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Role of two anti-cancer compounds from *Scutellaaria baicalensis*on type 2 Diabetes mellitus: An *in silico* approach

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ABSTRACT

Recently, potential anti-cancer compounds are screened for its anti-diabetic activity. Search for anti-diabetic compounds are vital among researchers, as the rise in the number of diabetic patients is increasing day today. In the present study, in silico approach is carried out to find the anti-diabetic activity of two anti-cancer compounds namely Baicalein and Wogonin from Scutellaria baicalensis. These two compounds were examined for anti-diabetic activity by docking against key molecular targets such as alpha glucosidase, alpha amylase, aldose reductase, lipase and nuclear receptors PPARα, PPARγ using PatchDock algorithm. Further, for better refinement FireDock was carried away. The complex binding interaction was defined by the Atomic Contact Energy (ACE) obtained and it was compared with the standard drugs. The effects of the current study clearly show the two bio active compounds, Baicalein and Wogonin, have potent diabetic activity. But which is moderate, when compared with standard drugs.This study illuminates the use of in silico docking for identification of potent anti-diabetic compounds in a short period.

Keywords: *In Silico*, *Scutellaaria baicalensis*, Baicalein, Wogonin, diabetes mellitus, anti-cancer compounds, PatchDock, FireDock.

INTRODUCTION

Diabetes mellitus is a metabolic disorder affects carbohydrates, fats and protein metabolism. Diabetes mellitus causes irregularity in carbohydrate metabolism, which leads to insulin resistance [2]. The prevalence of this disorder affects the majority of people both in developed and developing countries. Whereas, in most developed countries, diabetes mellitus is the fourth major cause of death and it is estimated to increase from 171 million in 2000 to 366 million by 2030 [3, 4].

Diabetes mellitus was typified by chronic hyperglycemia, ensuing as of defects in insulin secretion or action, increased in thirst and urinary output [5].There are different forms of diabetes namely spontaneous diabetes and malnutrition-related diabetes. Malnutrition-related diabetes is the major form in Asia and Africa. Whereas, spontaneous diabetes is of two types, Type 1 and Type 2 diabetes. The Type 1 diabetes [Insulin-dependent diabetes mellitus] is inborn and typically occurs early in life, where very less insulin is secreted or not all insulin is produced. The Type 2 diabetes [non-insulin dependent diabetes mellitus] is mostly occurring in later stages of life[6]. That is people more than 30 years of age are at risk Moreover, 90% of the diabetes in developed and developing countries are type-2 diabetes[7].

Today, medicinal Plants have been a dependable source of drugs. Currently, predominantly available drugs in the marketplace have been directly or indirectly resulted from plants. Since, many years in India, indigenous remedies have been used for the treatment of diabetes mellitus [8].The ethno botanical information reports that about 800 medicinal plants may have an anti-diabetic activity[9]. Medicinal plants have been used as whole plant or parts of plants for treatment. The Plant parts contain bioactive compounds such as alkaloids, flavonoids, glycosides, steroids, carbohydrates, glycopeptides, terpenoids, amino acids etc. These bioactive compounds are responsible for anti-diabetic activity[10]. Even though, the herbal drugs contain anti-diabetic activity they have not commercially formulated as modern medicines [11].

Recently, many studies have been carried out to find the association between the cancer and diabetes. Despite many advances and therapeutics were available for treating diabetes mellitus, the side effects associated with the current treatment concerns the patients over the years [12]. Traditional Chinese medicines (TCMs) are widely studies to discover wide range of medicinal products. Even though, many drugs were discovered and it was in practice of treating diabetic patients. Discovering the potentiality of TCM compounds in treatment of the diabetes mellitus will be useful in establishing the TCM importance to the modern world [13]. Among, the TCMs, *Scutellaria baicalensis Gerogi* (Huang Qin) is an important plant in producing phytochemicals and compounds, which is used for treating various diseases for years, particularly liver and kidney disorders[14].

The plant Huang Qin was potent inhibitory of Alpha glucosidase enzyme, a key target in type 2 diabetes mellitus[15]. The important plant compounds of Huang Qin, namely Baicalein and Wogonin, is shown Fig. 1,are two flavonoids and they play a critical role in treating various types of cancers by arresting its mechanisms[16].Azad et al. in 2014, found that Baicalein, a flavonoid is better in treating diabetes mellitus type 2 in the type 2 infected Wistar rats, when compared with standard drug rosiglitazone, without any side effects. The plant compound also restored the renal function to normal. Whereas, the drug rosiglitazone lead to liver toxicity[17].

