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Research Article

In silico Molecular Docking Studies of meroditerpenoids of *Stypopodium flabelliforme* against FOXO1

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ABSTRACT

In spite of the global occurrence of type-2 diabetes mellitus (T2DM) infection and lack of auspicious treatment for Diabetes patients, there are only a few drugs accepted for the managing of infected patients. The objective of this study is the evaluation of Mero-diterpenoid compounds for anti-T2DM activity. *In silico* anti-T2DM lead prioritization was performed on a set of known compounds from *Stypopodium flabelliforme*. The energy minimized structures of these molecules were docked into FOXO1. Docking experiments were done using Autodock software for nine compounds docking with FOXO1. In the present study, 9 compounds (Atomarianone-A, flabellinol, flabellinone, Isoepitaondiol, stypodiol, stypoldione, stypoquinonic-acid, stypotriol, taondiol.) were docked into FOXO1 and out of nine, one compound, Flabellinol indicated high binding score (-8.41 kcal/mol) and the residues SER:205,212 TRP:160,209 PHE:197 LYS:200 TYR:165,196 GLY:208 ASN:158 were might play important roles in binding with these compound..

1. Introduction

The term Diabetes mellitus (DM) is a metabolic disorder of multiple etiology characterized by abnormal fat, carbohydrate and protein metabolism resulting from defects in insulin secretion, insulin action, or both (Orbak et al, 2008 and Latti et al, 2018). It is one of the most challenging heterogeneous diseases, can be simply classified into type 1 diabetes mellitus and type 2 diabetes mellitus (Tuomi *et al*, 2014 and Yi *et al*, 2016) Historically, the excellence between type1 diabetes mellitus and type 2 diabetes mellitus has largely depended on the clinical presentation, such as age at disease onset, the presence of ketosis and also the dependence on insulin secretion. A recent study reported that majority adults with type 2 diabetes in Bangladesh have uncontrolled diabetes with a high prevalence of hazard factors crediting to early advancement of inconveniences (Islam *et al*, 2015). .

The use herbal medicine is gaining support and recognition across the world because most of these products are believed to have bioactive compounds responsible for healing various diseases without any side effects and at a lower cost. Brown algae (Phaeophyceae) produce a great variety of secondary metabolites possessing many different skeletal types and biological activities. Stypopodium is a tropical genus of the Phaeophyceae well-known for its rich complement of polycyclic diterpenoids fused to oxidized aromatic rings (meroditerpenoids). Interestingly, these components vary for a given species depending on collection, location, and season. Some of meroditerpenoids display potent biological activities, which may be of biomedical and pharmacological utility. For example, stypolactone and atomaric acid are cytotoxic to human lung and colon Carcinoma cells, while stypoldione are inhibitors of icrotubule assembly. Stypoldione, epistypodiol, stypodiol, stypotriol, and taondiol are ichthyotoxic, diacetylepitaondiol has a negative ionotropic effect on isolated rat atrium, and stypoquinonic acid and atomaric acid inhibit tyrosine kinase. So epitaondiol is reported to have insecticidal activity.

FOXO1 is a transcription factor that is normally found in the cytoplasm. FOXO1 is activated through MAPK (mitogen-activated protein kinase), AKT, and Pdx1 (promoting gene) pathway. FOXO1 phosphorylation in the cytoplasm activates cyclin D1 and Cdk4 (cyclin dependent kinase) protein that activates the cell cycle from G0 to G1 phase in preparation for the DNA synthesis (deoxyribonucleic acid) (Trott *et al*, 2010). FoxO1 transcription factor plays important roles in various cellular functions including proliferation, differentiation, cell survival, glucose metabolism, longevity and oxidative stress resistance (Islam *et al*, 2015).

This paper is aimed to report the in silico docking of phytochemicals present in *Stypopodium flabelliforme* against target protein FOXO1.

2. Material and Methods

2.1 Data and Databases:

The data from databases used in this study include PDB (Protein Data Bank) (Berman *et al,* 2000) and PubChem (Wang *et al,* 2014). PubChem is a public repository of small molecules and their biological properties. Currently, it contains more than 25 million unique chemical structures and 90 million bioactivity outcomes associated with several thousand macromolecular targets (Qingliang *et al,* 2010). The molecular properties and structure of the selected compounds (Atomarianone-A, flabellinol, flabellinone, Isoepitaondiol, stypodiol, stypoldione, stypoquinonic-acid, stypotriol, taondiol) were shown in table-1.

2.2 Ligand Preparation:

The structures of nine major representative compounds i.e (Atomarianone-A, flabellinol, flabellinone, Isoepitaondiol, stypodiol, stypoldione, stypoquinonic-acid, stypotriol, taondiol) were obtained from PubChem and Chem spider databases. The ligands were prepared with addition of charges and hydrogen bond was carried out using Autodock tools.

