PROGRESS IN MEDICAL SCIENCES, 2018
VOL 2, NO. 1, PAGE 1 – 6
DOI: doi.org/10.47363/PMS/2018(2)115

ORIGINAL ARTICLE

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In silico prediction of drug molecule from *Ipomoea sepiaria* against Type 2 diabetes

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ABSTRACT

Background: Diabetes mellitus is a complex disorder, hence following a systematic approach to the care of the disease is very important to control further complications. Current evidence suggests that the TCF7L2 gene influences the risk for type 2 diabetes (T2DM) by reducing glucose-induced insulin secretion. Even though there are various new advances and medicines are available in the management of T2DM, there is a need for an alternative medicine to avoid unnecessary side effects and high cost. Nowadays, computer-aided drug designing tool is available to create ligand-target molecule.

Aim: In the present study, we aim to elucidate the binding interaction of bioactive phytochemicals of *Ipomoea sepiaria* with *TCF7L2* gene and to find out potential drug molecule against T2DM.

Materials and Methods: Bioactive phytochemicals of *I. sepiaria* were derived from the ChemSpider database and *in silico* molecular docking analysis done with *TCF7L2* gene using Hex8.0.0 docking program. The results were analysed based on their molecular interactions binding energy values.

Results: A total of 25 bioactive phytochemicals were derived from *I. sepiaria* and considered as ligand molecules. Based on the molecular docking scores of protein-ligand complex, we characterized the important interacting residues of protein targets, which involved in the binding interaction.

Conclusion: The present study concluded that the quercetin showed a high affinity with *TCF7L2*, thus indicating that this compound is a potent inhibitor of the *TCF7L2* proteins and consider as a potential drug candidate against T2DM. The further *in vitro* studies are required to confirm these results.

ARTICLE HISTORY

Received September 24, 2018
Accepted October 23, 2018
Published November 01, 2018

KEYWORDS

Diabetes mellitus; *TCF7L2*; *Ipomoea sepiaria*; bioactive compound; molecular docking

Introduction

Diabetes mellitus (DM), commonly referred to as diabetes, is a group of physiological dysfunctions characterized by hyperglycemia resulting directly from insulin resistance, inadequate insulin secretion, or excessive glucagon secretion. The symptoms of high blood sugar are frequent urination, increased thirst, and increased hunger. If they left untreated, diabetes can cause many severe long-term complications which include cardiovascular disease, stroke, chronic kidney failure, foot ulcers, and diabetic retinopathy [1]. Among DM types, Type 2 diabetes mellitus (T2DM) accounts for more than 90% of all cases and nowadays, it become a major public health concern. People living with T2DM are highly susceptible to get various forms of both short- and long-term complications, which may lead to their premature death. A scientific report predicted that the prevalence of T2DM in adults, particularly the age between 45 and 64 years, are becoming prominent will increase in the next two decades and much of the increase will occur in the developing countries [2]. T2DM is primarily due to the lifestyle factors such as physical inactivity, sedentary lifestyle, cigarette smoking, generous consumption of alcohol, and genetics [3,4].

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Additionally, a recent report discovered that many genes were significantly associated with developing T2DM, among *TCF7L2 gene* (transcription factor 7-like 2) regulates pro-glucagon gene expression, and thus the production of glucagon-like peptide-1. Many reports have shown that the variants of the *TCF7L2* gene increase susceptibility to T2DM [5,6]. *TCF7L2* is implicated in a large variety of diseases and it was found as a major determinant of type 2 risk in European populations [7].

In the aspect of pharmaceutical science, although diabetic medicines such as metformin and thiazolidinedione have good effect in insulin resistance, they cannot be widely used for all patients because of their undesirable side effects. Thus, there is a need to find out alternate medicines to treat and manage the negative impacts of DM and its severe complications due to lesser side effects and low cost. Therefore, targeting *TCF7L2* gene would be helpful to discover alternate drug molecule to treat T2DM successfully. Recently, many researchers primarily used the molecular docking techniques as a virtual screening tool to predict whether and how a particular small drug molecule will stably bind to the target protein. These techniques further help to lead optimization and application in target identifications [8]. However, there are very limited studies are available to use *in silico* technique to find out herbal bioactive compounds against diabetes and none against in *TCF7L2* [9].

