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In-silico analysis for the confirmation of insulin receptor as a target for reported GLUT4 anti-diabetic natural compounds

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Abstract

Purpose of Research: There are 425 million people with diabetes in the World. There will be 629 million people with diabetes in the World in 2045. The insulin receptor controls glucose homeostasis, a physiological mechanism that can lead to diabetes and cancer if disrupted.

Scope of The Experiments: This study aimed to confirm the Insulin Receptor target for reported GLUT4 anti-diabetic natural compounds based on their pharmacokinetic properties, toxicity prediction, molecular docking, target analysis, similar FDA approved drugs prediction, and molecular dynamic simulation. We selected 24 compounds on the basis of their mode of action from the anti-diabetic natural compounds database (ADNCD). Initially, we performed ADME analysis for the selected 24 compounds.

Results: Among these 24 compounds, it has been found that 18 compounds followed the Lipinski Rule of Five. Further, we did a toxicity analysis of those 18 compounds, and it was found that 15 compounds were toxic in nature. We performed molecular docking against the Insulin Receptor (PDB ID: 1IR3) of the rest of the 3 compounds after ADME and toxicity analysis. To understand the dynamic motions of the ligand-protein complex, we perform a root mean square fluctuation analysis. We also checked the similarity of Apigenin from the FDA-approved drugs, but no similar molecule was found.

Findings and Conclusions: It has been found that Apigenin was selected as the best compound as it showed the lowest binding energy and satisfied all our study parameters. Our promising findings based on preliminary and in-silico analysis need to be validated further by *in-vitro* and *in-vivo* studies.

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Keywords: Insulin Receptor; Anti-Diabetic Natural Compounds; ADME; Toxicity; Molecular Docking; Swisssimilarity

1. Introduction

Diabetes mellitus (DM) is commonly recognised as an escalating, epidemic, complex disease. It has affected each and every age group without distinction [1]. The International Diabetes Federation estimates that in 2015, about 415 million individuals suffered from diabetes and that by 2040, this number will increase to 640 million [2]. Diabetes can be controlled with a good diet, frequent exercise, synthetic or natural medications, and a healthy lifestyle [3]. Two primary forms of diabetes exist (i.e., type 1 and type 2). In type I DM, the body ceases generating insulin, but in type II DM, insulin production and action are defective [4]. Type II DM, which affects more than 90 percent of diabetic patients, is a chronic disease of food metabolism brought on by diminished insulin action. Although a range of medications is available for the treatment of T2D, no single agent is effective for the majority of patients in achieving long-term control of normal blood glucose levels. Due to this, general practitioners prescribe a mixture of anti-diabetic agents for the treatment of T2D, and an overdose of anti-diabetic medications may result in severe hypoglycemia and severe toxic and adverse effects. This prompted the scientific community to seek out novel anti-diabetic medications. Current treatments for diabetes management are effective but have numerous adverse effects. The limitations of existing treatments are not only contributing to the rise in diabetes prevalence but are also exceeding the budgetary boundaries. All of these impacts necessitate a treatment that is safer, more effective, simple to administer, and economical [5]. The traditional method of treatment employs anti-diabetic chemicals derived from several plant species, and it is gaining popularity as natural medications have fewer negative effects than synthetic drugs [6]. It has been estimated that over 1200 plant species contain chemicals with hypoglycemic potential. Additionally, plant species with the corresponding bioactivity have been analysed to identify precise lead chemicals for desirable activity [7]. Diabetes mellitus is a difficult disease since it can be caused by abnormalities in a variety of organs, proteins, and enzymes. Due to the multifaceted character of this disease, one cannot rely on a single experimental model, nor can a single treatment overcome it. Protein receptors involved in the control of glucose throughout the body, such as insulin receptor and sodium-glucose cotransporter 1 and 2, serve as experimental models [14]. Insulin receptor (IR) is a transmembrane signalling protein and a member of the protein tyrosine kinase family. Numerous essential regulatory functions of IR involve cell development, differentiation, and metabolism. Its role in regulating glucose homeostasis distinguishes it from other family members [15]. Insulin secretion and glucose tolerance are lost when the insulin receptor gene is knocked out, which inactivates the receptor. The investigations have elucidated the role of IR in glucose homeostasis and demonstrated its significance in the treatment of diabetes [15]. Alterations in insulin receptor activity have also been found in studies of type I and type II diabetes [16]. Due to the superior efficacy and improved safety profile, current medicinal chemistry research focuses on polypharmacological compounds that act on multiple targets to treat complex diseases, such as diabetes, neoplastic diseases, neurodegenerative disorders, and certain infectious diseases, and ease of administration of multi-target drugs.

