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"Exploring Siddha Phytocomponents For Inhibition Of Gsk-3β In The Management Of Insulin Resistance And Type 2 Diabetes"

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Abstract
Insulin resistance, a key factor in the pathogenesis of obesity and Type 2 diabetes, arises from the impaired ability of tissues to respond to normal insulin levels, leading to reduced glucose uptake and increased hepatic glucose production. Molecular studies highlight defects in post-receptor signaling, identifying insulin signaling pathway components as promising therapeutic targets. Glycogen synthase kinase-3β (GSK-3β) has emerged as a critical regulatorof insulin resistance, influencing glycogen metabolism and insulin signaling by phosphorylating insulin receptor substrate-1 (IRS-1). Inhibition of GSK-3β has shown promise in improving insulin sensitivity and glucose regulation, making it a target for drug development.
Given the side effects of synthetic antidiabetic drugs, natural products and phytotherapy are gaining attention as safer alternatives. Siddha formulations, such as *Athiyadhi Kashayam*, contain bioactive compounds with antioxidant, anti-inflammatory, and antimicrobial properties. *In silico* studies, including molecular docking, suggest that components of *Athiyadhi Kashayam* may inhibit GSK-3β, thereby enhancing insulin receptor function and improving glucose homeostasis. This work aims to explore the potential of Siddha phytocomponents as therapeutic agents in the management of insulin resistance and Type 2 diabetes.

Keywords: Diabetes, *Athiyadhi Kashayam*, Glycogen synthase kinase - β, *In silico*

Introduction

Insulin resistance is a central factor in the development of obesity and Type 2 diabetes, the most widespread metabolic disorder globally. It is characterized by the inability of tissues to respond adequately to normal insulin levels, leading to impaired glucose uptake in peripheral tissues and increased glucose production by the liver. Research on the molecular mechanisms underlying insulin resistance has revealed that the primary defects occur in post-receptor signaling events. This suggests that components of the insulin signaling pathway downstream of the insulin receptor (IR) are promising therapeutic targets. One such target is glycogen synthase kinase-3 (GSK-3), a downstream element in the insulin signaling cascade. Among the GSK-3 isoforms, GSK-3β stands out due to its distinct role in regulating glycogen metabolism, insulin signaling, and inflammation. Inhibiting GSK-3β has shown potential in improving insulin sensitivity, reducing insulin resistance, enhancing glucose

regulation, mitigating inflammation, and preserving pancreatic β-cell function, making it an attractive target for drug development in the treatment of insulin resistance and Type 2 diabetes[1–7].

GSK-3β negatively impacts insulin signaling by phosphorylating and inactivating components of the insulin signaling pathway, such as insulin receptor substrate-1 (IRS-1). This leads to reduced insulin signaling efficiency and increased insulin resistance. Inhibitors of GSK-3β can enhance insulin receptor function and improve glucose uptake by cells, addressing the insulin resistance issue common in type 2 diabetes. By inhibiting GSK-3β, glucose utilization in peripheral tissues, such as skeletal muscle and adipose tissue, is improved. This results in better regulation of glucose homeostasis, helping to prevent excessive blood sugar levels after meals (postprandial hyperglycemia).[8]

In countries like India and China, the use of herbal medicines has been a longstanding practice, with these remedies regarded as safer and more affordable options for treating various diseases. Conducting rigorous scientific research on traditional herbal treatments can offer valuable insights and potential leads for developing alternative therapies, particularly for managing diabetes. While isolating pure compounds and evaluating their pharmacological properties is a lengthy, complex, and costly process, natural products serve as a rich source of ligands for nuclear receptors and hold promise as therapeutic agents in clinical settings. Plants, in particular, provide an abundant reservoir of biologically active molecules that have significantly influenced pharmacology[9–14].

Currently, synthetic antidiabetic drugs are associated with serious side effects, including hypoglycemic coma and hepatorenal issues. Additionally, Western diets high in saturated fat and fructose are linked to an increased risk of diseases like cancer and diabetes, whereas plant-based diets offer protective benefits. The growing concerns over the adverse effects of synthetic drugs have prompted a shift toward natural product-based therapies to reduce these risks. Phytotherapy, widely adopted due to its low cost and the accessibility of medicinal plants, is increasingly seen as a safer alternative for managing various health conditions[9,15–17].

