In-Silico Molecular Docking Investigation of Bioactive Therapeutics Retrieved from the Siddha Formulation *Mega Sanjeevi Chooranam* against Alpha-amylase and Alpha-glucosidase Enzymes

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ABSTRACT

Diabetes mellitus (DM) is a collection of metabolic changes impacting not just glucose but also protein and lipid metabolism. Treatment may involve a combination of several approaches, such as oral and injectable drugs, dietary and lifestyle modifications, exercise, and weight management. Herbal medicines are gaining paramount importance due to high lever of safety and wide efficacy margin. Siddha system of medicine pioneers the art of managing metabolic disorders due to its versatile nature of preparations. One such formulation is *Mega sanjeevi chooranam* comprises of 10 herbal ingredients prescribed in the siddha system for managing diabetes mellitus. Hence the present investigation aimed at exploring the target-specific binding potential of the phytotherapeutic leads retried from the ingredients of the formulation *Mega sanjeevi chooranam* against the targets alpha-amylase and alpha-glucosidase using molecular docking studies. Results of residual interaction analysis depicts that out of 11 phytotherapeutics present in the siddha formulation *Mega sanjeevi chooranam* the compounds such as beta-amyrin (-7.12 kcal/mol), tinosporide (-7.64 kcal/mol), and beta-sitosterol (-8.98 kcal/mol) revels potential interactions with the active site of the target alpha-glucosidase. Followed by this the compounds like brucine (-9.85 kcal/mol), kaempferol (-5.12 kcal/mol), tinosporide (-6.50 kcal/mol), beta-amyrin (-9.36 kcal/mol), thymol (-4.34 kcal/mol), and beta-sitosterol (-8.37 kcal/mol) reveals maximal interactions with the active site of the target alpha amylase. It was concluded from the results of the present investigation that structurally diverse phytotherapeutics which has the potential to inhibit the alpha-amylase and alpha-glucosidase may be considered as adjoining therapy in the clinical management of diabetes mellitus.

Key Words: Diabetes mellitus, *Mega sanjeevi chooranam*, Siddha, Molecular docking, Alpha-amylase, Alpha-glucosidase.

1.INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic condition characterized by increased blood glucose levels due to a depletion in insulin secretion [1]. The global prevalence of diabetes has risen from 108 million in 1980 to 463 million in 2019, with 1.6 million fatalities attributable to the disease in 2016. This figure is expected to rise to 578 million (10.2%) by 2030 and 700 million by 2045 [2]. Type 2 diabetes mellitus (T2DM) is an illness that often affects older people and has become a pandemic in many nations [3]. After cardiovascular disease and cancer, this is the third most significant cause of mortality in both developed and developing countries [4].

Carbohydrates are the primary components of the average human diet. Its main forms are starch and sucrose, which offer around 70-80% of the body's energy requirements. Their digestion begins in the mouth and continues even in the small intestine, creating glucose that is taken into circulation through the gut walls and then distributed to various regions of the body via the liver. The digested products are mostly glucose, with some fructose and galactose thrown in for good measure [5]. The enzyme alpha-amylase, present in saliva and pancreatic secretions, first decompose starch into oligosaccharides. In the small intestinal epithelium, a membrane-bound enzyme called alpha-glucosidase catalyzes the breakdown of glucose from disaccharides and oligosaccharides. As a result, -glucosidase inhibition is one of the most effective diabetic therapies because it delays glucose absorption [6].

Metformin has been used extensively worldwide in managing diabetes; nevertheless, the most common adverse effects of metformin are gastrointestinal (GI) disturbances, rashes, taste disturbances, and other symptoms [7]. The FDA has authorised thiazolidinediones like pioglitazone and rosiglitazone to treat type 2 diabetes. Clinical use of thiazolidinedione has been considerably reduced due to side effects, including weight gain, heart dysfunction, and fluid retention [8]. Acarbose, miglitol, and voglibose are three -glucosidase inhibitors (AGIs) used to treat type 2 diabetes in adults. This class is contraindicated in patients with cirrhosis, inflammatory bowel disease, colonic ulceration, intestinal blockage, obstruction susceptibility, and diabetic ketoacidosis [9].

According to the WHO, almost 80% of the population uses herbal medicines to treat a variety of diseases3, and they are gaining traction in global healthcare discussions [10]. Medicinal herbs are the earliest source of pharmacologically active therapeutics in the world. Many traditional medical systems, often known as folk medicine, have developed throughout the centuries and throughout a wide range of cultural contexts [11]. Even in modern times, the majority of people residing in less developed nations continue to rely on herbal remedies as their primary source of medical attention [12]. Phytotherapy is widely accepted as a natural and gentle alternative to synthetic pharmaceuticals among the general population in industrialised nations, and global sales of herbal medicines are steadily increasing. This is mainly due to the fact that phytotherapy has been shown to have fewer side effects than synthetic pharmaceuticals [13].

Molecular docking technique may be used to model the interaction between a small molecule and a protein at the atomic level [14]. Virtual screening paves a greater way to define the behavior of small molecules at the binding site of target proteins and to understand fundamentals of biochemical processes. There are two main phases of docking: predicting the

ligand conformation and its position and orientation inside these sites (commonly referred to as pose) and then evaluating the binding affinity. Both of these procedures, sampling, and scoring truly helps the researcher in identifying the lead candidate against specific disease [15].