The insulin receptor was chosen as the target protein in this study. Using in silico methods, the purpose of the study was to confirm the insulin receptor as a target for reported GLUT4 anti-diabetic natural substances. Lipinski's rule of five and ADMET profiling were utilised to examine the selected compounds. The ligands that meet all of these requirements are referred to as prospective antihyperglycemic medicines. It is expected that the selected compound as anti-diabetic medicines would be a superior and safe alternative to DM therapies now in use. This study's findings would be utilised as a novel method for screening anti-diabetic medicines.

2. Material and methods

2.1. Screening of Compounds

Using an extensive literature search list and a recent search report, we found some known anti-diabetic natural compounds from the Anti-diabetic natural compounds database known as ADNCD [17]. In ADNCD, there are 24 natural compounds listed with their validated reference, Physiochemical properties, and toxicity risks in vitro/vivo studies whose mode of action is GLUT4 (Glucose Transporter Type 4 activation**)** activators. GLUT4 is insulin-dependent and located in skeletal muscles, cardiac muscles, and adipose tissues. The function of GLUT4 is after taking the meal, insulin gets stimulated. We screened these anti-diabetic natural compounds through various in-silico methods, including ADME analysis and toxicity analysis.

2.2. ADME analysis

ADME **(**absorption, distribution, metabolism, and excretion) screening helps in detecting the drug likeliness of compounds. The canonical smiles format of the ligands was put into the SwissADME server (http://www.swissadme.ch), and ADME screening was performed at default parameters [18].

ADME is the process that determines Pharmacokinetics (PK). Phase 1 clinical trials measure safety and PK Thus, drug-like properties constitute a property profile that is consistent with the drug properties of most commercial drugs. Drug-like is defined as those compounds that have sufficiently acceptable ADME properties and sufficiently acceptable toxicity properties to survive through the completion of a human phase 1 clinical trial. Drug-like properties are intrinsic properties of the molecules, and it is the responsibility of medicinal chemists to optimize the pharmacological properties and the drug-like properties of these molecules. At this point, we had four parameters that we thought should be globally associated with solubility and permeability, namely molecular weight; Log P; the number of H-bond donors, and the number of H-bond acceptors. In a manner similar to setting the confidence level of an assay at 90 or 95%, we asked how these four parameters needed to be set so that about 90% of the USAN (United States Adopted Names) compounds had parameters in a calculated range associated with better solubility or permeability. This analysis led to a simple mnemonic which we called the 'rule of 5' or Lipinski Rule of Five.

2.3. Toxicity analysis

We used the ProTox-II web server for in silico prediction of toxicity of anti-diabetic natural compounds [19]. With the help of the ProTox-II webserver, we classified the compounds into different levels of toxicity such as oral toxicity, organ toxicity (hepatotoxicity), toxicological endpoints (such as mutagenicity, carcinogenicity, cytotoxicity, and immunotoxicity), toxicological pathways (AOPs) and toxicity targets thereby providing insights into the possible molecular mechanism behind such toxic response.

2.4. Molecular docking

Molecular docking is one of the most frequently used methods to predict the binding affinity between two molecules. We used AutoDock software to know the binding affinity of natural compounds. AutoDock Vina software is an open-source program for doing molecular docking [20]. To know the binding mode prediction of the compound, we use the AutoDock vina process. Molecular docking was used for the analysis of the interactions between the coumarin derivatives and the active site of phosphorylated insulin receptor tyrosine kinase in a complex with peptide substrate and ATP analog (PDB ID: 1IR3). Docking simulation was performed by employing the AutoDock Vina 1.1.2 program. The grid box was placed with a spacing of 1 Å. Grid dimensions were chosen large enough (20 x 20 x 20 Å in x, y, and z directions, respectively) to fit all the residues of the active site in the protein. The grid box was positioned in a way to cover the entire binding site and to allow larger molecules to dock properly (-23.77 x 29.16 x 6.97 Å in x, y, and z directions, respectively). Conformations of docked ligands were chosen according to their binding affinity and their conformation similarity to the native ligand.