Ipomoea sepiaria Koenig Ex. Roxb is considered as one of the classical herb Lakshmana and classified as an important medicinal plant in Convolvulaceae family. This herb has many medicinal values such as diuretic, laxative, aphrodisiac, and anti-ulcer property [10–12]. The literature, *I. sepiaria* roots used for the treatment of diabetes [13]. Recently, Majumder et al. [14] studied on *I. sepiaria* in which part of the plant has pharmacological effects and the control of DM. Even though phytoconstituents of this herb having many medicinal values, a little research work carried against DM and no major report available to create ligand molecule through molecular docking studies. Thus, the present study tried to predict potential ligand molecules from bioactive compounds of *I. sepiaria* against T2DM using *in silico* methods.

Materials and Methods

Target protein access

TCF7L2 gene and their products play a crucial role in causing T2DM. Accordingly, *TCF7L2* gene considered as a potential target protein and it was retrieved from UniProtKB/Swiss-Prot database (http://www.uniprot.org/).

Ligand selection

A list of bioactive compounds was retrieved from *I. sepiaria* using ChemSpider database (http://www.chemspider.com/) and further, these compounds were considered as ligands. Two-dimensional structures of these ligands were converted into 3D structure using Swiss-PdbViewer database (http://www.spdbv.vital-it.ch/).

Molecular docking analysis

The protein-ligand interaction plays an important role in structural-based drug designing. In this study, molecular docking analysis between target protein (*TCF7L2*) and ligand molecules from *I. serpiaria* were carried out by Hex8.0.0 docking program (http://www.hex.loria.fr/dist50/). It was performed by adjusting appropriate parameters such as twist range-360, receptor range-180, ligand range-180, FFT mode-3D fast lite, grid dimension-0.6, and distance range-40. The obtained scores of binding energy were tabulated and analysed.

Results and Discussion

In silico drug designing methodologies are emerging as an important role to design novel proteins or drugs in the field of biotechnology and pharmaceutical drug development. The drug designing softwares and programs have been used extensively to examine molecular modelling of gene, gene expression, gene sequence analysis, and 3D structure of proteins. These bioinformatics methods have been of great importance in the target identification and prediction of novel drugs against various human diseases [15–19]. Thus, the present study attempted to evaluate the screening of phytochemicals from *I. sepiaria* and docking against *TCF7L2* protein to find out the potential drug molecule.

Many reports have shown that variants of the *TCF7L2* gene increase susceptibility to T2DM. For people who inherit two copies of the variants, the risk of developing T2DM is about 80% higher than for those who do not carry the gene variant [7]. *TCF7L2*, also known as TCF4, is a protein acting as a transcription factor, which is encoded by the *TCF7L2* gene [5]. The single nucleotide polymorphism (SNP) within the *TCF7L2* gene is to date, the most significant genetic marker associated with T2DM risk [20]. SNPs in this gene are linked into

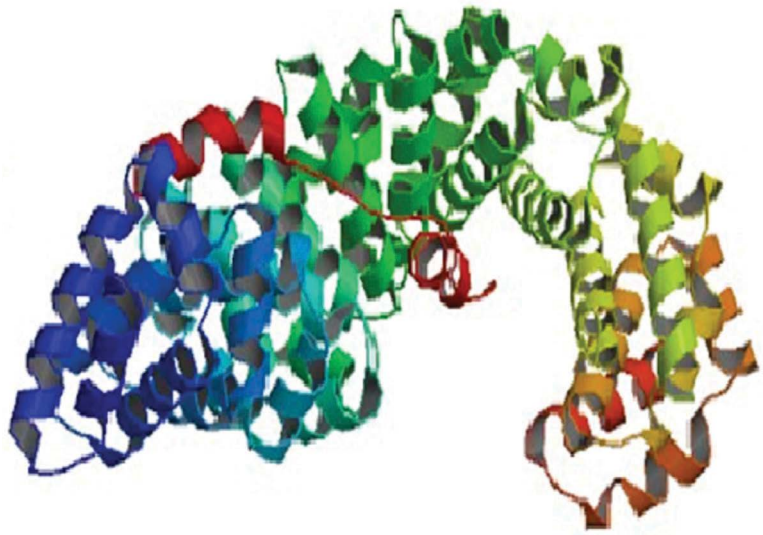

Figure 1. 3D structure of target protein *TCF7L2*.

