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Research Article

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In Silico docking analysis of bioactive compounds from Chinese medicine *Jinqi Jiangtang* Tablet(JQJTT) using Patch Dock

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ABSTRACT

Traditional Chinese medicine has been in use till date for the treatment of various diseases including diabetes. In this study, the binding affinity of bioactive compounds derived from Chinese medicine Jinqi Jiangtang Tablet (JQJTT) against different molecular targets, were analyzed using in silico docking method. The compound that forms best protein-ligand complex is identified, as these regulatory enzymes are said to play a vital role in therapeutic action of diabetes mellitus. The bioactive compounds of JQJTT was docked with the said molecular targets using Patch Dock. The complex binding interactions of various compounds was determined by their Atomic Contact Energy (ACE). The stronger binding affinity denotes strong inhibitory action of JQJTT antidiabetic compounds against the corresponding enzymes respectively. The result of the current study clearly indicates JQJTT compounds have potent antidiabetic activity. This study elucidates the use of in-silico docking for the identification of a potent antidiabetic drug.

Keywords: *In silico*, Patch Dock, Diabetes mellitus, Traditional Chinese Medicine, *Jinqi Jiangtang* Tablet

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INTRODUCTION

Diabetes mellitus is a metabolic disorder, where humans are unable to utilize the available glucose resulting in elevation of blood glucose level beyond threshold limits. Nearly 347 million people are affected globally with diabetes mellitus and it is predicted to reach 592 million people by 2035[1, 2].It is categorized into two types, Type 1 diabetes which results due to insulin deficiency and type 2 diabetes due to insulin resistance [3]. The increased prevalence of diabetes is due to various reasons such as life style, obesity, population, ethnicity and genetic predisposition [2]. Although many synthetic oral hypoglycemic agents and insulin are available for the treatment of diabetes, they do have some major disadvantages like incompetent oral consumption of insulin, side effects and toxicity caused due to synthetic agents. Thus, search for a safe and effective agent to treat diabetes seems to be an unreached target globally requiring active research [4]. According to World Health Organization (WHO), 90% of the populations in developing countries use plants and its products as traditional medicine for health care. WHO listed out 21,000 medicinal plants and a wide variety of plant-derived bioactive compounds around the world that have established their role in treatment of diabetes mellitus[5].

In China, for more than 1000 years, traditional Chinese medicine has played an important role in treating various diseases[6]. China's FDA has approved JQJTT as a therapeutic drug for the treatment of Diabetes Miletus. JQJTT is an antidiabetic formulation of three herbal plants namely *Coptischinensis*, *Astragalus membranaceus* and *Lonicera japonica*[7-9]. The alkaloid compounds such as berberine, epiberberine, coptisine, palmatine and jatrorrhizine are

isolated from Hunglian(*Coptis chinensis*)and phenolic compounds neochlorogenic acid, chlorogenic acid from Honey suckle plant (*Lonicera japonica*)[10, 11]. The main mechanism responsible for the antidiabetic activity of JQJTT compounds is they possess potentially rich antioxidant activity and they regulate the blood sugar level by inhibiting key enzymes namely as α-glucosidase, α-amylase, aldose reductase and lipase[12-15].

Nowadays bioinformatics tools have been widely used to identify drug targets and to determine their interaction with bioactive compounds. Identification of drug targets pays an important attention and is considered as an integral part of drug designing. Docking is a computational based analysis, which calculates the possible interaction between ligand and target enzyme[16]. Patch Dock is defined as an efficient algorithm for enzyme-ligand docking [17].

The present study was focused on the interaction of JQJTT compounds, as shown in Table. 1.with target enzymes such as α-glucosidase, α-amylase, aldose reductase and lipase. Among these enzymes, α-glucosidase and α-amylase regulates the carbohydrate metabolism. While aldose reductase regulates the conversion of glucose to sorbital, an essential step in polyol pathway. Lipase is the key enzyme for absorption of fat and triglyceride digestion involving lipid metabolism. Inhibition of these four enzymes by the compounds present in medicinal plants could turn out to be a potent therapeutic agent for the treatment of diabetes mellitus. It has been reported earlier that the compounds derived from Chinese medicine JQJTT is a potential inhibitor of these enzymes[14].