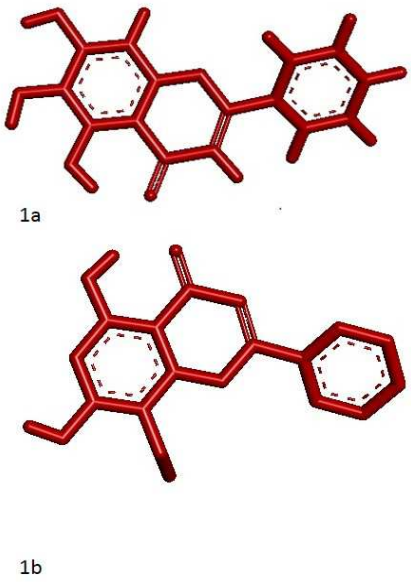

Fig. 1The structures of two anticancer compounds. (a) Baicalein, (b) Wogonin

The present study was focused to find out the interaction of two anti-cancer compounds the with target enzymes such as α-glucosidase, α-amylase, aldose reductase and lipase, shown in Fig 2. And also with the nuclear targets such as peroxisome proliferator-activated receptor alpha (PPARα) and peroxisome proliferator-activated receptor gamma (PPARγ), shown in Fig 3, is a key nuclear target receptor. The enzyme α-glucosidase and α-amylase majorly involved in regulating the carbohydrate metabolism. Aldose reductase involved in regulating an essential step in polyol pathway (conversion of glucose to sorbital). Lipase is the key enzyme involved in regulating lipid metabolism. Lipase functions in absorption of fat and triglyceride digestion. Inhibition of these four enzymes and

nuclear receptors by the compounds present in medicinal plants could turn out to be a potent therapeutic agent for the treatment of diabetes mellitus[18-22].

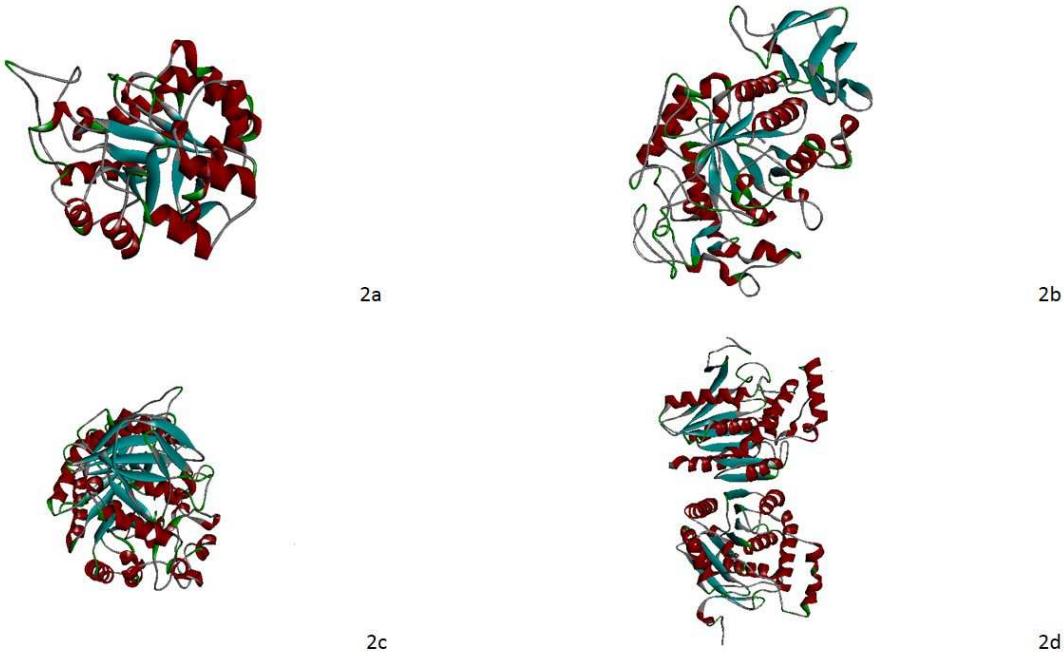

Fig.2 The structures of target enzymes. (a)Aldose reductase, (b)Alpha amylase, (c)Alpha Glucosidase, (d)Lipase