Siddha formulations are reported to have the potential to treat diabetes. *Athiyadhi Kashayam* mentioned in Siddha literature *Mega Nivarana Bothini Ennum Neerizhivu Maruthuvam*[18] for the treatment of *Madhumegam. Athiyadhi Kashayam* made up of *Ficus racemosa, Cassia auriculata, Cassia fistula, Syzygium cumini, Salacia reticulat*a which are rich in anti-oxidant, anti-inflammatory and anti-microbial[2,3,5,19–24]. In this work, the active components of *Athiyadhi Kashayam* were docked against GSK - 3β. Through docking GSK-3β is recognised for its ability to impede the function of insulin by phosphorylating and rendering inactive insulin receptor substrate-1 (IRS-1), a pivotal mediator of insulin signalling. Thereby phytocomponents which inhibit the target enzyme Glycogen synthase kinase beta may act as a potential therapeutic agent for management of diabetes.

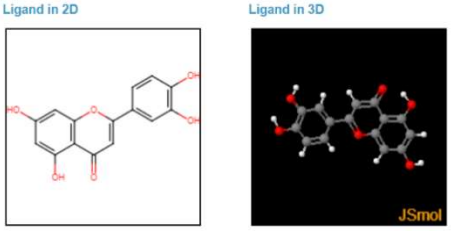
Materials and Methodology

The phytochemicals present in the *Athiyadhi Kashayam* like Lupeol from Ficus racemosa, Beta-Sitosterol from *Cassia auriculata*, Linoleic acid, Kaempferol from *Cassia fistula*, Ellagic acid from *Syzygium cumini*, Salacinol and Mangiferin from *Salacia reticulata* structures were retrieved and docked against the targetGSK-3β (Table 1). The 2D and 3D structures of these phytocomponents are given in Fig 1 and their details are given in Table 2.Certain modifications like essential hydrogen atoms, Kollman united atom type charges, and solvation parameters were made with the aid of AutoDock tools. The crystalline structure of the target protein Glycogen synthase kinase beta (GSK-3β) with PDB- 1Q3W was retrieved from the protein data bank, and a protein clean-up process was done, and essential missing hydrogen atoms were added (Fig. 2). Different orientation of the lead molecules with respect to the target protein was tested using Autodock program and the best dock posture was selected based on the interaction study analysis. Docking simulations were performed using the Lamarckian genetic algorithm (LGA) and the Solis & Wets local search method.The ligand molecules' initial position, orientation, and torsions were set randomly. All rotatable torsions were released during docking. Every docking experiment was the result of two separate runs that were intended to end after a maximum of 250000 energy assessments. 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[25,26]

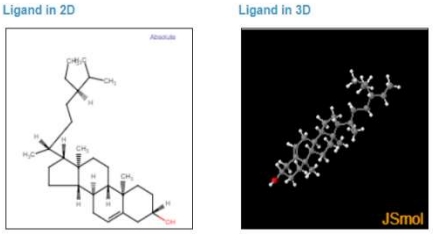
Table 1. List of Phytocomponents Selected for Docking

Herbs	Phytochemicals
Ficus racemosa	Lupeol
Cassia auriculata	Beta-Sitosterol
Cassia fustula	Linoleic acid Kaempferol
Syzygium cumini	Ellagic acid
Salacia reticulata	Salacinol Mangiferin

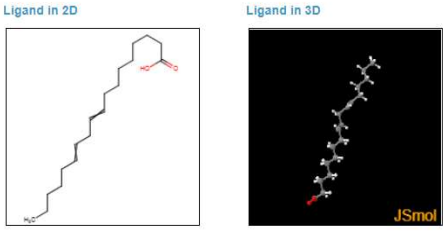
Fig. 12D and 3D Structure of Phytocomponents Lupeol