Siddha is one of the oldest healing modalities to restore an individual's vitality and health. Despite its traditional reliance on herbs, modern scientific inquiry has focused on the drug's natural mechanism of action [16]. Secondary metabolites, the physiologically active medicines found in herbal remedies, have been shown to prevent the course of a variety of illnesses [17]. Considering the originality of each siddha formulation, it comprises a combination of phytotherapeutics which acts synergistic in limiting the pathogenesis of diabetes and considerably reducing the likelihood of insulin resistance [18]. *Mega sanjeevi chooranam* (MSC) is a novel polyherbal formulation prescribed in the siddha system for managing type-2 diabetes mellitus. It consists of 10 herbal ingredients: Strychnos *Potatorum*, *Eugenia jambolana*, *Plectranthus vettiveroides*, *Vetiveria zizanioides*, *Syzigium aromaticum*, *Anacyclus pyrethrum*, *Cassia fistula*, *Cassia auriculata*, *Gymnema sylvestre* and *Tinospora cordifolia* [19].

Pre-clinical studies evident that the compounds brucine (*Strychnos potatorum*), kaempferol (*Cassia fistula*), and β-sitosterol (*Cassia auriculata*) was proven to be beneficial as a long-term antidiabetic drug in lowering HbA1C levels in a rat model [20-22]. Gallic acid is another viable therapeutics in *eugenia jambolana* and reveals significant antidiabetic properties by delineating the upregulation of pAkt, PPAR-γ, and Glut4 activity [23]. Literature shows that the rats fed with varying doses of thymol were found to significantly lower the level of HbA1c dose-dependently significantly [24]. Lupeol is the bioactive compound present in *Gymnema sylvestre*, which is widely used in different traditional medicines advocates pronounced anti-hyperglycaemic activity in combination with iso-orientin [25]. β-amyrin retrieved from *Gymnema sylvestre* reveals remarkable anti-hyperglycaemic activity in glucose-loaded rats by blocking the entry of glucose from the intestine [26]. Beta-caryophyllene is a pharmacologically active sesquiterpenoid found in *Syzigium aromaticum* shown to have insulinotropic effect by its agonistic activity in triggering beta cells of pancreatic islet cells [27].

Tinospora cordifolia is the primary source of the bioactive compound called tinosporide, which is found to regulate cholesterol synthesis and glycolysis in animal model [28]. The extracts of the herbs *Anacyclus pyrethrum* and *Vetiveria zizanioides* possess promising antihyperglycaemic activity in alloxan-induced diabetic rat models. Where in the

mechanism of action of levulinic acid and β-guaiene in controlling diabetic pathogenies is still not explored [29]. Available literature showcases the biological significance exerted by phytotherapeutics in managing hyperglycemia. Still, no proper documentary evidence claims the alpha-amylase and alpha-glucosidase enzyme inhibition potential of the phytotherapeutic leads present in the formulation MSC. Hence the present investigation aimed at exploring the target-specific binding potential of the phytotherapeutic leads retried from the ingredients of the formulation *Mega sanjeevi chooranam* against the targets alpha-amylase and alpha-glucosidase using molecular docking studies.

2. MATERIAL AND METHODS

2.1. Docking simulation Software

Molecular docking investigations were used to predict the residual interaction between the selected lead molecules with the enzyme target alpha-glucosidase (PDB 4J5T) and alpha-amylase (PDB 1HNY) with the aid of Auto Dock *in-silico* screening tool version 4.

2.2. Protein preparation

The crystalline structure of the target proteins (alpha-glucosidase and alpha-amylase) was retrieved from the Research Collaboratory for Structural Bioinformatics database (RCSB). As per the standardized protocol, the protein structure was subjected to purification by eliminating the ligands and water molecules. Protonation levels were maintained by adding missing hydrogen atoms at pH 7.0. The degree of polarity on the protein surface was adjusted by adding polar hydrogen atoms and the fusion of non-polar hydrogens. The final purified structure of the target protein was exported into a dockable format as shown in figure 1 (A&B) and subjected to molecular docking investigation.

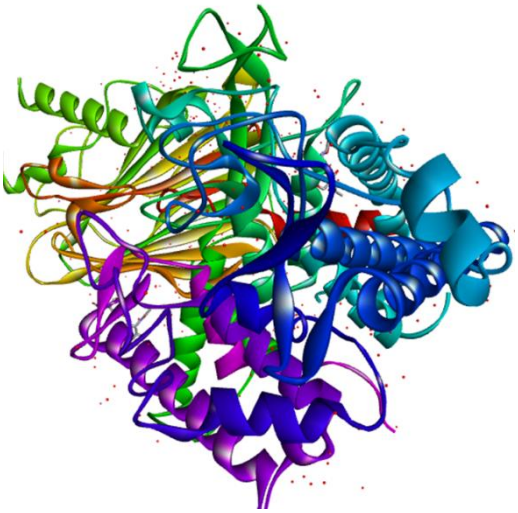

Figure 1 A: 3D structure of alpha-glucosidase (4J5T)

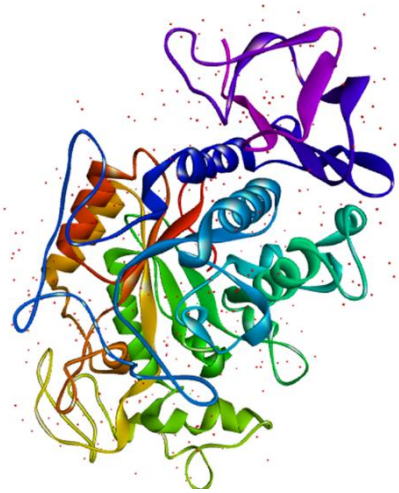

Figure 1 B: 3D structure of alpha-amylase (1HNY)

2.3. Ligand Preparation

The ChemDraw prof 12.0 online program was used to construct the selected phytochemical leads for docking investigations. Optimized-geometry ligands developed (MMFF94) under a pH value of 7, the electronegativity, atomic charge, dissociation constant, stability constant, rotatable bond, and donor bond. Aromatic ring count and randic index were all computed using gasteiger partial charge calculation. Figure 2 depicts the two-dimensional orientations of the phytochemicals retrieved from *Mega Sanjeevi Chooranam*. Table 1 lists the physiochemical characteristics of the active herbal lead components.