In this study, *in silico* docking analysis was performed between bio active compounds of JQJTT with four different Enzymes using Patch Dock and their binding potential was determined. The main objective of docking is to identify the finest bio active compound of JQJTT using *in silico* analysis.

EXPERIMENTAL SECTION

Preparation of Receptor

The crystal 3D structure of molecular targets aldose reductase, α Glucosidase, α amylase and lipase were retrieved from Protein Data Bank through Research Collaborator for Structural Bioinformatics (RCSB) Enzyme Data Bank (http://www.rcsb.org/pdb/home/home.do).

Preparation of Ligand

The 3D structures of antidiabetic compounds namely Neochlorogenic acid (Fig. 1a), Chlorogenic acid (Fig. 1b), Rutin (Fig. 1c), Coptisine (Fig. 1d), Luteoloside (Fig. 1e), Epiberberine (Fig. 1f), Isoquercitrin (Fig. 1g), Jatrorrhizin (Fig. 1h), Berberine (Fig. 1i), Palmatine (Fig. 1j) and Isochlorogenic acid B (Fig. 1k)of *JQJTT* was collected from Pubchem(http://pubchem.ncbi.nlm.nih.gov),a compound database. The SDF compound structures from PubChem database were converted into PDB structures using the PyMOL Molecular Graphics System, Version 1.7.4 Schrödinger, LLC.

Protein Ligand Docking

Docking was performed using PatchDock algorithm in order to investigate enzyme-ligand interactions in bio active compounds of JQJTT. PatchDock Algorithm docks the ligand with the target receptor based on complementarity. The Enzyme-ligand interaction among the compounds was analyzed and determined based on Atomic Contact Energy (ACE) [17, 18].

Visualization of Binding Interaction

The PDB structures of 11 antidiabetic compounds, Enzymes and the Enzyme-ligand interaction were visualized using the PyMOL.

RESULTS AND DISCUSSION

Diabetes mellitus is one of the most serious metabolic disorders, which has a significant impact on health, quality of life, and life expectancy of patients as well as on the health care system in the modern world. It is a chronic disease characterized by a high blood glucose level [4] caused due to lack of insulin and/or impaired beta cells of the pancreas. Majority of the world population is affected by type 2 diabetes [19]. Mostly it is accompanied by characteristic long term applications. The burden of diabetes is increasing globally with 346 million people having diabetes according to WHO stats. Currently, many synthetic drugs are being used for the treatment of diabetes and its complications. Though, these drugs are efficient in treating diabetes, continuous usage results in various side

effects such as liver toxicity and intestinal disorders. This increases the necessity to develop antidiabetic medicines, Jinqi Jiangtang Tablet (JQJTT) is one such antidiabetic formula synthesized from the medicinal plants *Coptis chinensis, Astragalus membranaceus,* and *Lonicera japonica.* It was previously reported that JQJTT reduced the levels of blood glucose and elevated insulin levels in alloxan induced hyperglycemic mice [20]. In this study, molecular docking was performed to predict best antidiabetic compound synthesized by JQJJT based on their interaction with target enzymes using various *in silico* tools, as shown in Table. 2. The aim of docking is to check the transformation of one molecule's fit with other molecule at optimal level. Molecular docking is an effective approach to screen antidiabetic compounds. The main objective was to identify binding potential of known antidiabetic compounds in JQJTT with enzymes aldose reductase, α glucosidase, α amylase and lipase using PatchDock docking program.