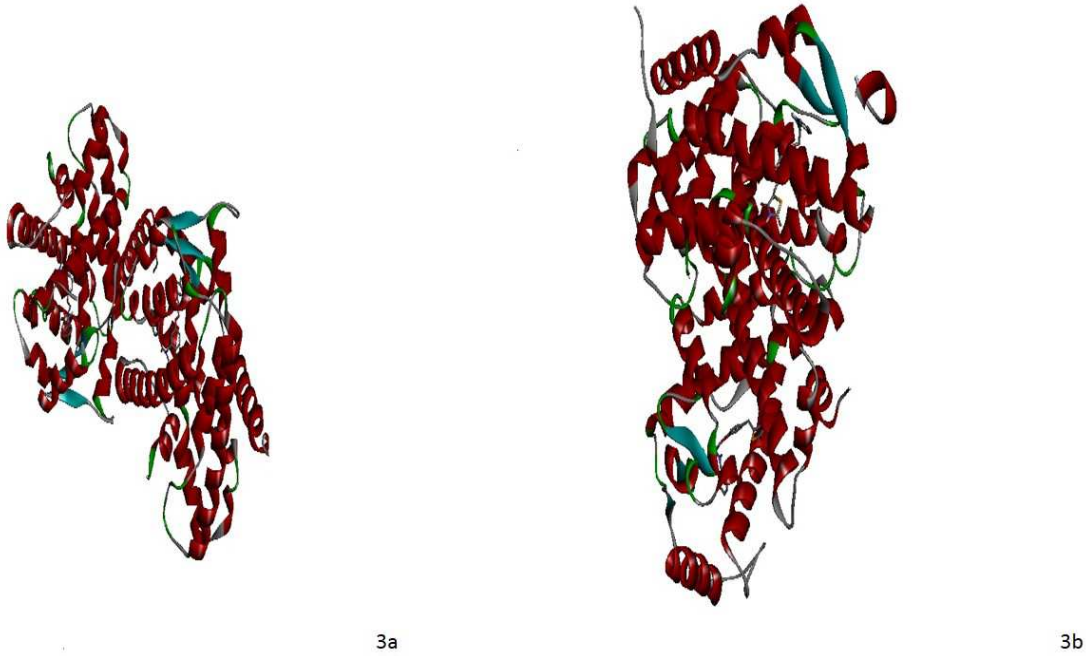

Fig. 3 The structure of nuclear receptors (a) PPAR*α*, (b) PPAR*γ*

Hence, present study is an attempt to know the potentiality of two TCM compounds namely Baicalein and Wogonin, through *in silico* approach. In which, docking a computational based analysis is performed, which calculates the possible interaction between ligand and target enzyme using PatchDock, an efficient algorithm for enzyme-ligand docking [23]and FireDock was carried out for better refinement[24, 25].

MATERIALS AND METHODS

Preparation of Receptor

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

Preparation of Ligand

The 3D structures of anti-cancer compounds namely wogonin, baicalein, was shown inTable 1.

Table 1 The bioactive anticancer compounds of *Scutellaaria baicalensis* along with their Pubchem structural IDs

Compound Name	Pubchem Structure ID
Baicalein	5281605
Wogonin	5281703

The standard drugs such as Epalrestat, Acorbose, and Orlistat, as shown in Fig. 4,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. Further, the ligands were analyzed for Lipinski of 5, using Lipinski Filter, a free web server, IIT Delhi, India. (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp) [26, 27]

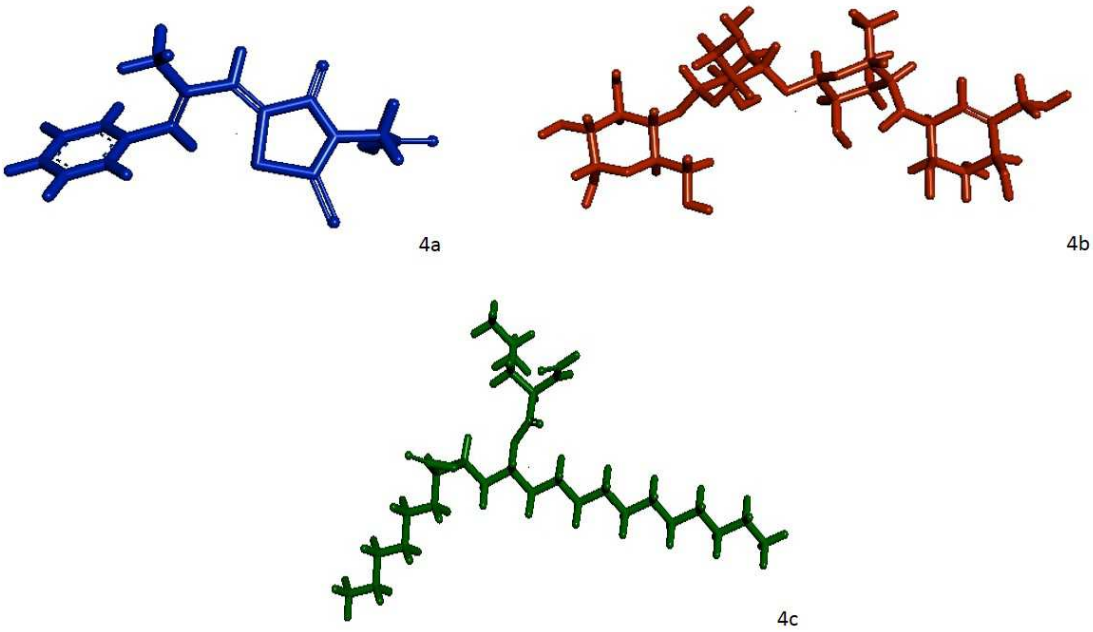

Fig. 4 The structure of standard drugs. (a) Epalrestat, (b) Acorbose, (c) Orlistat

Protein Ligand Docking

Docking was performed using PatchDock in order to investigate enzyme-ligand interactions in bio active compounds. PatchDockAlgorithm docks the ligand with the target receptor based on complementarity ACE [23, 28]. For better refinement, FireDock was carried out. The Enzyme-ligand interaction among the compounds was analyzed and determined based on ACE.