higher risk to develop T2DM as well as gestational diabetes [21]. *TCF7L2* is a transcription factor influencing the transcription of several genes thereby exerting a large variety of functions within the cell. It is a member of the Wnt-signalling pathway [22]. Stimulation of the pathway leads to the association of β-catenin with BCL9, translocation to the nucleus and association with *TCF7L2*, which in turn results in the activation of Wnt target genes, specifically repressing proglucagon synthesis in enteroendocrine cells. By considering these factors in the present study, *TCF7L2* was selected as a receptor molecule to find out suitable ligand molecules using molecular docking studies. The 3D structure of this compound was derived from Swiss-PdbViewer database (Fig. 1) and it contains 529 amino acids.

Ipomoea sepiaria is a classical herb and its phytochemicals having tremendous medicinal values [10,11]. In literature, further specified use of *I. sepiaria* roots has been using the treatment against diabetes and constipation [12,13]. Therefore, we considered this medicinal plant for achieving the aim of the present work. A total of 25 molecules were retrieved from *I. sepiaria* using ChemSpider database. These bioactive compounds were taken into consideration for docking as ligand molecules such as 10-Heneicosene, 9-Hexacosene, Quercetin, Phytol, 3,7,11,15-Tetramethyl-1-hexadecen-3-yl acetate, Z-9-Hexadecen-1-ol, Octadecamethylcyclononasiloxane, Tetracosamethyl-cyclododecasiloxane, Hexasiloxane, Erucic amide, Icosamethyl cyclodecasiloxane, Linoleic acid, Heptadecane, 2E,9Z,12Z-octadecatrienoicacid,Lauricacid,Octasilaheptadecane, 9-cis-Oleamide, Supraene, Tetracosapentaen, Campesterin, Lycopen-16-ol, Stigmasterin, Triacontan, 2,3-Dimethylheptadecane, and 1-Monolinoleoylglycerol trimethylsilyl ether.

The objective of this ligand-protein docking was to explore their predominant binding model of 25 different ligands with 3D structure of TCF7L2. The intermolecular flexible docking simulation was performed using Hex 8.0.0 docking software to explore the binding site of the 25 bioactive compounds individually with TCF7L2. Based on the Hex docking analysis, the binding affinity between ligand and protein molecules was calculated from the conformations of ligand-inhibitor complexes (Table 1). The binding affinity, also expressed as energy value (e value), was measured in terms of KJ/mol. Furthermore, the crucial interaction information of binding pockets and their orientation of inhibitors in the target protein were obtained from the Hex docking analysis.

The nature of the complex and inhibition property of the ligands also analysed based on their binding affinities and free energy simulations. The docking results and crucial interactions between *TCF7L2* receptor and 25 phytochemical compounds were reported in Table 1. Among 25 ligand molecules tested with target *TCF7L2*, a highest energy value (−320.13 KJ/mol) obtained in quercetin-*TCF7L2* complex (Figs. 2 and 3) followed by 1-Monolinoleoylglycerol trimethylsilyl ether with *TCF7L2* (Fig. 4), Linoleic acid with *TCF7L2*, Erucic amide with *TCF7L2*, with docking scores −288.55, −260.9, and −260.77 KJ/mol, respectively. The lowest *e*-value (201.18 KJ/mol) was observed in 9-cis-Oleamide and *TCF7L2* complex.

Table 1. Molecular interaction results of *TCF7L2* with bioactive compounds from *Ipomoea sepiaria.*