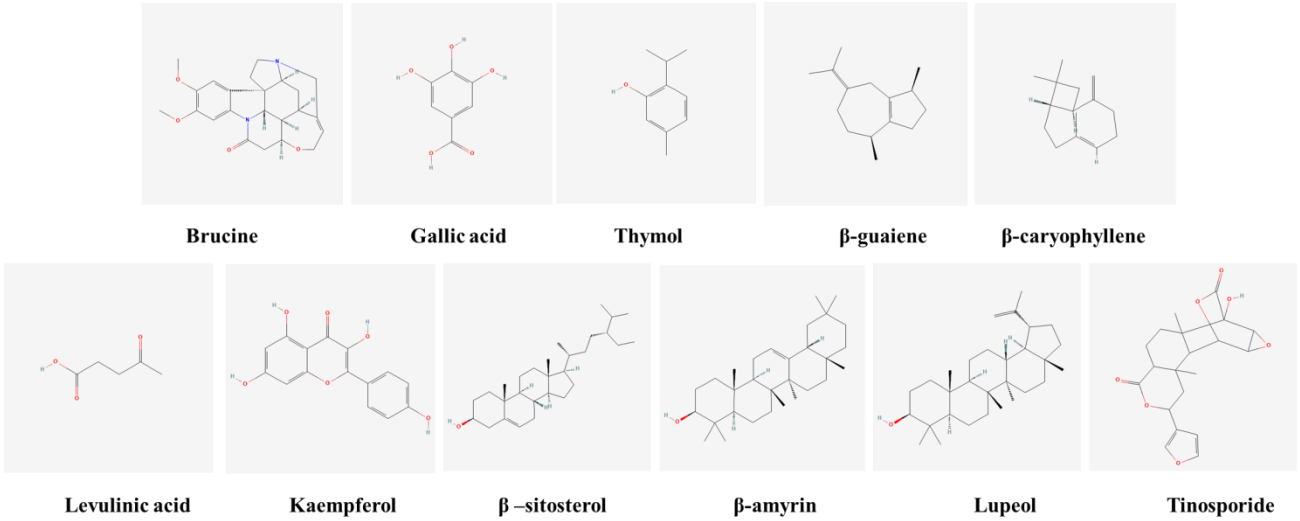

Figure 2: 2D structure of phytotherapeutics subjected to molecular docking investigation

2.4. Protein Confirmation

The protein's torsional conformation was visualized using Ramachandran plots, featuring a unique projection of high-energy residues on the protein backbone [30]. Ramachandran plot signifies the prominent arrangement of 788 (alpha-glucosidase) and 495 (alpha-amylase) amino acids. Refinement was carried out with Z-score analysis for

glucosidase was -0.31 ± 0.27 with and for amylase it was -1.54 ± 0.35. The protein structure was solved at 2.04 Å resolution R = 0.225 for glucosidase and 1.80 Å with R = 0.174 for amylase. The stability of the target protein (PDB 1HNY) was validated using the MolProbity server [31].

2.5. Active site prediction on the target protein

The catalytic site of the protein under investigation, such as alpha-glucosidase (PDB 4J5T) and alpha-amylase (PDB 1HNY), was predicted using the CASTp server [32]. Residual amino acids, which mediate the pronounced interactions with ligand molecules further confirmed through a literature survey [33].

2.6. Docking methodology

The Autodock simulation tool was utilized to ascertain the binding efficiency of the selected ligands under investigation since the docking score is the summation of the bonding nature, atomic force field, and electrostatic and steric interaction between the ligand and receptor [34]. The Lamarckian genetic algorithm (LGA) and the Wets local search approach are used in this study to falcate the flexible rotation of receptor and ligand to capture the optimal docking posture and its close interaction [35]. The affinity (grid) of the simulation box was customized with an expansion size of 60x60x60 Å grid points and 0.37 Å spacing using the auto grid software and the van der Waals and electrostatic terms. Before arriving at the final docking position, over a hundred distinct runs were tallied. The exponential energy value was set to 2500000, a modest population volume of 150, 0.2 Å, and five torsion steps.

3.RESULTS

3.1. Physicochemical properties of Lead compounds

The binding conformation of the ligands rigidly enforces the physicochemical properties. The drug-likeness and interaction properties of molecules are strongly influenced by their molecular weight, arrangement of functional groups, and bonding potential. The binding affinity of the ligand is predicted by the spatial orientation of the functional groups and their efforts to form stable bonding with the physiologically active residue preside over the receptor protein. The affinity of the ligands towards the receptors is determined by the spatial orientation of the functional groups and their efforts to build stable bonding with the physiologically active residue. The physicochemical properties of the phytotherapeutics present in the siddha formulation *Mega sanjeevi chooranam* with respect to molecular weight, molecular formula, and H bond profile are listed in Table 1.