Visualization of Binding Interaction

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

RESULTS AND DISCUSSION

The results of each target are as follows.

Molecular Docking Study on α-glucosidase

The enzyme α-glucosidase, regulates the blood glucose by converting polysaccharides into monosaccharaides, which increases the absorption of glucose in blood. The observed docking results for the molecular targets. In this study, the anti-cancer compound Baicalein showed ACE value of -54.51 kcal/mol using PatchDock, the bioactive compound showed comparativelyless binding affinity with the enzyme α-glucosidase than Acorbose(-165.46 kcal/mol), a standard drug. Whereas, FireDock results shows the ACE value of Baicalein -9.76, which is comparatively nearer to the ACE value of standard drug Acorbose (-11.82 Kcal/mol).

Similarly, Wogonin showed ACE value of -56.67 kcal/mol using PatchDock, showed comparatively less binding affinity with the enzyme α-glucosidase than Acorbose(-165.46 kcal/mol).Whereas, FireDock results of wogonin -14.74 Kcal/mol, which is comparatively greater than the ACE value of standard drug Acorbose (-11.82 Kcal/mol).

Molecular Docking Study on α-amylase

The enzyme α-amylase is a carbohydrate-hydrolyzing enzyme. The anti-cancer compound Baicalein showed ACE value of -33.55 kcal/mol using PatchDock, showed very less binding affinity with the enzyme α-amylase than Acorbose(-165.46 kcal/mol), a standard drug. Whereas, FireDockresults shows the ACE value of Baicalein -2.21, which is comparatively very less to the ACE value of standard drug Acorbose (-7.58 Kcal/mol).

Wogonin showed ACE value of -49.15 kcal/mol using PatchDock, When it was compared with the standard commercial drug Acorbose, showed comparatively less binding affinity with the enzyme α-amylase than Acorbose(-180.7 kcal/mol). Whereas, FireDock results shows the ACE value of wogonin -9.89, which is comparatively greater than the ACE value of standard drug Acorbose (-7.58 Kcal/mol).

Molecular Docking Study on Aldose reductase

Aldose reductase involves in the polyol pathway (conversion of glucose to sorbitol). Impairment leads to the accumulation of sorbitol that could activate aldose reductase, resulting in various diabetic complications [18]. The bioactive compound Baicalein showed ACE value of-181.73 kcal/mol using PatchDock, When it was compared with the standard commercial drug Epalrestat, showed comparatively less binding affinity with the enzyme aldose reductase than Epalrestat(-270.07 kcal/mol). Whereas, FireDockresults shows the ACE value of Baicalein -11.64 Kcal/mol, which is comparatively nearer to the ACE value of standard drug Epalrestat (-15.51 Kcal/mol).

Wogonin showed ACE value of -206.67 kcal/mol using PatchDock, When it was compared with the standard commercial drug Epalrestat, showed comparatively nearer binding affinity with the enzyme aldose reductase than Epalrestat(-270.07 kcal/mol). Whereas, FireDockresults shows the ACE value of Wogonin -12.31, which is comparatively nearer than the ACE value of standard drug Epalrestat (-15.51 Kcal/mol).

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 anti-cancer compound Baicalein showed ACE value of -218.47 kcal/mol using PatchDock, When it was compared with the standard commercial drug Orlistat, showed comparatively less binding affinity with the enzyme lipase than Orlistat(-409.08 kcal/mol). Whereas, FireDockresults shows the ACE value of Baicalein -13.47 Kcal/mol, which is comparatively nearer to the ACE value of standard drug Orlistat (-14.29 Kcal/mol).

Wogonin showed ACE value of -229.77 kcal/mol using PatchDock, When it was compared with the standard commercial drug Orlistat, showed comparatively less binding affinity with the enzyme lipase than Orlistat(-409.08 kcal/mol). Whereas, FireDockresults shows the ACE value of Wogonin -13.76, which is comparatively similar than the ACE value of standard drug Orlistat(-14.29 Kcal/mol).

Molecular docking with PPARα and PPARγ

Both Baicalein and Wogonin have strong binding affinity with the nuclear receptors PPARα and PPARγ, as shown in Table. 7.

Diabetes mellitus is a metabolic disorder, which shows major impact on health of the diabetic patients [29]. Diabetes mellitus was caused due to lack of insulin and/or impaired beta cells of the pancreas. Whereas, majority of the world population is affected by this disorder [30]. This disorder is increasing globally with high mortality rates, nearly 346 million people having diabetes according to WHO. Currently, many treatment methods are being in use and though these drugs are efficient in treating diabetes, these drugs results in various side effects. This increases the necessity to develop anti-diabetic medicines without side effects.