S. no	Ligands	Molecular mass (Da)	Molecular formula	*e*-values (KJ/mol)
1	10-Heneicosene	294.558	$C_{21}H_{42}$	−205.86
2	9-Hexacosene	364.691	$C_{26}H_{52}$	−209.17
3	Quercetin	302.236	$C_{15}H_{10}O_7$	−320.13
4	Phytol	296.531	$C_{20}H_{40}O$	−213.19
5	3,7,11,15-Tetramethyl-1-hexadecen-3-yl acetate	338.568	$C_{22}H_{42}O_2$	205.86
6	Z-9-Hexadecen-1-ol	240.425	$C_{16}H_{32}O$	−234.72
7	Octadecamethylcyclononasiloxane	667.385	$C_{18}H_{54}O_9Si_9$	−203.39
8	Tetracosamethyl-cyclododecasiloxane	889.847	$C_{24}H_{72}O_{12}Si_{12}$	−254.54
9	Hexasiloxane,	430.940	$C_{12}H_{38}O_5Si_6$	−235.91
10	Erucic amide	337.583	$C_{22}H_{43}NO$	−263.73
11	Icosamethylcyclodecasiloxane	741.539	$C_{20}H_{60}O_{10}Si_{10}$	−206.28
12	Linoleic acid	498.886	$C_{27}H_{54}O_4Si_2$	−263.90
13	Heptadecane	464.893	$C_{33}H_{68}$	−249.43
14	2E,9Z,12Z-octadecatrienoic acid	278.430	$C_{18}H_{30}O_2$	−229.21
15	Lauric acid	418.759	$C_{21}H_{46}O_4Si_2$	−215.36
16	Octasilaheptadecane	579.248	$C_{16}H_{50}O_7Si_8$	−210.56
17	9-cis-Oleamide	281.477	$C_{18}H_{35}NO$	−201.18
18	Supraene	410.718	$C_{30}H_{50}$	−233.61
19	Tetracosapentaen	328.574	$C_{24}H_{40}$	−239.21
20	Campesterin	400.680	$C_{28}H_{48}O$	−220.20
21	Lycopen-16-ol	552.872	$C_{40}H_{56}O$	−251.50
22	Stigmasterin	412.691	$C_{29}H_{48}O$	−258.64
23	Triacontan	422.813	$C_{30}H_{62}$	−247.00
24	2,3-Dimethylheptadecane	268.521	$C_{19}H_{40}$	−239.75
25	1-Monolinoleoylglycerol trimethylsilyl ether	498.886	$C_{27}H_{54}O_4Si_2$	−288.55

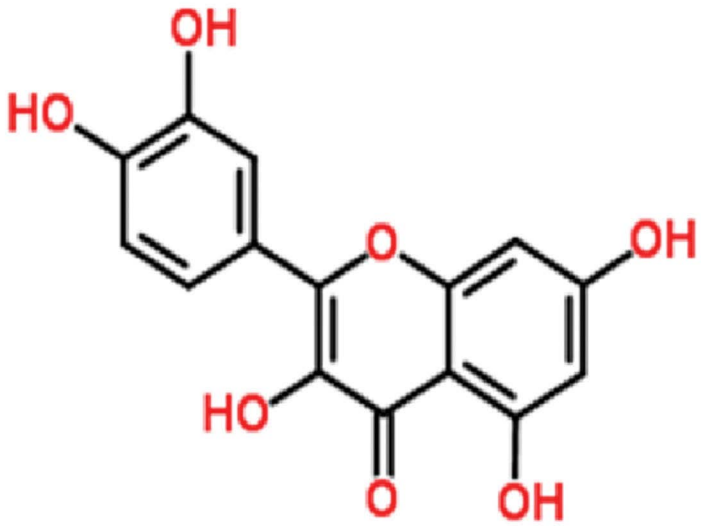

Figure 2. Molecular structure of potential ligand molecule of "quercetin."

In this study, quercetin and 1-monolinoleoylglycerol trimethylsilyl ether are considered as potential inhibitors against *TCF7L2* causing T2DM. As these molecules showed a higher *e* values and give a strong interaction between ligand and receptor that leads to the activation of receptors. This finding is comparable with many scientific reports, Hyun *et al*. [23] tested that rutin, quercetin, and myricetin are potential α-glucosidase inhibitors of T2DM through structure-based computational method. Another study by Kalaiselvi *et al.* [24] were conducted *in silico* study of bioactive compounds from *Ixora coccinea* were docked with insulin receptor proteins. They reported that quercetin exhibited a good docking profile with tyrosine and AMP Kinase [24]. Various authors studied molecular docking of bioactive compounds, reported that quercetin as a potential drug candidate, and showed high binding