Table 1: Physicochemical properties of the herbal lead compounds selected for docking analysis

Source	Compound	Category	Molar weight g/mol	Molecular Formula	H Bond Donor	H Bond Acceptor	Rotatable bonds
Strychnos Potatorum	Brucine	Alkaloid	394.5	$C_{23}H_{26}N_2O_4$	0	5	2
Eugenia jambolana	Gallic acid	Phenolic acid	170.12	$C_7H_6O_5$	4	5	1
Plectranthus vettiveroides	Thymol	Monoterpene	150.221	$C_{10}H_{14}O$	1	1	1
Vetiveria zizanioides	β-guaiene	Sesquiterpenoid	204.35	$C_{15}H_{24}$	0	0	0
Syzigium aromaticum	β-caryophyllene	Sesquiterpenoid	204.35	$C_{15}H_{24}$	0	0	0
Anacyclus pyrethrum	Levulinic acid	Phenolic acid	116.11	$C_5H_8O_3$	1	3	3
Cassia fistula	Kaempferol	Flavonoid	286.24	$C_{15}H_{10}O_6$	4	6	1
Cassia auriculata	β-sitosterol	Phytosterol	414.7	$C_{29}H_{50}O$	1	1	6
Gymnema sylvestre	β-amyrin	Triterpenoid	426.7	$C_{30}H_{50}O$	1	1	0
Gymnema sylvestre	Lupeol	Triterpenoid	426.7	$C_{30}H_{50}O$	1	1	1
Tinospora cordifolia	Tinosporide	Diterpenoid	374.4	$C_{20}H_{22}O_7$	1	7	1

3.2. Molecular Docking Simulation

The outcome of molecular docking studies between the phytotherapeutics present in the siddha formulation *Mega sanjeevi chooranam* against the target alpha-glucosidase emphasizes that the molecule beta-sitosterol showcases the best binding affinity of -8.98 kcal/mol followed by brucine (-8.82 kcal/mol), tinosporide (-7.64 kcal/mol), β-amyrin (-7.12 kcal/mol) and lupeol (-7.25 kcal/mol) with regard to its binding free energy as tabulated in table 2. Results of molecular docking studies against the target alpha-amylase showcase that the molecule brucine advocates the best binding affinity with a docking score of -9.85 kcal/mol followed by β-amyrin (-9.36 kcal/mol), beta-sitosterol (-8.37 kcal/mol), lupeol (-7.95 kcal/mol) and tinosporide (-6.50 kcal/mol) with regard to its binding free energy as tabulated in table 3 and illustrated in figure 3 and 4.

Table 2: Table representing the docking parameters of lead compounds present in *Mega Sanjeevi Chooranam* against the target alpha-glucosidase with PDB - 4J5T

Compound	Est. Free Energy of Binding	Est. Inhibition Constant, Ki	Electrostatic Energy	Total Intermolecular Energy	Total Interaction Surface
Brucine	-8.82 kcal/mol	342.89 nM	-1.48 kcal/mol	-9.32 kcal/mol	797.295
Gallic acid	-3.93 kcal/mol	1.31 mM	-0.22 kcal/mol	-3.85 kcal/mol	416.468
Thymol	-4.61 kcal/mol	416.18 uM	-0.20 kcal/mol	-5.23 kcal/mol	450.834
β-guaiene	-6.45 kcal/mol	18.72 uM	-0.04 kcal/mol	-6.49 kcal/mol	555.339
β-caryophyllene	-6.40 kcal/mol	20.52 uM	-0.01 kcal/mol	-6.40 kcal/mol	552.181

Levulinic acid	-2.75 kcal/mol	9.60 mM	-0.63 kcal/mol	-4.27 kcal/mol	282.599
Kaempferol	-4.77 kcal/mol	317.41 uM	-0.53 kcal/mol	-5.70 kcal/mol	634.723
β –sitosterol	-8.98 kcal/mol	261.89 nM	-0.03 kcal/mol	-10.05 kcal/mol	937.274
β-amyrin	-7.12 kcal/mol	6.01 uM	-0.07 kcal/mol	-7.49 kcal/mol	949.245
Lupeol	-7.25 kcal/mol	4.82 uM	-0.02 kcal/mol	-7.90 kcal/mol	903.914
Tinosporide	-7.64 kcal/mol	2.51 uM	-0.19 kcal/mol	-8.21 kcal/mol	679.786

Table 3: Table representing the docking parameters of lead compounds present in *Mega Sanjeevi Chooranam* against the target alpha-amylase with PDB - 1HNY

