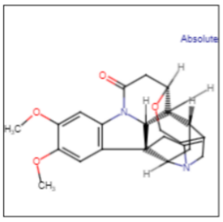
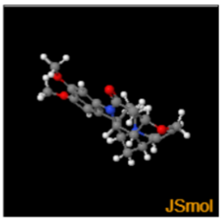
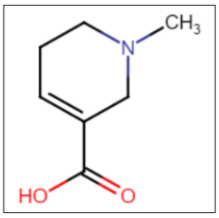
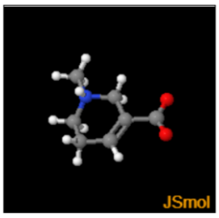
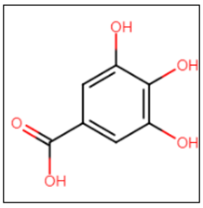
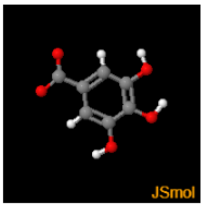
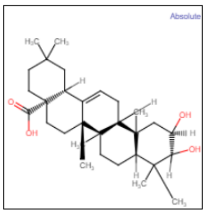
Brucine with Alpha-Glucosidase (PDB) - 4J5T 		
Arecaine with Alpha-Glucosidase (PDB) - 4J5T 		
Gallic acid with Alpha-Glucosidase (PDB) - 4J5T 		
Maslinic acid with Alpha-Glucosidase (PDB) - 4J5T 		

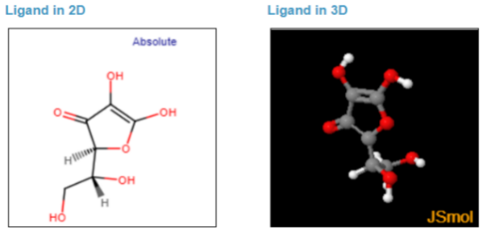
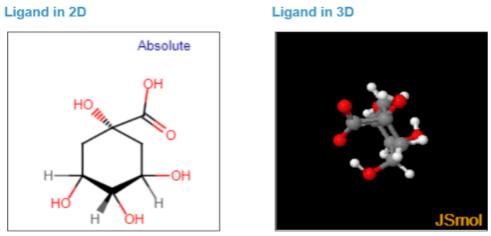
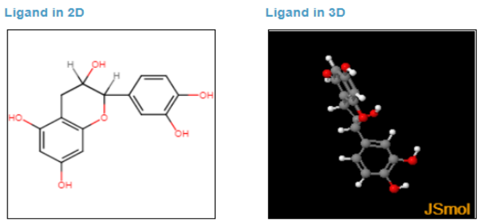
Ascorbic acid with Alpha-Glucosidase (PDB) - 4J5T 		
Quinic acid with Alpha-Glucosidase (PDB) - 4J5T 		
Epicatechin with Alpha-Glucosidase (PDB) - 4J5T 		

2D and 3D Structure of Phytocomponents

S.no	Phytochemical	2D & 3D structure
1	Arjunic acid	Ligand in 2D  Ligand in 3D 

2	**Ellagic acid**	Ligand in 2D  Ligand in 3D 
3	**Kaempferol**	Ligand in 2D  Ligand in 3D 
4	**Arabinose**	Ligand in 2D  Ligand in 3D 
5	**Catechol**	Ligand in 2D  Ligand in 3D 
6	**Amyrin**	Ligand in 2D  Ligand in 3D 
7	**Lupeol**	Ligand in 2D  Ligand in 3D 
8	**Beta-Sitosterol**	Ligand in 2D  Ligand in 3D 

9	**Salacinol**	 
10	**Mangiferin**	Ligand in 2D  Ligand in 3D 
11	**Diaboline**	Ligand in 2D  Ligand in 3D 
12	**Brucine**	Ligand in 2D  Ligand in 3D 
13	**Arecaine**	Ligand in 2D  Ligand in 3D 
14	**Gallic acid**	Ligand in 2D  Ligand in 3D 
15	**Maslinic acid**	Ligand in 2D  Ligand in 3D 

16	**Ascorbic acid**	
17	**Quinic acid**	
18	**Epicatechin**	

Ligand Properties of the Compounds Selected for Docking Analysis

4. CONCLUSION

α-Glucosidase is the key enzyme catalysing the carbohydrate metabolism and reducing the postprandial hypoglycemia. Based on the results of the computational analysis, it was concluded that among the 18 bio-active compounds of MPK lead compounds such as Ellagic acid, Catechol, Amyrin, Lupeol, Beta-Sitosterol, Salacinol, Diaboline, Maslinic acid, and Epicatechin reveal a maximum of 4-5 interactions (80-100% affinity) with the core active amino acid residues present on the target protein enzyme alpha-Glucosidase. Therefore, it can be concluded that the phytochemicals present in the traditional Siddha formulation MPK can provide pharmaceutical leads for traditional hypoglycemic agents . The study recommends further preclinical and clinical studies to validate the traditional literature claims of MPK.

Conflict of Interest

The authors declare that there is no conflict of interest.

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