The present manuscript discusses about the anti-diabetic effects of Wogonin and Baicalein. Since many *in silico* approaches are being carried out to screen the anti-diabetic activity. It is well known that the bioactive compounds are especially effective in the treatment of diabetes.Molecular docking studies has been considered the best method to find the efficacy of drug in efficient way and it is cost less [31]. Both Baicalein and Wogonin were proven to be are be likely to bind to biological molecule bovine serum albumin. The binding is established by van der walls forces and hydrogen bonds [32, 33]. In an *in silico* experiment, Baicalein is proven to be effective against Parkinson's disease targets. This is an example that Baicalein molecule is active molecule for docking [34]. Binding efficacy of Wogonin is proven to be effective against human serum albumin, gamma globulin[35-37]. The flavonoids have excellent binding interactions with aldose reductase, α-amylase and α–glucosidase enzymes. The *in silico* studies in contradiction of these enzymesis useful to develop potential chemical entities for the prevention and treatment of diabetes.The docking calculations showed that van der Waals, electrostatic, and desolvation energies play a key role in binding. These factors are considered in designing new inhibitors for α-amylase and α-glucosidase[38, 39].Many studies have been carried out to find the efficacy of known diabetic compounds. Even then, finding the new anti-diabetic compounds was need of the hour. But, synthesizing a new compound is time talking. Alternatively, a new approach has been adopted in this study, instead of synthesizing new compounds, anticancer compounds have been screened through *in silico* docking methods in order to find out their potentiality on diabetes mellitus. The validated compounds, which are proven to be active, can be further analyzed in animal models.

In order to prove this hypothesis, the two anti-cancer compounds from the TCM plant *Scutellaaria baicalensis* were selected in this study. Molecular docking was performed to predict anti-diabetic potential. The potential is evaluated based on bioactive compounds interaction with target enzymes using various *in silico* tools. Previously, a study have reported that compounds from *Scutellaaria baicalensis* has anti-oxidant and alpha glucosidase inhibitory activity in *in vitro* analysis[15]. So far, important compounds like Wogonin and Baicalein have not been evaluated for its anti-diabetic activity in detail. Hence, in this study,the anti-cancer compounds are docked with target enzymes such as aldose reductase, α glucosidase, α amylase, lipase and nuclear receptors PPARα and PPARγ using PatchDock docking program and FireDock was carried out for better refinement.

In detail, prior to docking analysis the SDF structures of anti-cancer compounds, namely, Baicalein and Wogonin was converted to PDB structure format using PyMol. Further, the compounds were analyzed to check for Lipinski s rule of 5 using Lipinski Filter and found that two compounds follow the pattern. Finally, the docking scores were obtained and it is represented as ACE, as shown in Fig 5, 6, 7 and 8.The obtained ACE was compared with standard anti-diabetic drugs as shown in Tables 2.3.4.5 and 6.Whereas, higher the energy, higher is the binding affinity between compounds and enzymes [40].