Compound	Est. Free Energy of Binding	Est. Inhibition Constant, Ki	Electrostatic Energy	Total Intermolecular Energy	Total Interaction Surface
Brucine	-9.85 kcal/mol	60.30 nM	-2.54 kcal/mol	-10.36 kcal/mol	745.928
Gallic acid	-4.28 kcal/mol	725.82 uM	-0.84 kcal/mol	-3.84 kcal/mol	369.276
Thymol	-4.34 kcal/mol	654.78 uM	-0.15 kcal/mol	-4.95 kcal/mol	451.651
β-guaiene	-5.70 kcal/mol	66.30 uM	-0.01 kcal/mol	-5.70 kcal/mol	543.889
β-caryophyllene	-5.92 kcal/mol	46.08 uM	-0.01 kcal/mol	-5.92 kcal/mol	546.963
Levulinic acid	-2.83 kcal/mol	8.39 mM	-0.40 kcal/mol	-3.70 kcal/mol	301.477
Kaempferol	-5.12 kcal/mol	176.23 uM	-0.65 kcal/mol	-5.52 kcal/mol	485.794
β –sitosterol	-8.37 kcal/mol	738.15 nM	-0.03 kcal/mol	-9.57 kcal/mol	859.091
β-amyrin	-9.36 kcal/mol	136.87 nM	-0.30 kcal/mol	-9.66 kcal/mol	839.149
Lupeol	-7.95 kcal/mol	1.48 uM	-0.02 kcal/mol	-8.55 kcal/mol	907.36
Tinosporide	-6.50 kcal/mol	17.10 uM	-0.69 kcal/mol	-6.90 kcal/mol	710.188

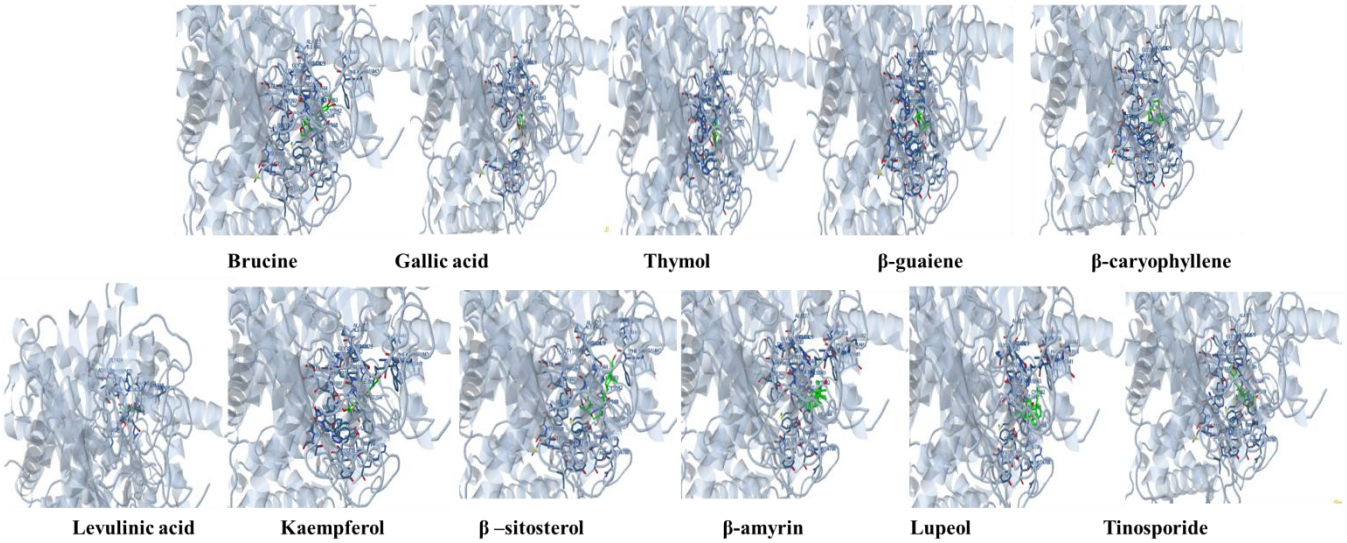

Figure 3: Docking conformation of lead compounds with alpha-glucosidase (4J5T)

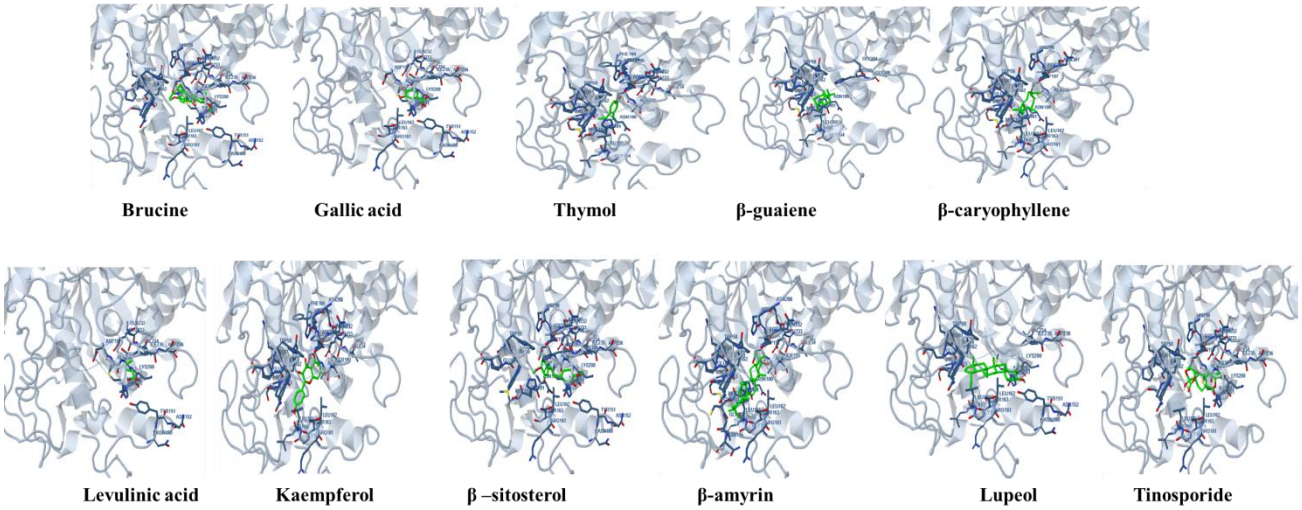

Figure 4: Docking conformation of lead compounds with alpha-amylase (1HNY)