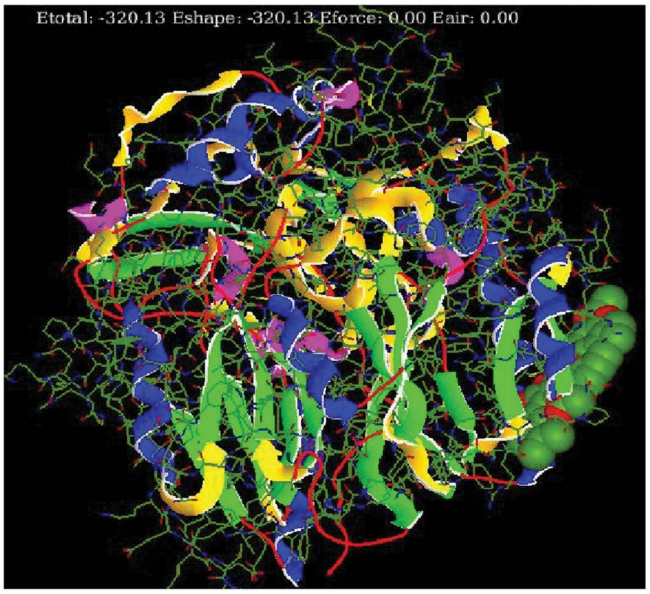

Figure 3. Molecular docking of *TCF7L2* with "quercetin" (green colour indicates antiparallel sheet of receptor, yellow colour shows parallel sheet, red colour indicates loop, and blue colour indicates helix).

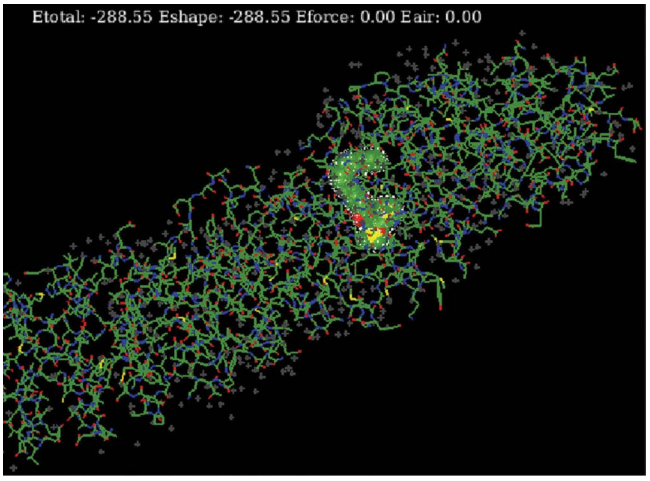

Figure 4. Molecular docking of *TCF7L2* with 1-Monolinoleoylglycerol trimethylsilyl ether.

affinity with target protein to synthesize anti-diabetic drug molecules [25–27]. The present study reports are reaffirmed that quercetin considered as the potential drug candidate for *TCF7L2* protein. In addition to that, quercetin has proven to protect against the development of diabetic neuropathy by the inhibition of lipid peroxidation and restoration of antioxidant enzyme in animal model [28]. Very recently, Srinivasan *et al.* (2018) reported that different concentrations of quercetin showed remarkable anti-hyperglycemic effects in rat model and they confirmed the effects with both *in silico* and *in vitro* approaches [29]. Furthermore, Singh *et al*. [30] conducted *in silico* and *in vivo* studies and reported that quercetin is a potential ligand with antidiabetic and antihyperglycemic action mediated by changes in the levels of glucose, cholesterol, and triglycerides.

Next, considering the second molecule1-Monolinoleoylglycerol trimethylsilyl ether showed strong binding with *TCF7L2* and *e* value was −288.55 KJ/mol. This is coincides with recent study by Senthil *et al*. [9] isolated 1-Monolinoleoylglycerol trimethylsilyl ether from *I. sepiaria* and the molecular docking studies showed high affinity with *TCF7L2*. These data are of interest for the researchers who are developing further studies to evaluate drugs in future.

In conclusion, from the list of 25 bioactive compounds retrieved from the data bank of *I. sepiaria*, quercetin and 1-Monolinoleoylglycerol trimethylsilyl ether were identified by selecting the suitable ligands for *TCF7L2* protein receptor for controlling T2DM. Quercetin-*TCFL2* molecular docking studies reveals best dock score as −320.13 KJ/mol. Thus, we concluded that the quercetin could inhibit *TCF7L2* protein and considered as a potential drug candidate against T2DM and further *in vitro* studies are required to confirm these results. The molecular docking in the current study was concrete enough to discover the binding mechanism and interaction between the 25 different compounds, which are the ligands and TCF7L2. The results obtained in this study shall be useful for future drug designing and development of novel compounds with higher inhibitory activity against T2DM. However, it is mandatory need to validate these compounds in in vitro and in vivo studies for establishing them as potential novel drug candidates.

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