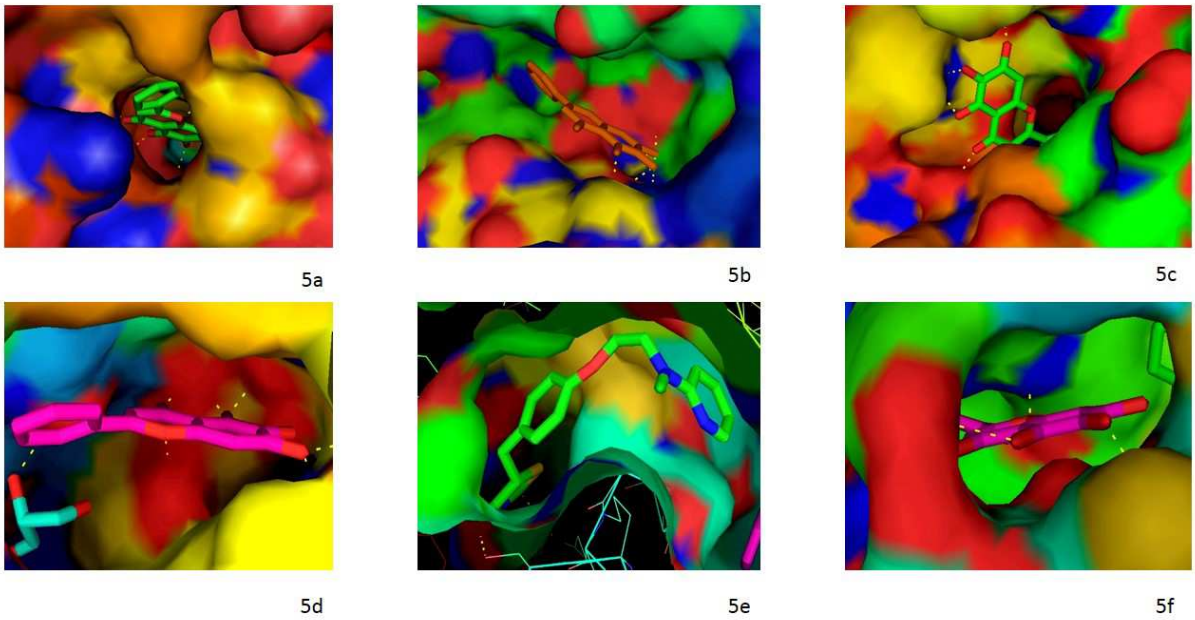

Fig. 5 The structural view of the best docked compound (surface view) of baichalein with its related enzyme (stick view) using PatchDock. (a)Aldosereductase-baichalein, (b)Alphaamylase-baichalein, (c)Alphaglucosidase-baicalein, (d)Lipase-baicalein, (e)PPRAα-baicalein, (f)PPARγ-baicalein

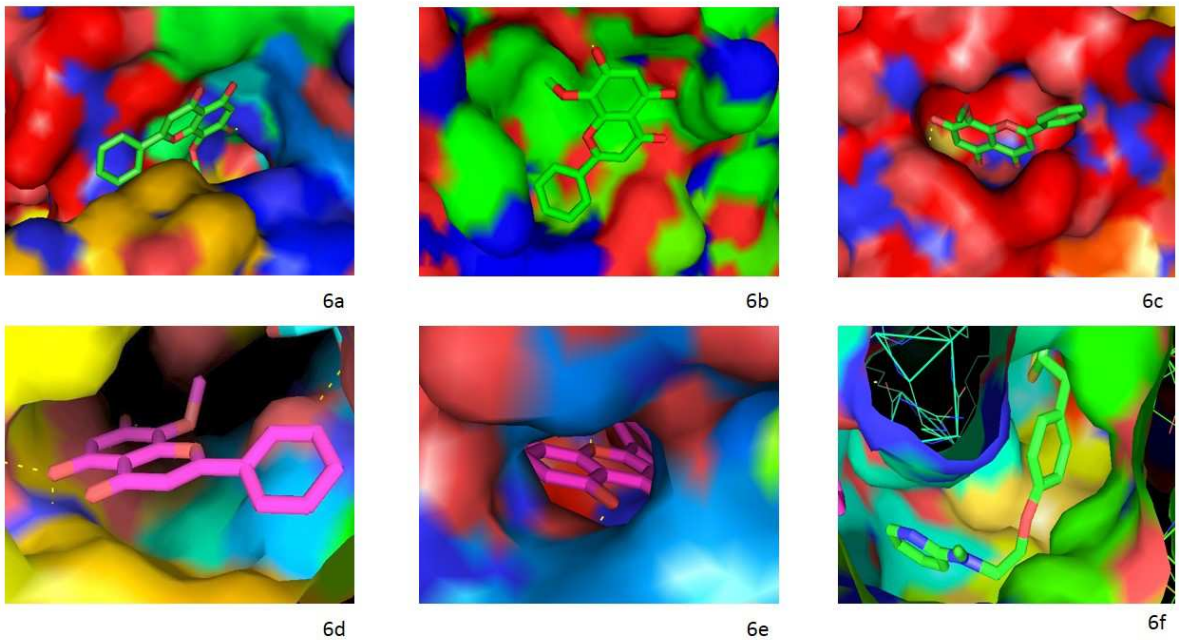

Fig. 6 The structural view of the best docked compound (surface view) of wogolin with its related enzyme (stick view) using PatchDock.(a)Aldose reductase-wogolin, (b)Alphaamylase-wogolin, (c)Alphaglucosidase-wogonin, (d)Lipase-wogonin, (e)PPARα-wogonin, (f)PPARγ-wogolin