3.3. Residual interaction with active site

Results of amino acid residual analysis with the target protein alpha-amylase depict that out of 11 phytotherapeutics present in the siddha formulation *Mega sanjeevi chooranam* the compound brucine reveals ten viable interactions with the active site of the target, followed by this, other compounds such as kaempferol, tinosporide, beta-amyrin, thymol, and beta-sitosterol reveals a maximum of seven to nine interactions as shown in table 4 and illustrated in figure 5. Results of amino acid residual analysis with the target protein alpha-glucosidase signifies that the compound beta-amyrin, tinosporide, and beta-sitosterol revels five potential interactions with the active site of the target, followed by this, other compounds such as beta-caryophyllene guaiene, gallic acid, kaempferol, lupeol, and brucine reveals a maximum of three to four possible interactions as shown in table 5 and illustrated in figure 6.

Table 4: Sequential amino acid residue binding analysis of lead compounds present in *Mega Sanjeevi Chooranam* against the target alpha-glucosidase with PDB - 4J5T

Compound	Interactions	Amino Acid residues												
Brucine	3	385 PHR	389 PHE	391 TRP	392 ASP	428 ARG	429 GLU	444 PHE	563 LEU	568 ASP	710 TRP	715 TRP	789 TRP	
β-caryophyllene	4	389 PHE	391 TRP	392 ASP	428 ARG	568 ASP	710 TRP	715 TRP	771 GLU	786 PHE	789 TRP			
β-guaiene	3	380 PRO	385 PHR	389 PHE	391 TRP	392 ASP	428 ARG	710 TRP	715 TRP	771 GLU	786 PHE	789 TRP		
Gallic acid	3	389 PHE	391 TRP	392 ASP	428 ARG	453 ASN	563 LEU	715 TRP	771 GLU					
Kaempferol	3	385 PHR	387 ARG	389 PHE	392 ASP	428 ARG	429 GLU	440 VAL	444 PHE	710 TRP	771 GLU	786 PHE	789 TRP	
Tinosporide	5	385 PHR	389 PHE	391 TRP	392 ASP	428 ARG	568 ASP	709 TYR	710 TRP	715 TRP	771 GLU	789 TRP		
β-amyrin	5	385 PHR	389 PHE	391 TRP	392 ASP	428 ARG	568 ASP	709 TYR	710 TRP	715 TRP	771 GLU	789 TRP		
Levulinic Acid	1	425 TRP	428 ARG	447 GLN	451 ILE	453 ASN								
Lupeol	4	384 PHE	385 PHR	387 ARG	428 ARG	441 PRO	444 PHE	563 LEU	568 ASP	709 TYR	710 TRP	771 GLU		
Thymol	2	380 PRO	389 PHE	391 TRP	392 ASP	428 ARG	453 ASN	563 LEU	710 TRP	789 TRP				
β-sitosterol	5	391 TRP	392 ASP	428 ARG	429 GLU	444 PHE	447 GLN	563 LEU	568 ASP	709 TYR	710 TRP	715 TRP	771 GLU	789 TRP

Table 5: Sequential amino acid residue binding analysis of lead compounds present in *Mega Sanjeevi Chooranam* against the target alpha-amylase with PDB - 1HNY

Compound	Interactions	Amino Acid residues												
Brucine	10	58 TRP	62 TYR	151 TYR	162 LEU	197 ASP	198 ALA	200 LYS	201 HIS	233 GLU	235 ILE	300 ASP		
β-caryophyllene	5	58 TRP	59 TRP	62 TYR	63 GLN	101 HIS	165 LEU	197 ASP	300 ASP					
β-guaiene	3	58 TRP	59 TRP	62 TYR	63 GLN	101 HIS	165 LEU	305 HIS						
Gallic acid	5	62 TYR	63 GLN	101 HIS	165 LEU	197 ASP	198 ALA	233 GLU	299 HIS	300 ASP				
Kaempferol	8	58 TRP	59 TRP	63 GLN	162 LEU	163 THR	165 LEU	195 ARG	197 ASP	198 ALA	233 GLU	299 HIS	300 ASP	
Tinosporide	9	58 TRP	62 TYR	162 LEU	165 LEU	197 ASP	198 ALA	200 LYS	201 HIS	233 GLU	235 ILE	300 ASP		
β-amyrin	8	58 TRP	59 TRP	62 TYR	63 GLN	101 HIS	162 LEU	163 THR	165 LEU	197 ASP	198 ALA	233 GLU	299 HIS	300 ASP
Levulinic Acid	4	151 TYR	198 ALA	200 LYS	201 HIS	233 GLU	235 ILE							
Lupeol	4	59 TRP	62 TYR	63 GLN	151 TYR	162 LEU	163 THR	165 LEU	201 HIS	235 ILE				
Thymol	7	58 TRP	59 TRP	62 TYR	63 GLN	101 HIS	165 LEU	195 ARG	197 ASP	233 GLU	300 ASP			
β-sitosterol	7	58 TRP	59 TRP	101 HIS	151 TYR	162 LEU	197 ASP	198 ALA	200 LYS	201 HIS	233 GLU	235 ILE	300 ASP	305 HIS