The SDF structures of antidiabetic compounds retrieved from pubchem compound database was docked with enzyme structures taken from Protein Data Bank. Prior to docking analysis the SDF structures of JQJTT antidiabetic compounds was converted to PDB structure format using PyMol. The present study reveals the binding potential of JQJTT antidiabetic compounds against molecular targets using *in silico* docking analysis, represented as ACE, as shown in Table. 3. Higher the energy higher is the binding potential/affinity between compounds and enzymes[21].The obtained ACE was compared among different antidiabetic compounds and their corresponding molecular targets and the docked complexes that show higher affinity were identified. The results of each target is as follows.

Molecular Docking Study on α-glucosidase

The enzyme α-glucosidase functions as a significant enzyme as it cleaves complex carbohydrates into simple saccharides, thus enabling absorption of glucose in blood. The observed docking results for the molecular targets Rutin, Epiberberine, Palmatine, Neo chlorogenic acid, Berberine, Jatrorrhizin, Coptisine, Isochlorogenic acid B, Chlorogenic acid, Luteoloside and Isoquercitrin against α-glucosidase is -261.43kcal/mol, -260.72kcal/mol, -255.06kcal/mol, -255.06kcal/mol, -255.03kcal/mol, -252.08kcal/mol, -235.88kcal/mol, -228.97kcal/mol, -140.51kcal/mol, –136.91kcal/mol and -86.62kcal/mol respectively. Rutin showed highest binding affinity with the enzyme α-glucosidase comparatively.

Molecular Docking Study on α-amylase

The enzyme α-amylase is a carbohydrate-hydrolyzing Enzyme. The observed docking results for the molecular targets Rutin, Epiberberine, Palmatine, Neo chlorogenic acid, Berberine, Jatrorrhizin, Coptisine, Isochlorogenic acid B, Chlorogenic acid, Luteoloside and Isoquercitrin against α-amylase is-111.68kcal/mol, -94.08kcal/mol, -57.86kcal/mol, -36.39kcal/mol, -53.80kcal/mol, -171.45kcal/mol, -95.54kcal/mol, -89.93kcal/mol, -67.33kcal/mol, -65.20kcal/mol and -80.09kcal/mol respectively. Jatrorrhizin showed highest binding affinity with the enzymeα-amylase comparatively.

Molecular Docking Study on Aldose reductase

Aldose reductase is a key Enzyme in the polyol pathway that controls the conversion of glucose to sorbitol. The accumulation of sorbitol could activate aldose reductase, resulting in various diabetic complications[14].The observed docking results for the molecular targets Rutin, Epiberberine, Palmatine, Neo chlorogenic acid, Berberine, Jatrorrhizin, Coptisine, Isochlorogenic acid B, Chlorogenic acid, Luteoloside and Isoquercitrin against α-glucosidase is -221.27kcal/mol, -237.86kcal/mol, -283.22kcal/mol, -214.63kcal/mol, -232.36kcal/mol, -261.12kcal/mol,-235.88kcal/mol, -319.47kcal/mol,-163.26kcal/mol,-250.00kcal/mol,-273.91kcal/mol.Isochlorogenic acid B showed highest binding affinity with the enzyme aldose reductase comparatively.

Molecular Docking Study on Lipase

Lipase is a key Enzyme for the digestion of dietary triglycerides. It is well known that dietary fat is absorbed from the intestine after it has been subjected to the action of lipase [22].The observed docking results for the molecular targets Rutin, Epiberberine, Palmatine, Neo chlorogenic acid, Berberine, Jatrorrhizin, Coptisine, Isochlorogenic acid B, Chlorogenic acid, Luteoloside and Isoquercitrin against α-glucosidase is -306.59kcal/mol, -243.62kcal/mol, -295.18kcal/mol, -259.18kcal/mol, -240.99kcal/mol, -238.76kcal/mol, -277.46kcal/mol, -315.39kcal/mol,-303.65kcal/mol and -314.54kcal/mol. Isochlorogenic acid B showed highest binding affinity with the enzyme lipase comparatively.