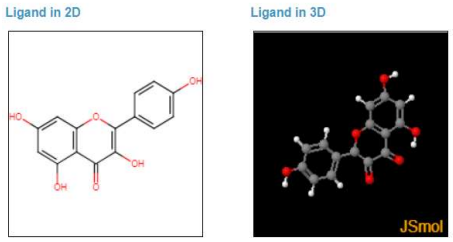
Beta-Sitosterol



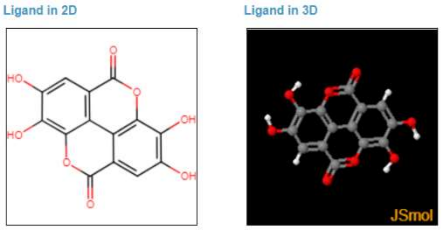
Linoleic acid



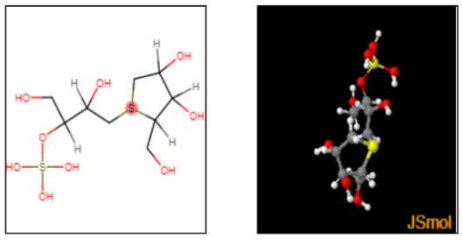
Kaempferol



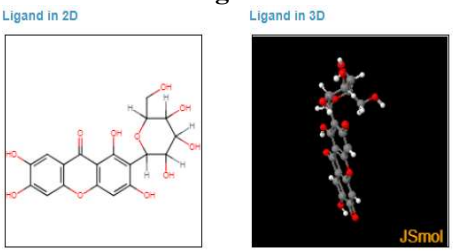
Ellagic acid



Salacinol



Mangiferin



GSK-3β Inhibitor VII

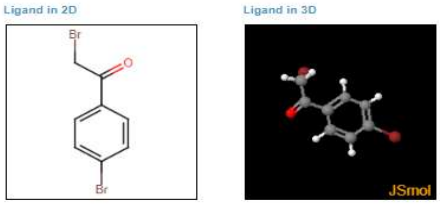
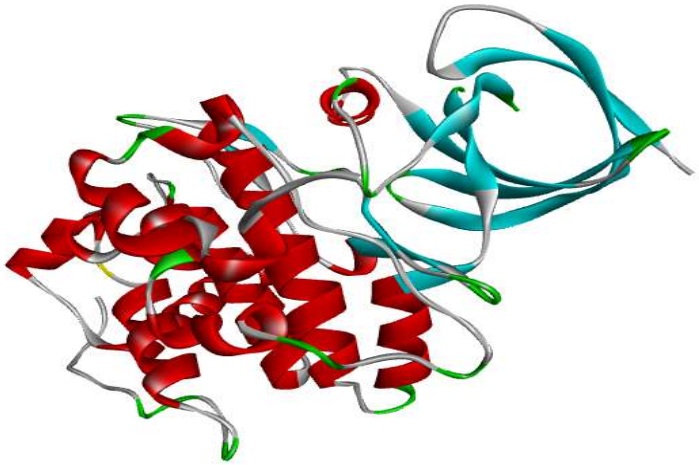


Table 2. Details about the phytocomponents

Compound	Molar weight g/mol	Molecular Formula	H Bond Donor	H Bond Acceptor	Rotatable bonds
Lupeol	426.7g/mol	$C_{30}H_{50}O$	1	1	1
Beta-Sitosterol	414.7g/mol	$C_{29}H_{50}O$	1	1	6

Linoleic acid	280.452 g/mol	$C_{18}H_{32}O_2$	1	2	14
Kaempferol	286.24 g/mol	$C_{15}H_{10}O_6$	4	6	1
Ellagic acid	302.19 g/mol	$C_{14}H_6O_8$	4	8	0
Salacinol	334.354 g/mol	$C_9H_{18}O_9S_2$	5	9	6
Mangiferin	422.3 g/mol	$C_{19}H_{18}O_{11}$	8	11	2
GSK-3β Inhibitor VII	277.94 g/mol	$C_8H_6Br_2O$	0	1	2

Fig. 2 3D- Structure of Glycogen synthase kinase beta with PDB- 1Q3W



Results and Discussion

GSK-3β is involved in the phosphorylation and inactivation of glycogen synthase, the enzyme responsible for converting glucose to glycogen. In people with insulin resistance (a hallmark of type 2 diabetes), GSK-3β activity is often increased, suppressing glycogen synthesis and contributing to hyperglycemia. By inhibiting GSK-3β, glycogen synthase activity can be restored, allowing more glucose to be stored as glycogen, thereby reducing blood glucose levels and improving insulin sensitivity.Chronic inflammation is associated with the development of insulin resistance in type 2 diabetes. GSK-3β also regulates the activity of several transcription factors involved in inflammation, such as NF-κB. Inhibition of GSK-3β can reduce inflammatory pathways, which might further help improve insulin sensitivity and reduce diabetes-associated complications.

GSK-3β inhibitors have shown potential in protecting pancreatic beta-cells responsible for producing insulin. Hyperactivation of GSK-3β can lead to beta-cell dysfunction and apoptosis, contributing to the progressive decline in insulin production seen in diabetes. By inhibiting GSK-3β, beta-cell survival may be enhanced, and their insulin-secreting function can be preserved.Due to its involvement in insulin resistance, glucose metabolism, and beta-cell survival, GSK-3β is considered a promising therapeutic target in the treatment of type 2 diabetes. Several GSK-3β inhibitors are being researched and developed as potential drugs to manage diabetes by improving glycemic control, reducing insulin resistance, and protecting beta-cell function.