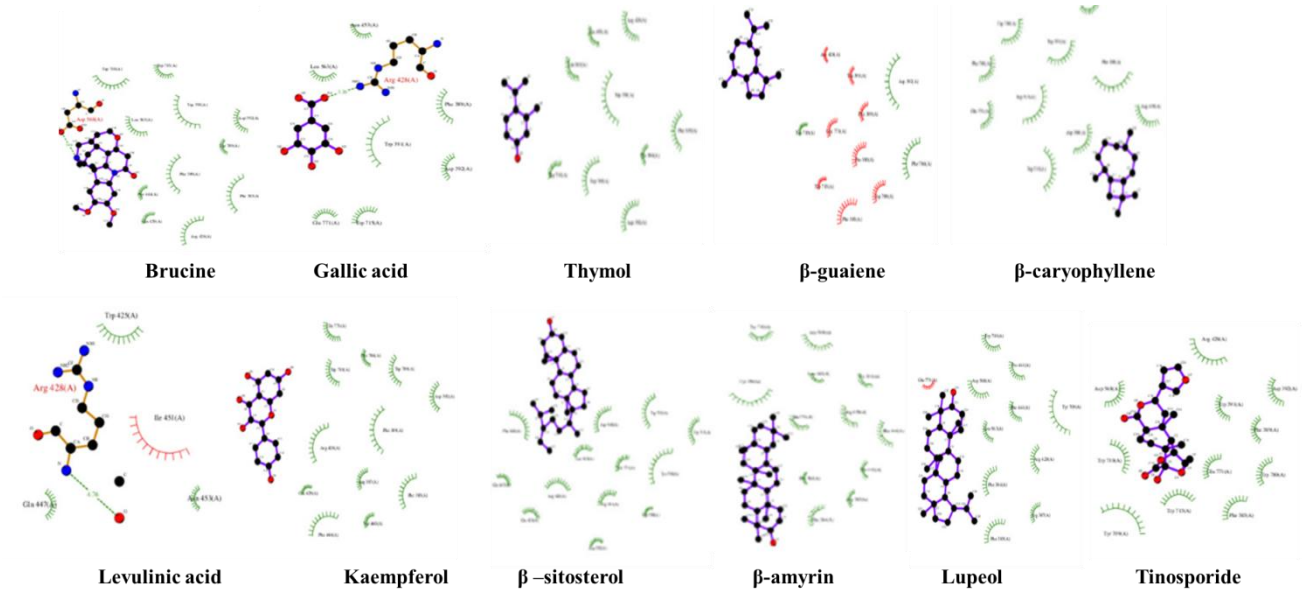

Figure 5: 2D interaction plot of lead compounds with residual amino acids of alpha-glucosidase (4J5T)

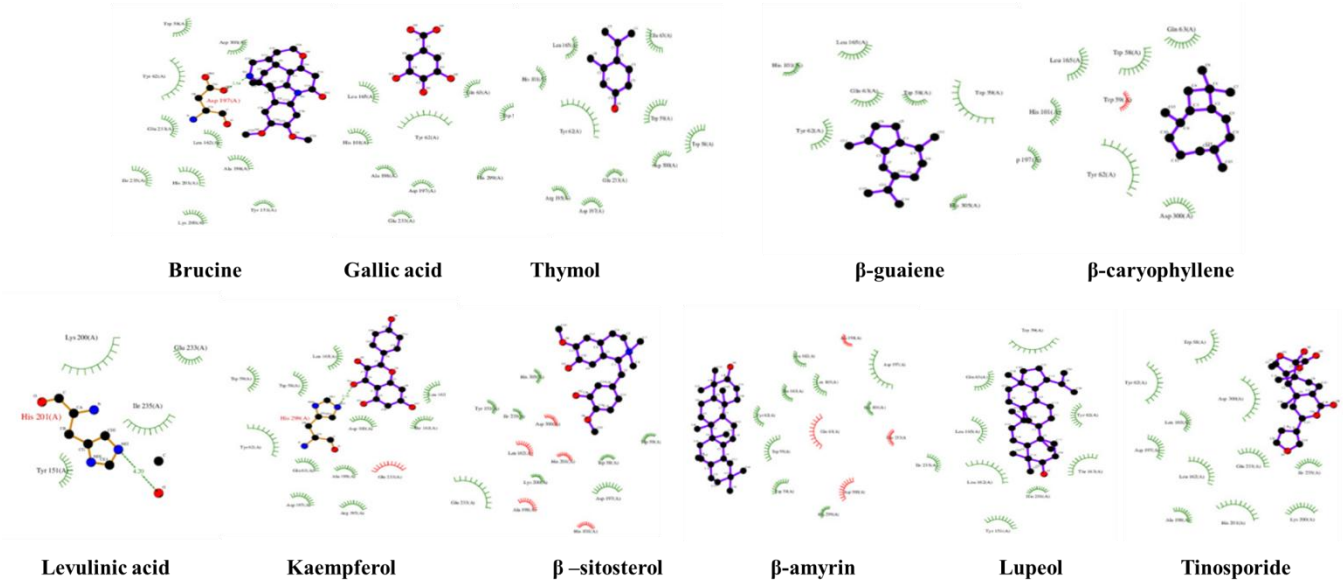

Figure 6: 2D interaction plot of lead compounds with residual amino acids of alpha-amylase (1HNY)

4.DISCUSSION

Type 2 diabetes mellitus is the most common type of diabetes, accounting for more than 90% of all DM morbidity and death [36]. This is usually characterised by pancreatic -cell dysfunction and insulin resistance, resulting in an increase in blood glucose [37]. The availability of diabetes medications such as insulin, biguanides, sulphonylureas, glucosidase inhibitors, and other types of diabetes medications has provided some respite to diabetic people. Unfortunately, some of these medications are expensive and not completely available, particularly in economically weaker zone, and are associated with adverse effects such as hypoglycemia, disorientation, lactic acidosis, and others [38]. These concerns fuelled a major push for the development of effective ethnomedicines, which are thought to be less expensive, more accessible to diabetes patients in impoverished nations, and safe [39].