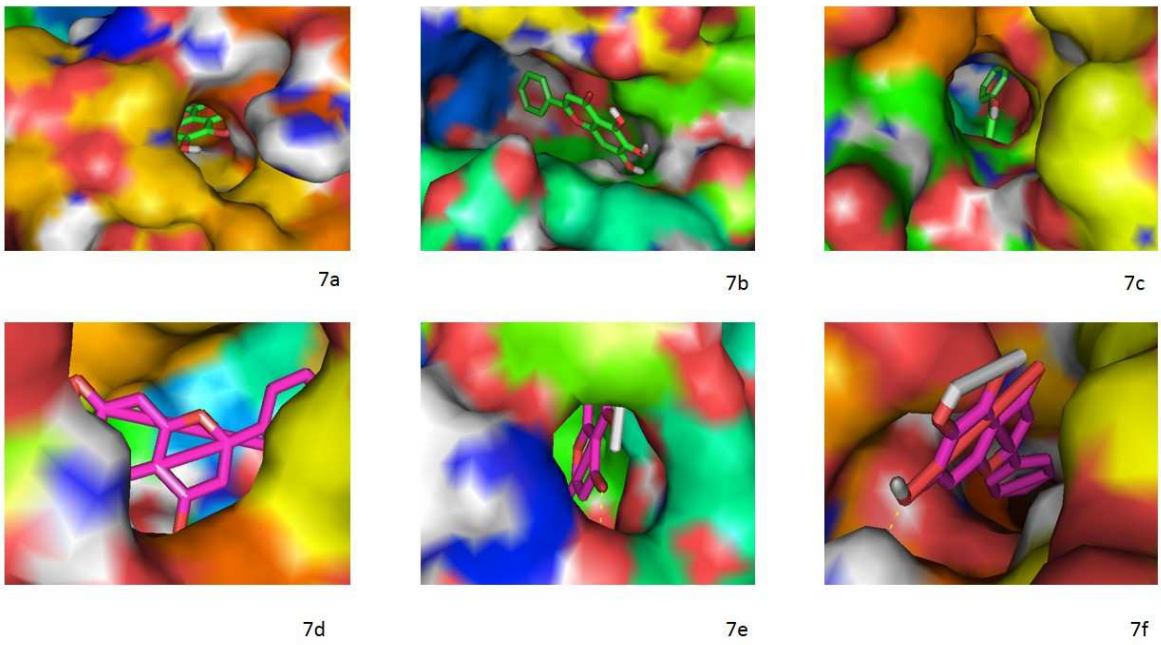

Fig. 7 The structural view of the best docked compound (surface view) of baichalein with its related enzyme (stick view) using FireDock. (a)Aldosereductase-baichalein, (b)Alphaamylase-baichalein, (c)Alphaglucosidase-baicalein, (d)Lipase-baicalein, (e)PPRAα-baicalein, (f)PPARγ-baicalein

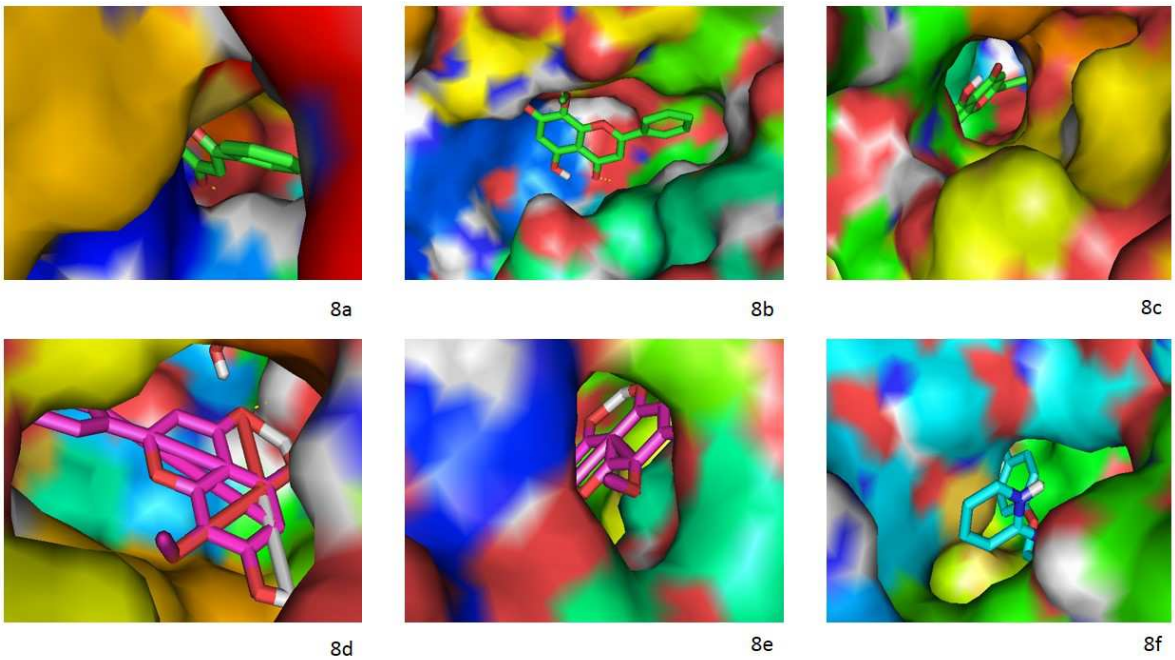

Fig. 8 The structural view of the best docked compound (surface view) of wogolin with its related enzyme (stick view) using FireDock. (a)Aldose reductase-wogolin, (b)Alphaamylase-wogolin, (c) Alphaglucosidase-wogonin, (d) Lipase-wogonin, (e) PPARα-wogonin, (f)PPARγ-wogolin