Total of seven bioactive lead compounds were retrieved from the herb. Results of the present investigation signifies that the phytochemicals such as Beta-Sitosterol, Linoleic acid, Kaempferol, Ellagic acid, Salacinol and Mangiferin reveals maximum of three to four interactions with the core active amino acid residues present on the target enzyme Glycogen synthase kinase beta with the active site of the target enzyme GSK-beta in comparison with the standard GSK-3β Inhibitor VII. The total interaction energy of kaempferol, ellagic acid, salacinol were in line with the GSK - 3β Inhibitor. The electrostatic energy of Lupeol, Beta – sitosterol was

similar to that of the inhibitor value of 0.01 (Table 3). Binding of phytocomponents with the core amino acids (62 ILE ,85 LYS, Glu97, Asp133,134 TYR,135 VAL, 200 ASP) of the target by forming hydrogen bond will hinder the function of the target protein enzyme Glycogen synthase kinase beta with PDB- 1Q3W (Table 4). The docking of the phytocomponents against Glycogen synthase kinase beta with PDB- 1Q3W is represented in Fig.4. Overall, the phytocomponents of Athiyadhikashayam had synergistic effect against GSK - 3β proving its potential in treating diabetes.

Table 3. Summary of the molecular docking studies of compounds against Glycogen synthase kinase beta with PDB- 1Q3W

Compound	Est. Free Energy of Binding	Est. Inhibition Constant, Ki	Electrostatic Energy	Total Intermolec. Energy	Interact. Surface
Lupeol	-8.62 kcal/mol	482.67 nM	-0.04 kcal/mol	-9.24 kcal/mol	860.052
Beta-Sitosterol	-9.90 kcal/mol	55.57 nM	-0.09 kcal/mol	-11.14 kcal/mol	854.153
Linoleic acid	-6.02 kcal/mol	38.43 uM	-0.77 kcal/mol	-9.63 kcal/mol	737.142
Kaempferol	-6.59 kcal/mol	14.77 uM	-0.33 kcal/mol	-7.06 kcal/mol	602.042
Ellagic acid	-7.42 kcal/mol	3.61 uM	-0.50 kcal/mol	-6.74 kcal/mol	595.335
Salacinol	-7.48 kcal/mol	3.28 uM	-0.10 kcal/mol	-4.38 kcal/mol	628.149
Mangiferin	-9.66 kcal/mol	83.67 nM	-0.89 kcal/mol	-6.65 kcal/mol	756.958
GSK-3β Inhibitor VII	-4.94 kcal/mol	239.21 uM	-0.01 kcal/mol	-5.35 kcal/mol	393.987

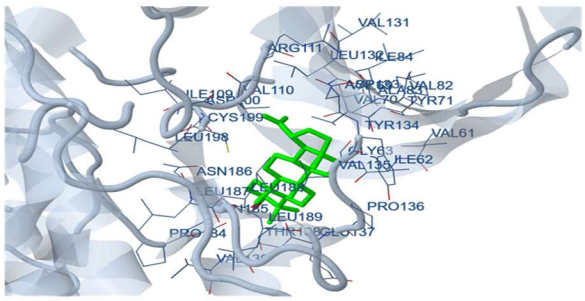
Table 4 Amino acid Residue Interaction of Lead against Glycogen synthase kinase beta with PDB-1Q3W

Compounds	Interaction	Amino acid Residues											
Lupeol	2	62	70	83	110	132	134	138	185	188	199		
		ILE	VAL	ALA	VAL	LEU	TYR	THR	GLN	LEU	CYS		
Beta-Sitosterol	4	70	83	85	97	110	132	134	138	141	188	199	200
		VAL	ALA	LYS	GLU	VAL	LEU	TYR	THR	ARG	LEU	CYS	ASP
Linoleic acid	4	83	85	97	110	132	134	138	141	188	199	200	

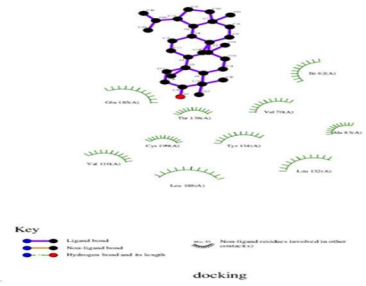
		ALA	LYS	GLU	VAL	LEU	TYR	THR	ARG	LEU	CYS	ASP	
Kaempferol	3	83	85	97	110	132	134	138	188	199			
		ALA	LYS	GLU	VAL	LEU	TYR	THR	LEU	CYS			
Ellagic acid	3	62	70	83	110	132	134	135	188				
		ILE	VAL	ALA	VAL	LEU	TYR	VAL	LEU				
Salacinol	3	62	70	134	185	186	188	199	200				
		ILE	VAL	TYR	GLN	ASN	LEU	CYS	ASP				
Mangiferin	3	70	83	110	132	134	135	186	188	200			
		VAL	ALA	VAL	LEU	TYR	VAL	ASN	LEU	ASP			
GSK-3β Inhibitor VII 4		83	85	97	101	110	132	133	134	188	199		
		ALA	LYS	GLU	MET	VAL	LEU	ASP	TYR	LEU	CYS		