2.5. Molecular Target analysis

SwissTarget is a web server for targeting small bioactive molecules; the potential protein target analysis was performed in the SwissTarget Prediction server (http;//www.swisstargetprediction.ch) by using the canonical SMILES of compounds and selected homo sapiens as the source of the target [21]. Just like drugs and metabolites are connected to protein or other macromolecules, targets to handle their activity. In SwissTarget Prediction, both 2D similarity and 3D similarity values are computed against a set of known ligands. SwissTarget is a server for targeting small bioactive molecules, just like drugs and metabolites are connected to protein or other macromolecules targets to handle its activity. The result we get in the observed phenotypic effects is the reason for mapping the target of small bioactive molecules is an important step toward unraveling the molecular mechanism under their bioactive and also predicting potential side effects or cross-reactivity.

2.6. Similar FDA approved drug analysis

We further analyze our hit compound for similarity, if any, with FDA-approved drugs using the SWISS similarity tool (http://www.swisssimilarity.ch) [22, 23].

2.7. Molecular Dynamics simulations

The molecular dynamics simulations were carried out using the CABS-flex 2.0 server to evaluate the structural flexibility and stability of the ligand-protein complex [24]. The root-mean-square fluctuations (RMSF) were obtained based on the MD trajectory or NMR ensemble with the default options.

3. Results and discussion

3.1. Compound selection

These compounds are selected from the Anti-diabetic natural compounds database (ADNCD) and are shown below (Table 1)

Table 1 Selected compounds from the Anti-diabetic natural compounds database (ADNCD)

S. No	Compound Name	PubChem ID
01	Andrographolide	5318517
02	Apigenin	5280443
03	Arecoline	2230
04	Tormentic Acid	73193
05	Caffeic acid	689043
06	Rutin	5280805
07	Aegeline	15558419
08	Nymphayol	44591829
09	Cinnamaldehyde	637511
10	Gentianine	354616
11	Palmitic Acid	985
12	Aspalathin	11282394
13	Carnosic acid	65126
14	Palmatine	19009
15	Ginsenoside Rh2	119307
16	Methyl caffeate	689075
17	Myricetin	5281672
18	Ginsenoside Rb1	9898279
19	Diallyl disulphide	16590
20	6-Gingerol	442793
21	Nobiletin	72344
22	Tannic acid	16129778
23	Lupeol	259846
24	Kaempferol	5280863

3.2. ADME

We used the SwissADME webserver to check the drug-likeness property of natural anti-diabetic compounds, which are shown below (Table 2)

Table 2 ADME analysis of selected compounds from the Anti-diabetic natural compounds database (ADNCD)

S. No.	Compound Name	M.W. (g/mol)	H Bond acceptors	H Bond donors	Molar Refractivity	Consensus (log P o/w)	Lipinski	Bioavaility score
1	Andrographolide	350.45	5	3	95.21	2.30	Yes, 0	0.55
2	Apigenin	270.24	5	3	73.99	2.11	Yes, 0	0.55
3	Arecoline	155.19	3	0	46.08	0.80	Yes, 0	0.55
4	Tormentic Acid	488.7	5	4	139.28	4.33	Yes, 0	0.56
5	Caffeic acid	180.16	4	3	47.16	0.93	Yes, 0	0.56
6	Rutin	610.5	16	10	141.38	-1.12	No, 3	0.17
7	Aegeline	297.35	3	2	86.10	2.49	Yes, 0	0.55
8	Nymphayol	358.61	1	1	114.00	6.19	Yes, 1	0.55
9	Cinnamaldehyde	132.16	1	0	41.54	1.97	Yes, 0	0.55
10	Gentianine	175.18	3	0	48.46	1.67	Yes, 0	0.55
11	Palmitic Acid	256.42	2	1	80.80	5.20	Yes, 1	0.85
12	Aspalathin	452.41	11	9	108.66	-0.49	No, 2	0.17
13	Carnosic acid	332.43	4	3	95.43	3.80	Yes, 0	0.56
14	Palmatine	352.40	4	0	101.80	2.64	Yes, 0	0.55
15	Ginsenoside Rh2	622.97	8	6	172.26	4.33	No, 2	0.17
16	Methyl caffeate	194.18	4	2	51.48	1.35	Yes, 0	0.55
17	Myricetin	318.24	8	6	80.06	0.79	Yes, 1	0.55
18	Ginsenoside Rb1	1109.29	23	15	269.41	-0.96	No, 3	0.17
19	Diallyl disulphide	146.27	0	0	45.19	2.39	Yes, 0	0.55
20	6-Gingerol	294.39	4	2	84.55	3.13	Yes, 0	0.55
21	Nobiletin	402.39	8	0	106.87	3.02	Yes, 0	0.55
22	Tannic acid	1701.20	46	25	391.51	1.78	No, 3	0.17
23	Lupeol	426.72	1	1	135.14	7.31	Yes, 1	0.55
24	Kaempferol	286.24	6	4	76.01	1.58	Yes, 0	0.55