On the whole, the antidiabetic compound Rutin showed good inhibitory activity for α-glucosidase (ACE: -261.43kcal/mol); Jatrorrhizin for α-amylase (ACE:-171.45 kcal/mol); Isochlorogenic acid B for Aldose reductase (ACE:-319.47kcal/mol) and Lipase (ACE: -315.39kcal/mol), as shown in Table. 4. The docking results reveal the efficiency of JQJTT antibiotic compounds in controlling diabetes. Through these results, it is essential to understand the important structural features enhancing inhibitory activities which might aid us further to develop augmented inhibitory compounds in future.

Table 1 The various bioactive antidiabetic compounds of JQJTT along with their Pubchem structural IDs

Compound Name	Pubchem Structure ID
Neo chlorogenic acid	5280633
Chlorogenic acid	1794427
Rutin	5280805
Coptisine	72322
Luteoloside	5280637
Epiberberine	160876
Isoquercitrin	5280804
Isochlorogenic acid B	6325421
Jatrorrhizin	72323
Berberine	2353
Palmatine	19009

Table 2 The Atomic Contact Energy (ACE) of various JQJTT antidiabetic compounds docked with enzymes forming docked complexes

Compound Name	ACE values (kcal/mol)			
	α-Glucosidase	α-amylase	Aldose reductase	Lipase
Neochlorogenic acid	-255.06	-36.39	-214.63	-259.18
Chlorogenic acid	-140.51	-67.33	-163.26	-191.33
Rutin	-261.43	-111.68	-221.27	-306.59
Coptisine	-235.88	-95.54	-235.88	-277.46
Luteoloside	-136.91	-65.20	-250.00	-303.65
Epiberberine	-260.72	-94.08	-237.86	-243.62
Isoquercitrin	-86.62	-80.09	-273.91	-314.54
Isochlorogenic acid B	-228.97	-89.93	-319.47	-315.39
Jatrorrhizin	-252.08	-171.45	-261.12	-238.76
Berberine	-255.03	-53.80	-232.36	-240.99
Palmatine	-255.06	-57.86	-283.22	-295.18

Table 3 The Atomic Contact Energy (ACE) of the best docked complexes of JQTT antidiabetic compounds and enzymes

Enzyme	Compound	ACE value (kcal/mol)
α-Glucosidase	Rutin	-261.43
α-amylase	Jatrorrhizin	-171.45
Aldose reductase	Isochlorogenic acid B	-319.47
Lipase	Isochlorogenic acid B	-315.39

Table 4 The various bioinformatics databases and tools used in this study

S.no	Tools/Data bases	Function/output
1	PatchDock	Docking analysis
2	PubChem	Compound Structure retrieval
3	PyMol	Binding Interaction visualization
4	Research Collaborator for Structural Bioinformatics	Enzyme Structure retrieval