Fig. 4 Docking analysis of phytocomponents a) Lupeol b) β-sitosterol c)Linoleic acid d)Kaempferol e)Ellagic acid f)Salacinol g) Mangiferin h) GSK – 3 β inhibitor against *Glycogen synthase kinase beta with PDB- 1Q3W*

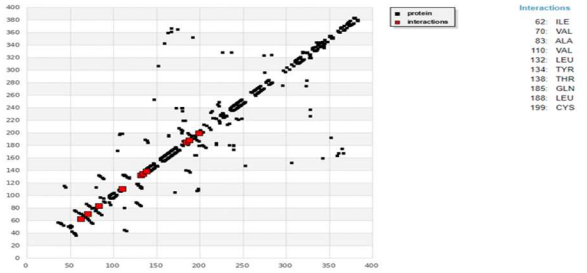
a. Lupeol



Glycogen synthase kinase beta with PDB- 1Q3W

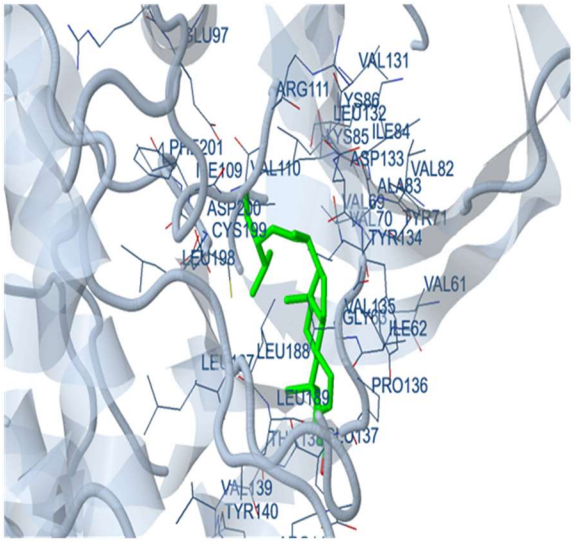


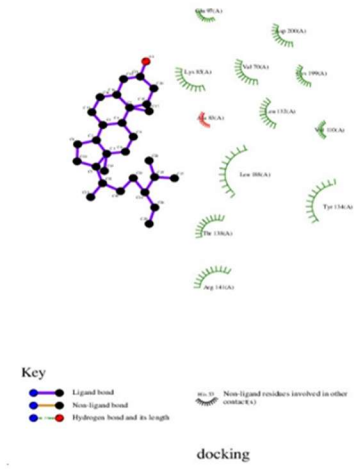
2D Interaction Plot Analysis



Hydrogen bond plotting

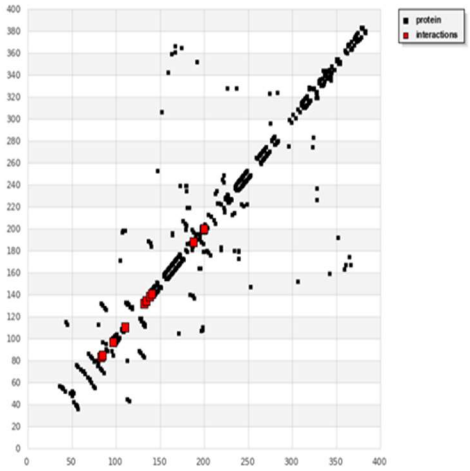
b. Beta-Sitosterol

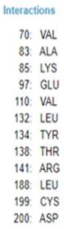




Glycogen synthase kinase beta with PDB- 1Q3W

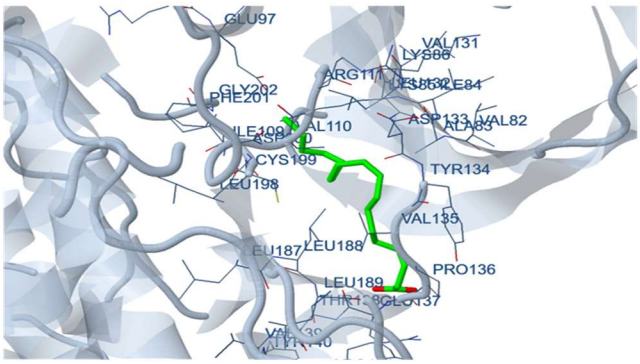
2D Interaction Plot Analysis



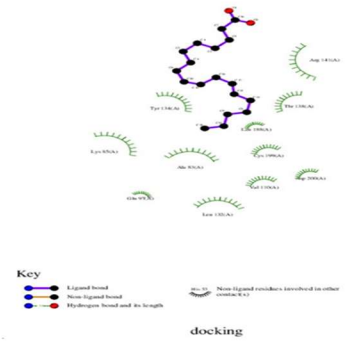


Hydrogen bond plotting

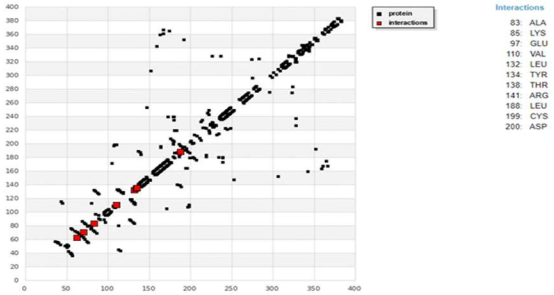