Medicinal plants refer to the herbs which possesses structurally diverse chemicals that may be utilized for therapeutic purposes or which are precursors for the production of medications that are of use to humans. Because of this description, it is now possible to differentiate between plants that are considered medicinal but have not yet been subjected to an in-depth scientific study, on the one hand, and plants whose therapeutic properties and constituents have been scientifically established, on the other hand [40].

In silico approaches are used in virtual screening to find potential compounds in chemical databases [41]. High-throughput screening (HTS) is an example of an experimental technique used in biology that has a computer counterpart [42]. Large, chemically varied compound libraries are widely used in drug development for computational and biological screening [43]. Because of this, virtual screening has become more popular as a quick and

cheap way to assess several compound collections. In our present investigation the physicochemical properties of the phytotherapeutics present in the siddha *Mega sanjeevi chooranam* with respect to molecular weight, molecular formula, and H bond represent the nature of functional group that exist in the lead molecules that tend to necessitates the binding interaction.

The metabolic enzyme alpha-amylase initiates starch digestion, transforming it into maltose, elevating the postprandial hyperglycemia by digestion and absorption of simple sugar molecules produced during carbohydrate metabolism [44]. Results of molecular docking studies against the target alpha-amylase showcase that the compound brucine advocates the best binding affinity with a docking score of -9.85 kcal/mol followed by β-amyrin (-9.36 kcal/mol), beta-sitosterol (-8.37 kcal/mol), lupeol (-7.95 kcal/mol) and tinosporide (-6.50 kcal/mol) with regard to its binding free energy.

The bioactive enzyme alpha-glucosidase plays an essential part in monitoring the glucose level in the blood after a meal. Alpha-glucosidase, expressed at the brush boundaries of the small intestine, catalyzes the conversion of maltose and sucrose into glucose and fructose. Medications that tend to decrease alpha-glucosidase activity are utilized extensively in treating type II diabetes and may be predicted to have superior regulation in regulating postprandial hyperglycaemia [45]. The outcome of molecular docking studies between the phytotherapeutics present in the siddha formulation *Mega sanjeevi chooranam* against the target alpha-glucosidase emphasizes that the molecule beta-sitosterol showcases the best binding affinity of -8.98 kcal/mol followed by brucine (-8.82 kcal/mol), tinosporide (-7.64 kcal/mol), β-amyrin (-7.12 kcal/mol) and lupeol (-7.25 kcal/mol) with regard to its binding free energy.

Inhibition of carbohydrate hydrolyzing enzymes like alpha-amylase and glucosidase is considered the most effective therapeutic strategy for lowering postprandial hyperglycemia. The use of insulin secretagogues and insulin sensitizers constitutes the central line of therapy at present; nevertheless, carbohydrate-digesting enzyme inhibitors play a crucial role in regulating hyperglycemia by limiting the intestinal absorption of glucose [46]. In our present investigation, the residual interaction between the phytotherapeutics present in the siddha formulation MSC with that of the target protein alpha-amylase depicts that the compound brucine reveals ten viable interactions with the active site of the target, followed by this, other compounds such as kaempferol, tinosporide, beta-amyrin, thymol, and beta-sitosterol displays a maximum of seven to nine. Further results of the amino acid residual analysis with the target protein alpha-glucosidase signify that the compound beta-

amyrin, tinosporide, and beta-sitosterol revels five potential interactions with the active site of the target, followed by this, other compounds such as beta-caryophyllene guaiene, gallic acid, kaempferol, lupeol, and brucine reveals a maximum of three to four possible interactions with the active site of the target. From the data of the molecular docking investigation, it was concluded that the lead compounds which reveals a potential binding affinity with the target may exert promising antidiabetic property by hindering the catalytic activity of the metabolic enzymes.

5. CONCLUSION

Diabetes has become the most critical public health problem due to its chronic nature, the complications that can arise from the disease, and the financial burden that impose on the patients and their families. Phytotherapeutics provide unlimited opportunities for new drug discoveries because of the unmatched availability of chemical diversity. Molecular docking investigation paves a greater way for the researcher in discovering novel therapeutic leads in combatting dreadful disease and disorders. In the present investigation the compounds such as beta-amyrin, tinosporide, and beta-sitosterol revels potential interactions with the active site of the target alpha-glucosidase. Amino acid residual analysis with the target protein alpha-amylase depict that out of 11 phytotherapeutics present in the siddha formulation *Mega sanjeevi chooranam* the compound brucine, kaempferol, tinosporide, beta-amyrin, thymol, and beta-sitosterol reveals maximal interactions with the active site of the target. From the data's of the present investigation it was concluded that formulation like *Mega sanjeevi chooranam* may be considered as a drug of choice in management of diabetes with prior clinical validation.

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CONFLICTS OF INTEREST

Authors declare that they have no conflicts of interest.

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