3.3. Toxicity Analysis

After performing ADME analysis then, we carried out toxicity analysis of compounds with the use of Protox-II web server are shown below (Table 3)

Table 3 Toxicity analysis of selected compounds from the Anti-diabetic natural compounds database (ADNCD)

S. N.	Compounds	Hepatotoxicity	Immunotoxicity	Mutagenicity	Carcinogenicity	Cytotoxicity
01	Andrographolide	Inactive	Active	Inactive	Inactive	Inactive
02	Apigenin	Inactive	Inactive	Inactive	Inactive	Inactive
03	Arecoline	Inactive	Active	Active	Active	Active
04	Tormentic Acid	Inactive	Active	Inactive	Active	Inactive
05	Caffeic Acid	Inactive	Inactive	Inactive	Active	Inactive
06	Aegeline	Inactive	Inactive	Inactive	Inactive	Inactive
07	Nymphayol	Inactive	Active	Inactive	Inactive	Inactive
08	Cinnamaldehyde	Inactive	Inactive	Active	Inactive	Inactive
09	Gentianine	Inactive	Inactive	Inactive	Active	Inactive
10	Palmitic Acid	Inactive	Inactive	Inactive	Inactive	Inactive
11	Carnosic Acid	Inactive	Active	Inactive	Inactive	Inactive
12	Palmatine	Inactive	Active	Active	Active	Active
13	Methyl Caffeate	Inactive	Active	Inactive	Active	Inactive
14	Diallyl Disulphide	Inactive	Inactive	Inactive	Active	Inactive
15	6-Gingerol	Inactive	Active	Inactive	Inactive	Inactive
16	Nobiletin	Active	Active	Inactive	Inactive	Inactive
17	Cyanidin-3-Glucoside	Inactive	Active	Inactive	Inactive	Inactive
18	Kaempferol	Inactive	Inactive	Inactive	Inactive	Inactive

3.4. Molecular Docking

Conformations of docked compounds were ranked by their energies and then selected based on their similarity to the co-crystallized ligand by means of superposition. Ligand docking was visualized using UCSF Chimera. Hydrogen bonds nearby interacting hydrophobic amino acids were visualized using Discovery Studio Visualizer. Molecular docking results are shown in Table 4.

Table 4 Molecular docking results of the selected natural compounds against insulin tyrosine kinase receptor

SN.	Compound	PubChem ID	ΔG_b (kcal/mol)	Hydrogen bonds	Hydrophobic interactions	Aromatic interactions
	Apigenin	5280443	-8.2	Glu1047, Lys1030, Asn1137, Asp1150, Gly1082	Met1076, Met1079, Leu1078	Leu1002, Ala1028, Met1139, Val1010
	Aegelin	15558419	-7.0	Asp1150	Gly1003, Gln1004, Ser1006, Asn1137, Met1079, Leu1078, Gly1082, Gly1149	Leu1002, Val1010, Ala1028, Met1076, Val1060, Glu1047, Met1139
	Kaempferol	5280863	-8.1	Leu1002, Glu1047	Asp1083, Gly1082, Met1079, Leu1078, Lys1030, Asp1150	Val1010, Ala1028, Met1139