c. Linoleic acid



Glycogen synthase kinase beta with PDB- 1Q3W

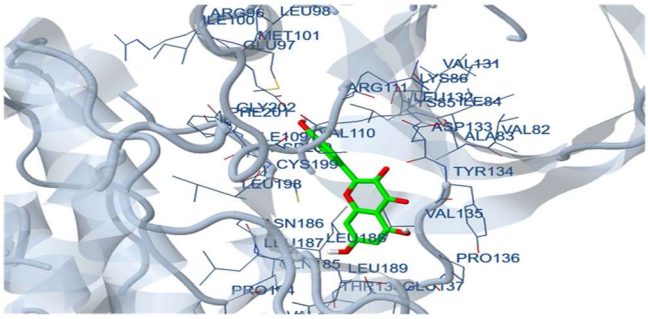


2D Interaction Plot Analysis

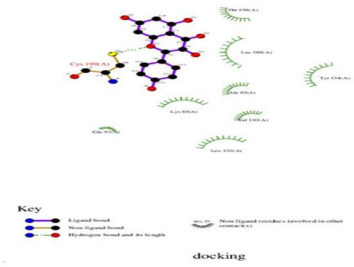


Hydrogen bond plotting

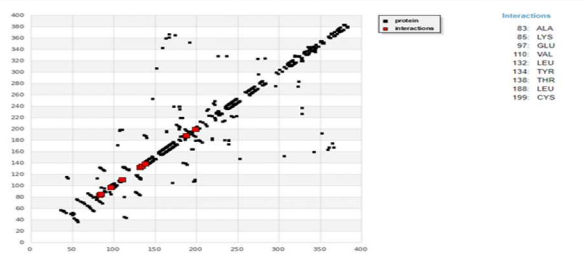
d. Kaempferol



Glycogen synthase kinase beta with PDB- 1Q3W

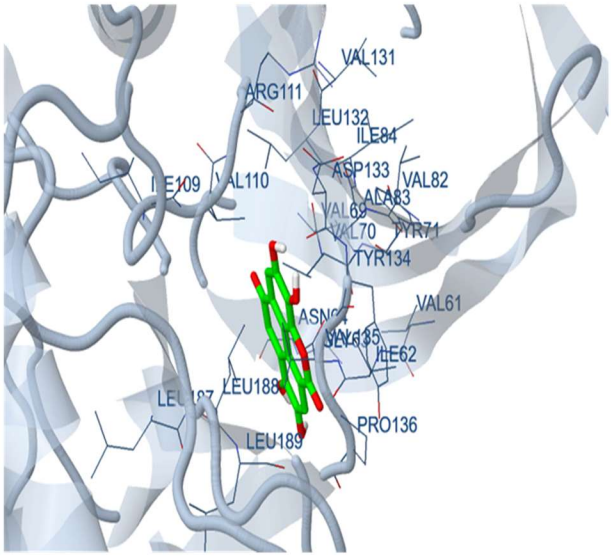


2D Interaction Plot Analysis

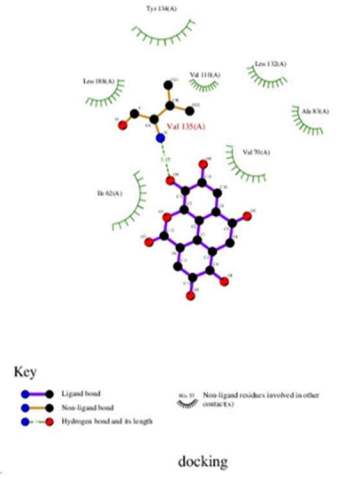


Hydrogen bond plotting

e. Ellagic acid

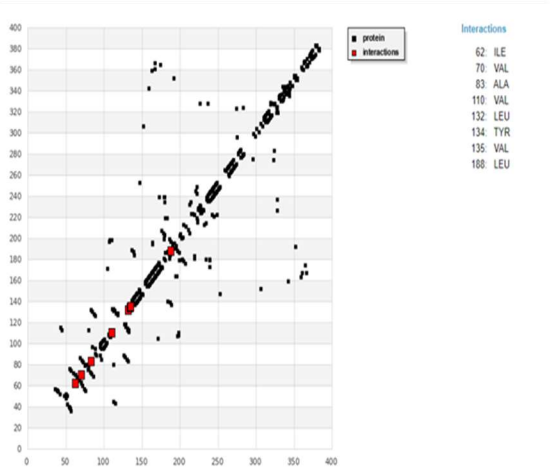


Glycogen synthase kinase beta with PDB- 1Q3W



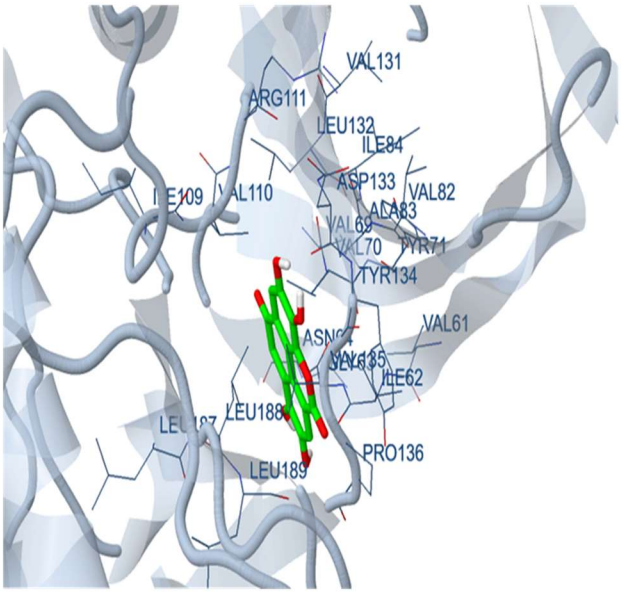
docking

2D Interaction Plot Analysis

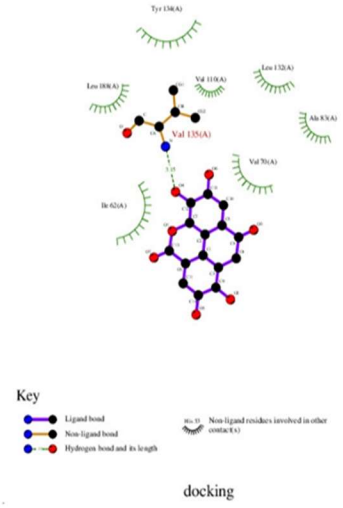


Hydrogen bond plotting

e. Ellagic acid

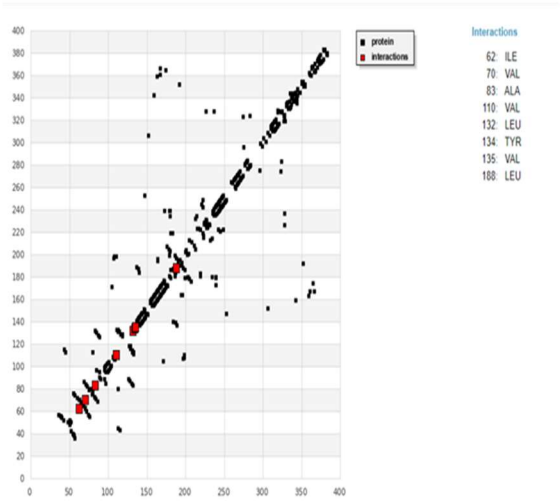