Table 2 The Atomic Contact Energy (ACE) of bioactive anticancer compound baicalein of *Scutellaaria baicalensis* docked with enzymes forming docked complexes and enzymes compared with standard drugs using PatchDock

Enzyme	Compound	ACE value (kcal/mol)	Standard Drug	ACE value (kcal/mol)
α-Glucosidase	Baicalein	-54.51	Acorbose	-165.46
α-amylase	Baicalein	-33.55	Acorbose	-180.7
Aldose reductase	Baicalein	-181.73	Epalrestat	-270.07
Lipase	Baicalein	-218.47	Orlistat	-409.08

Table 3 The Atomic Contact Energy (ACE) of bioactive anticancer compound wogonin of *Scutellaaria baicalensis* docked with enzymes forming docked complexes and enzymes compared with standard drugs using PatchDock

Enzyme	Compound	ACE value (kcal/mol)	Standard Drug	ACE value (kcal/mol)
α-Glucosidase	Wogonin	-56.67	Acorbose	-165.46
α-amylase	Wogonin	-49.15	Acorbose	-180.7
Aldose reductase	Wogonin	-206.67	Epalrestat	-270.07
Lipase	Wogonin	-229.77	Orlistat	-409.08

Table 4 The Atomic Contact Energy (ACE) of bioactive anticancer compound baicalein of *Scutellaaria baicalensis* docked with enzymes forming docked complexes and enzymes compared with standard drugs using FireDock

Enzyme	Compound	ACE value (kcal/mol)	Standard Drug	ACE value (kcal/mol)
α-Glucosidase	Baicalein	-9.76	Acorbose	-11.82
α-amylase	Baicalein	-2.21	Acorbose	-7.58
Aldose reductase	Baicalein	-11.64	Epalrestat	-15.51
Lipase	Baicalein	-13.47	Orlistat	-14.29

Table 5 The Atomic Contact Energy (ACE) of bioactive anticancer compound wogonin of *Scutellaaria baicalensis* docked with enzymes forming docked complexes and enzymes compared with standard drugs using FireDock

Enzyme	Compound	ACE value (kcal/mol)	Standard Drug	ACE value (kcal/mol)
α-Glucosidase	Wogonin	-14.74	Acorbose	-11.82
α-amylase	Wogonin	-9.89	Acorbose	-7.58
Aldose reductase	Wogonin	-12.31	Epalrestat	-15.51
Lipase	Wogonin	-13.76	Orlistat	-14.29

Table 6 The Atomic Contact Energy (ACE) of bioactive anticancer compound baicalein and wogonin of *Scutellaaria baicalensis* docked with nuclear receptor forming docked complexes using PatchDock

Nuclear receptors	Compound	ACE value (kcal/mol)
PPARα	Baicalein	-137.19
	Wogonin	-171.76
PPARγ	Baicalein	-65.84
	Wogonin	-52.30

Table 7 The Atomic Contact Energy (ACE) of bioactive anticancer compound baicalein of *Scutellaaria baicalensis* docked with nuclear receptor forming docked complexes using FireDock

Nuclear receptors	Compound	ACE value (kcal/mol)
PPARα	Baicalein	-14.07
	Wogonin	-11.41
PPARγ	Baicalein	-11.68
	Wogonin	-11.98

The PatchDock analysis showed that the anti-cancer compounds, Baicalein and Wogonin showed good inhibitory activity against α-glucosidase, α-amylase, Aldose reductase and Lipase and also with the nuclear receptors PPARα and PPARγ. Which reveals their efficiency in controlling diabetes. But when compared with standard drugs the ACE values of anti-cancer compounds are moderate, whereas, FireDock results shows nearby ACE vales with the standard. However, in future *in vivo* evaluation is needed to confirm their efficacy. Through these results, it is essential to understand the important structural features enhancing inhibitory activities which might aid us further to develop improved inhibitory compounds in future.

CONCLUSION

This study analyzed the interaction between the two anti-cancer compounds of *Scutellaria baicalensis* against different molecular targets computationally using various bioinformatics tools, as shown in Table. 8, hypothesizing that these compounds may play a key role in regulating blood sugar level.

Table 8 The various bioinformatics databases and tools used in this study

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

Best interactions of enzyme-ligand complexes were analyzed. The purpose of this study is to identify anti-diabetic compounds having highest binding affinity using *in silico* approach of molecular docking algorithmPatchDock through which the compound can be used in therapeutic applications of diabetes. For better refinement FireDock was carried out. The study results showed the interaction between the two anti-cancer compounds, Baicalein and Wogonin, which has potential activity on diabetes mellitus. However, animal model experiments are essential to prove their efficacy in future. 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. Thereby, these two compounds can be used to design effective anti-diabetic drugs in future. This type of analysis could revolutionize the research field in identifying the finest therapeutic compounds in short period of time.

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