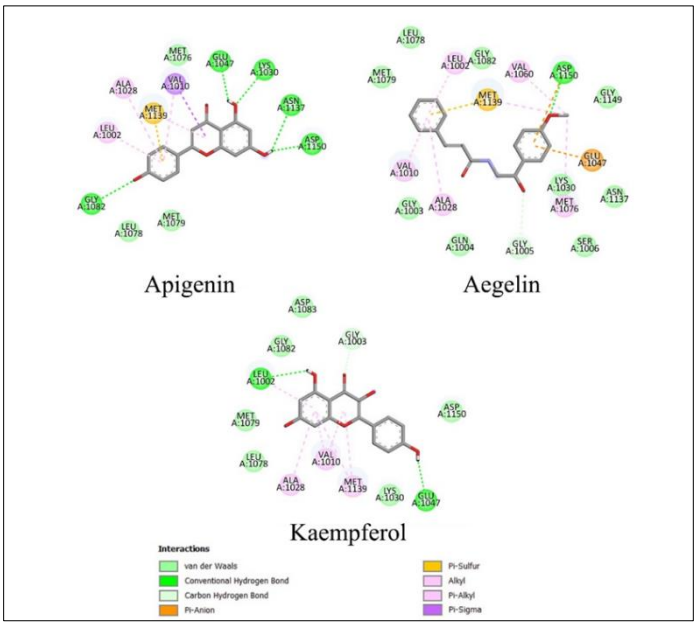

Figure 1 Protein-ligand interactions between Apigenin, aegelin, and kaempferol in complex with insulin tyrosine kinase receptor

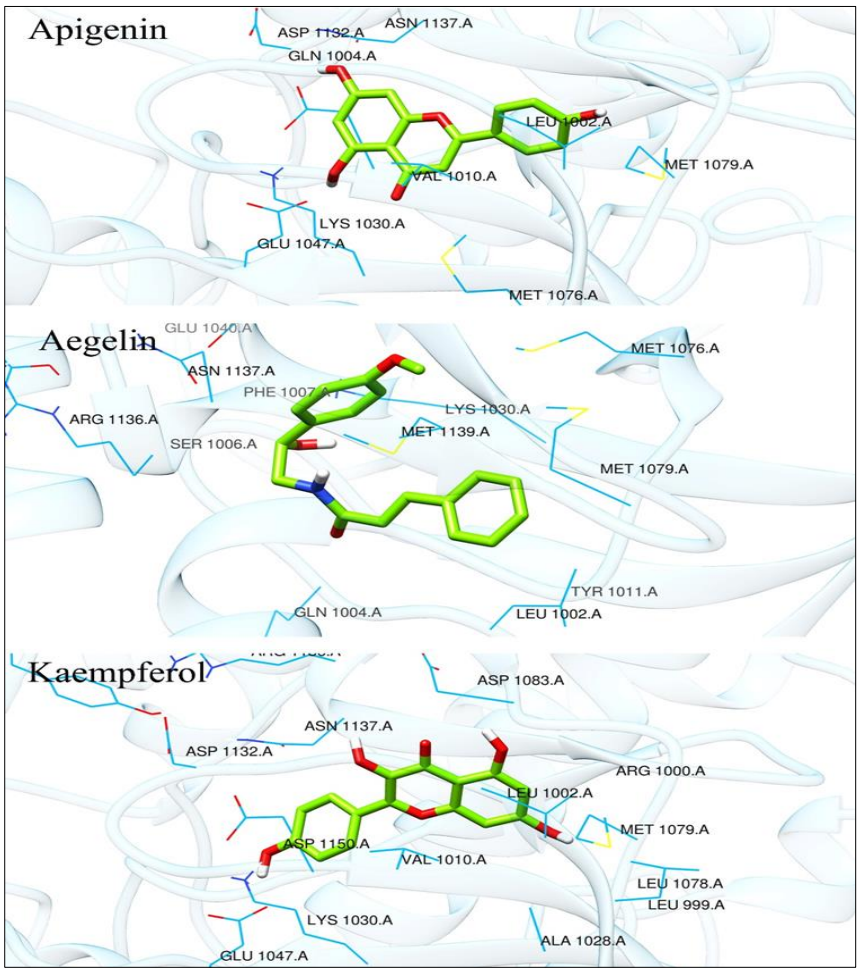

Figure 2 Docking poses of Apigenin, aegelin, and kaempferol in complex with insulin tyrosine kinase receptor

3.5. Molecular Target Analysis

We further analyse the molecular targets of our hit compound, i.e., Apigenin (Figure 3), after the screening and molecular docking analysis. For Apigenin, it predicted 20% of Oxidoreductase, 20 % of kinase, 13.3% of enzymes, 13.3% of family A G protein-coupled receptor, 6.7% of Hydrolase, 6.7% of other cytosolic protein, 6.7% of Cytochrome P450, 13.3% of nuclear receptor.