Glycogen synthase kinase beta with PDB- 1Q3W



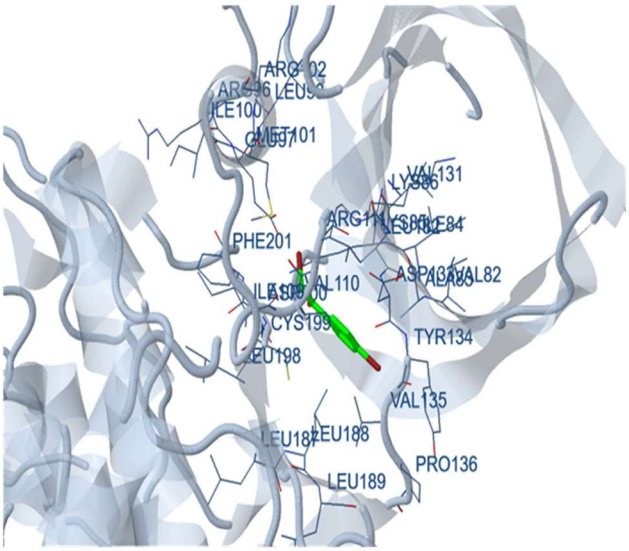
docking

2D Interaction Plot Analysis

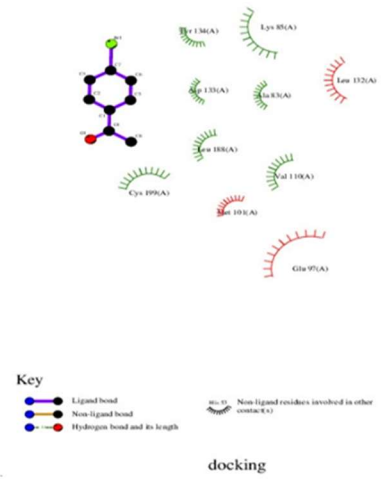


Hydrogen bond plotting

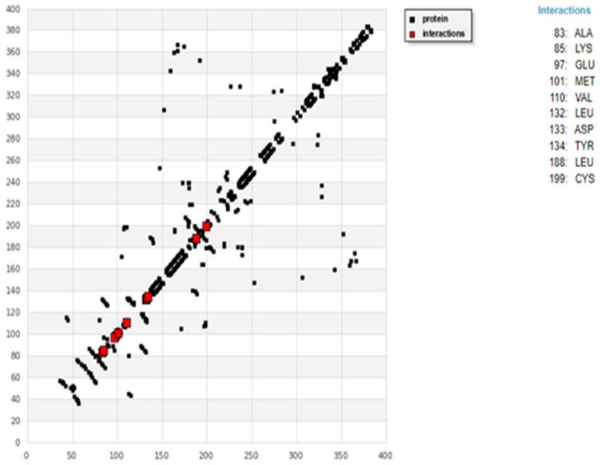
h. GSK-3β Inhibitor



Glycogen synthase kinase beta with PDB- 1Q3W

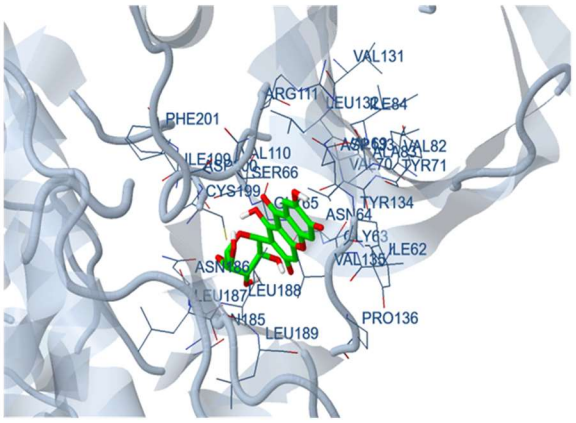


2D Interaction Plot Analysis

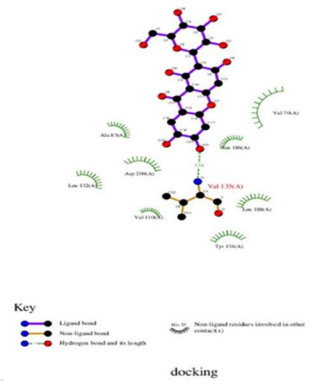


Hydrogen bond plotting

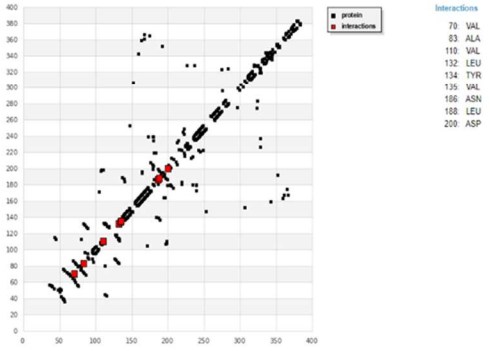
g. Mangiferin



Glycogen synthase kinase beta with PDB- 1Q3W



2D Interaction Plot Analysis



Hydrogen bond plotting

Conclusion

Based on the results of the computational analysis it was concluded that the bio-active compound's like Beta-Sitosterol, Linoleic acid, Kaempferol, Ellagic acid, Salacinol and Mangiferin reveals significant binding affinity against the target enzyme Glycogen synthase kinase beta by interacting with active amino acid present on the active site thereby it was concluded that these compounds may exerts promising anti-diabetic activity by promoting function of insulin by phosphorylating and rendering active insulin receptor substrate-1 (IRS-1). It was concluded that the phytocomponents may act as a potential therapeutic agent for the management of diabetes. It was concluded that the phytochemicals present in the herbs possess significant anti-diabetic activity.

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Conflict of Interest

There is no conflict of interest

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