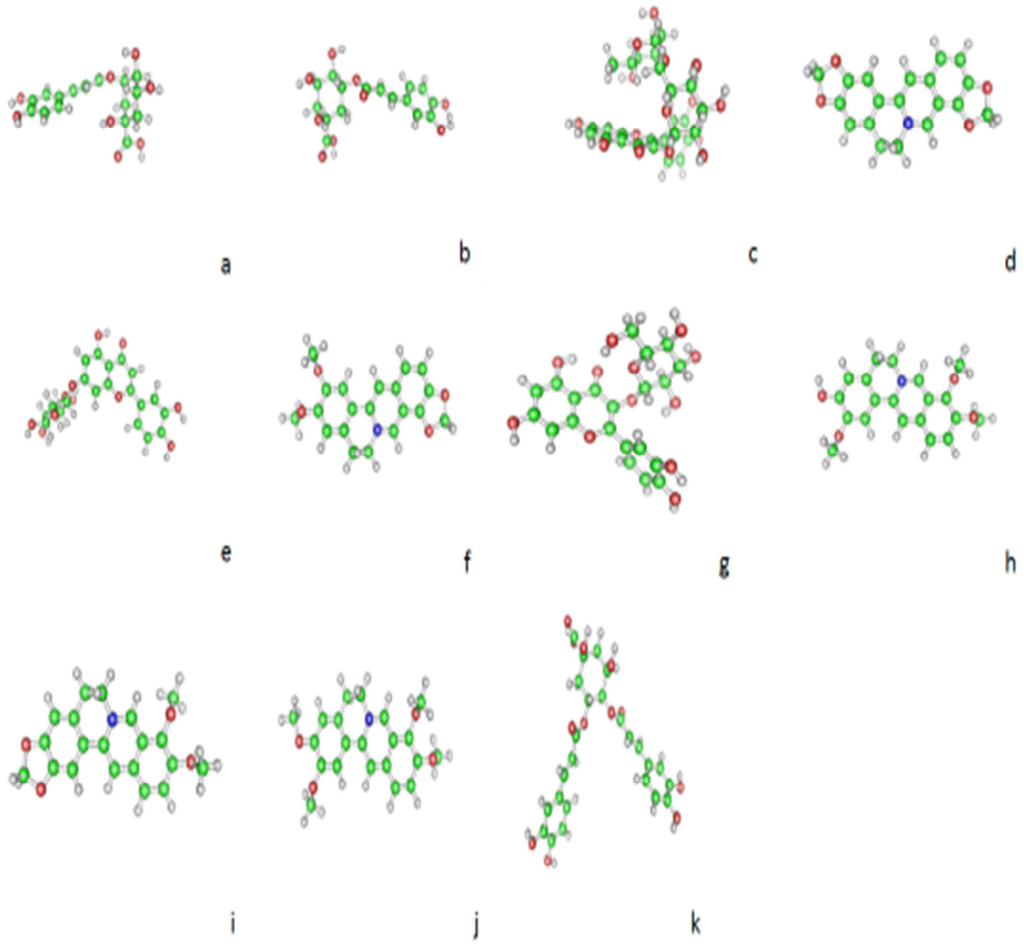

Figure 1 The ball and stick structures of various antidiabetic compounds (a) Neochlorogenic acid, (b) Chlorogenic acid, (c) Rutin, (d) Coptisine, (e) Luteoloside, (f) Epiberberine, (g) Isoquercitrin, (h) Jatrorrhizin, (i) Berberine, (j) Palmatine and (k) Isochlorogenic acid B