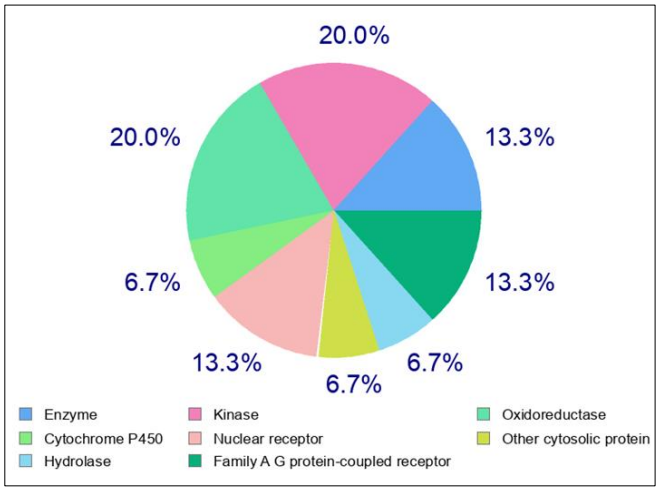

Figure 3 Molecular targets of Apigenin

3.6. Similar FDA approved drug analysis

We further checked the similarity of Apigenin, if any, with the FDA-approved drugs using the SWISS similarity check. Swiss Similarity web tool is used for rapid ligand-based virtual screening. No similar FDA-approved drugs were found.

3.7. Molecular Dynamics simulations

The investigations of interactions of the selected compound, i.e., Apigenin, with the target protein complex on molecular dynamics are presented in Figure 4. The RMSF graph showed the stability and flexibility of the amino acids for the structures with bound phytochemicals.

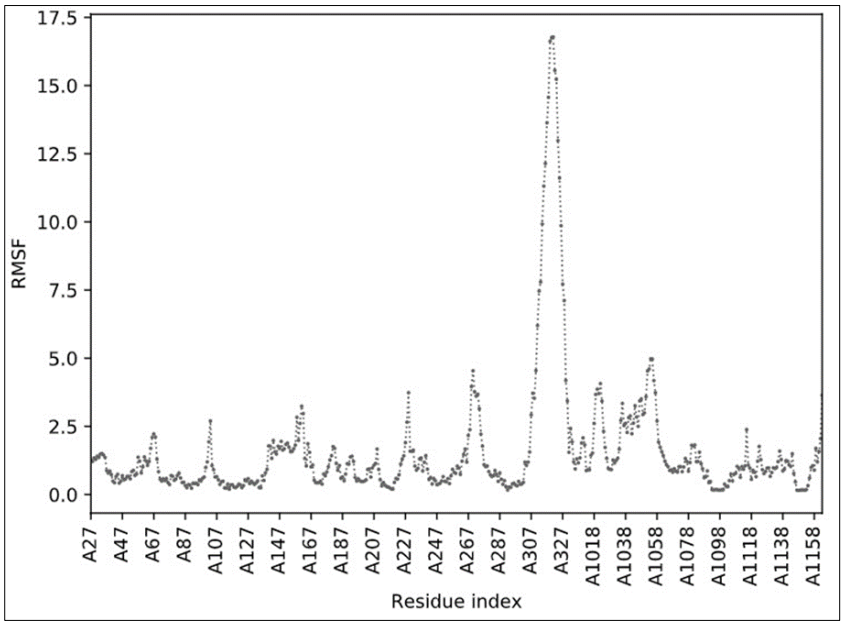

Figure 4 RMSF graph of Apigenin

4. Conclusion

Metabolically, the insulin receptor plays a key role in the regulation of glucose homeostasis, a functional process that under degenerate conditions may result in a range of clinical manifestations, including diabetes and cancer. Insulin signaling controls access to blood glucose in body cells. Here in this study, we used the crystal structure of Insulin Receptor (PDB ID: 1IR3). This protein is a 2-chain structure with a sequence from humans. It is a phosphorylated insulin receptor tyrosine kinase in complex with peptide substrate and ATP analog. This study aimed to confirm the Insulin Receptor target for reported GLUT4 anti-diabetic natural compounds based on their pharmacokinetic properties, drug-likeness, and ability to specially bind to the active sites of Insulin Receptor protein. Initially, we performed ADME analysis for the selected 24 compounds. Among these 24 compounds, it has been found that 18 compounds followed the Lipinski Rule of Five. Further, we did toxicity analysis, and it was found that 15 of the compounds showed toxicity, and 3 compounds were non-toxic in nature. After the screening of 24 compounds, it was found that Apigenin was selected as the best compound as it showed the lowest binding energy and satisfied all our study parameters. Our promising findings based on preliminary and in-silico analysis need to be validated further by *in-vitro* and *in-vivo* studies.

Compliance with ethical standards

Disclosure of conflict of interest

All the authors disclose no conflicts of interest/competing interests.

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