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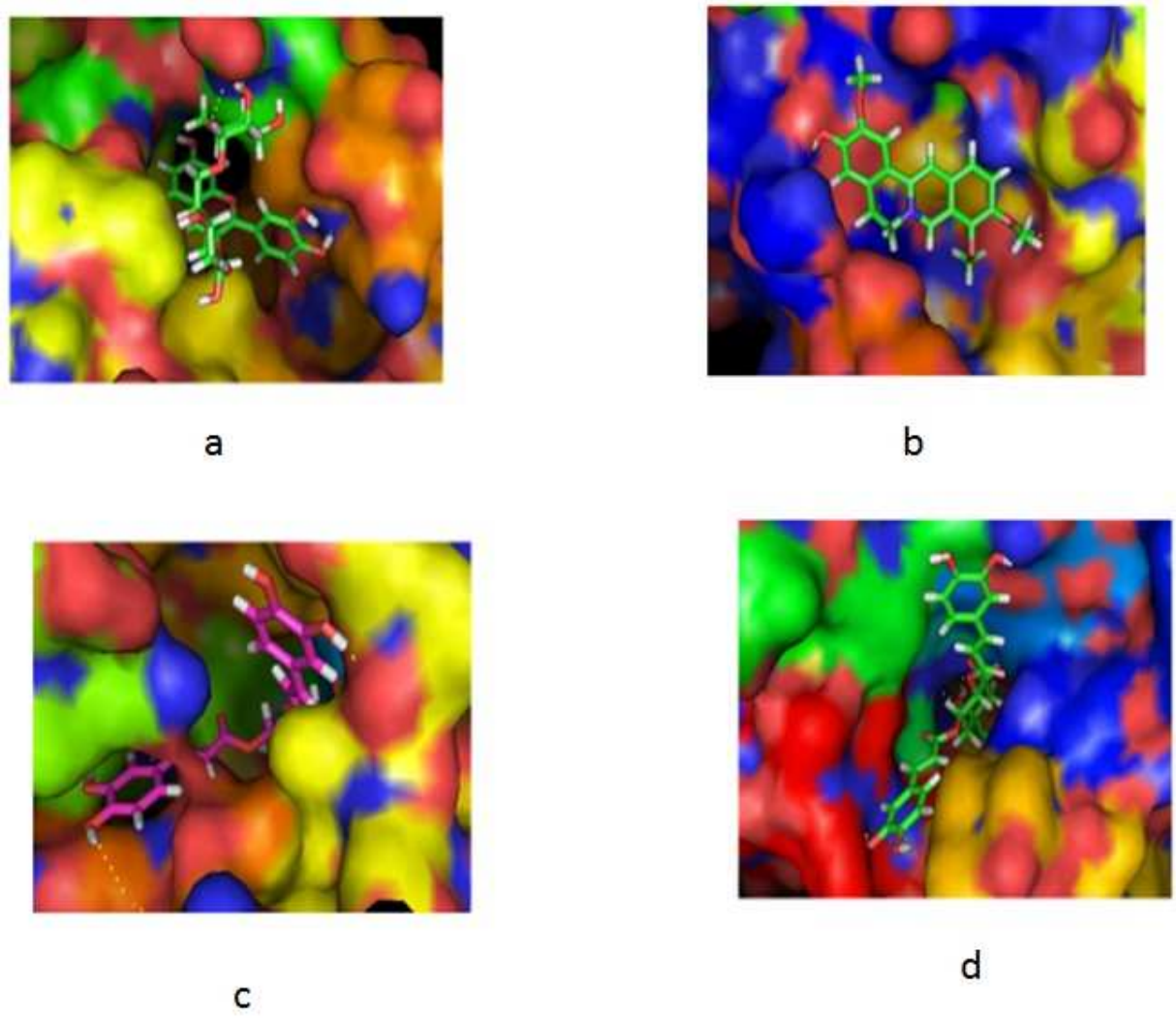

Figure 2 The structural view of the best docked antidiabetic compounds (surface view) with its related enzyme (stick view) (a) Rutin-alpha glucosidase, (b) Jatrorrhizin-alpha amylase, (c) Isochlorogenic acid B-aldose reductase and (d) Isochlorogenic acid B-Lipase complex

CONCLUSION

This study analyzed the interaction between the different antidiabetic compounds of Chinese medicine *Jinqi Jiangtang* Tablet(JQJTT)against different molecular targets computationally, which play a key role in regulating blood sugar level. Best interactions of enzyme-ligand complexes were analyzed. The purpose of this study is to identify antidiabetic compounds having highest binding affinity using *in silico* approach of molecular docking algorithm Patch Dock through which the best compound can be used in therapeutic applications of diabetes. Herewith, it has been obvious that identifying of finest compound using *in silico* analysis will help the researchers for preliminary screening and in determining the efficacy of the drug. On the whole, the antidiabetic compound Rutin showed good inhibitory activity for α-glucosidase (ACE: -261.43kcal/mol); Jatrorrhizin for α-amylase (ACE:-171.45 kcal/mol); Isochlorogenic acid B for Aldose reductase(ACE:-319.47kcal/mol) and Lipase (ACE: -315.39kcal/mol). Thereby, these three compounds can be used to design effective antidiabetic drugs in future. This type of analysis could revolutionize the research field in pinpointing the finest therapeutic compounds in short period of time.

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