2.3 Protein Preparation:

The 3D structures of protein target identified by Swiss target prediction server were retrieved from the Protein data bank (http://www.rcsb.com). The protein for docking was prepared using the protein preparation wizard of Auto dock. Water molecules present in the crystal structure were removed in the protein preparation process (Veeramchaneni *et al*, 2015 and Sainath Namthabad *et al,* 2014).

2.4 Docking Methodology

Molecular docking was performed using the AutoDock program. Ligands were docked individually to the receptor with grid coordinates (grid center) and grid boxes of certain size for receptor. The grid size was set to 114 × 114 × 114 xyz points with grid spacing of 0.375 Å and grid center was designated at dimensions (x, y, and z): -4.076, 1.891 and 15.038. A scoring grid is calculated from the ligand structure to minimize the computation time. The ligand was in a flexible condition when interacting with macromolecule under rigid conditions. The configuration file was engaged by opening notepad to run AutoDock. ADT was required to prepare the input. During the docking procedure, both the protein and ligands are considered as rigid. The results less than 1.0 Å in positional root-mean-square deviation (RMSD) was clustered together and represented by the result with the most favorable free energy of binding. The pose with lowest energy of binding or binding affinity was extracted and aligned with FOXO1 structure for further analysis.

Post-docking analyses were visualized using Discovery Studio Biovia 2017, which showed the sizes and locations of binding sites, hydrogen-bond interactions, hydrophobic interactions, and bonding distances as interaction radii of <5 Ă from the position of the docked ligand. Compounds were docked to the active site of FOXO1. Subsequently, binding poses of each ligand were observed and their interactions with the FOXO1 protein were characterized, and the best and most energetically favorable conformations of each ligand were selected.

3. Results and Discussion

In this study, the binding mode of the FOXO1 protein was investigated by doing computational analysis and docking. Grid-based docking study was used to analyze the binding modes of molecules with the amino acids present in the active pocket of the protein. To identify the potential antidiabetic lead molecule, we have subjected the docking analysis of the active compounds of *Stypopodium flabelliforme.* (L.) to the active site of FOXO1. In order to study the interaction of the compounds with FOXO1 (PDB id: 3CO7), we performed in *silico* docking analysis by Autodock 4. All the mediterpenoids reveal docking scores greater than -7 kcal/mol (Table-1). Only two compounds i.e., Flabellinol (-8.41 kcal/mol) and Atomarianone-A (-8.15 kcal/mol) reveal better docking scores than the others (flabellinol, Iso-epitaondiol, stypodiol, stypoldione, stypoquinonic acid, stypotriol, taondiol) and involved in interactions with different amino acids (Figure-1 & 2).

Flabellinol formed two hydrogen bond interactions with FOXO1, involving the amino acid residues SER205 and SER215. An electrostatic interaction was also identified with PHE197, LYS200, TYR196, TRP160, TYR165 and TRP209 (Figure-1).

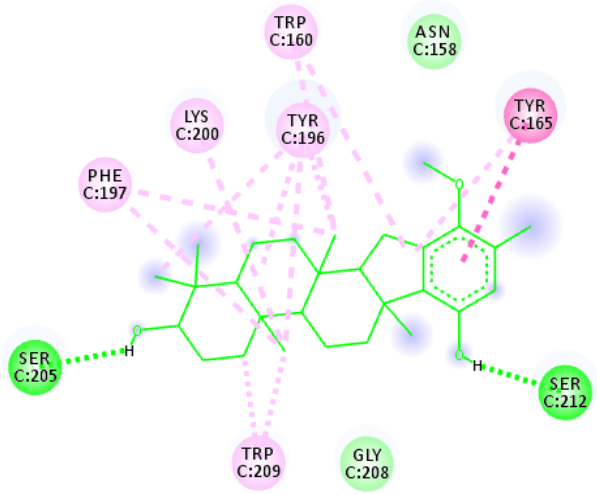

Figure-1. Molecular Docking interaction view of Flabellinol compound with FOXO1 (2D diagram)

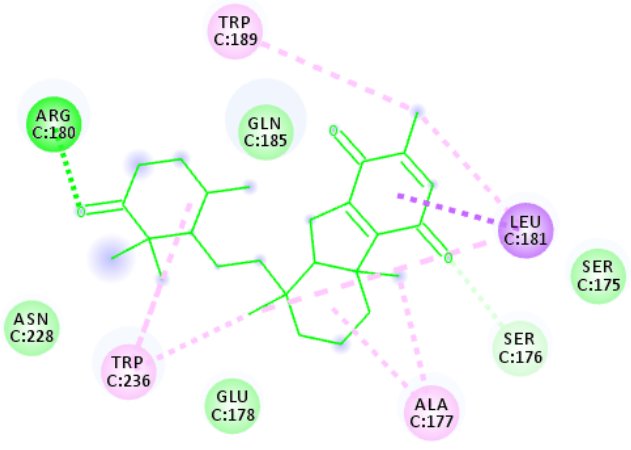

Figure-2. Molecular Docking interaction view of Atomarianone-A compound with FOXO1 (2D diagram)

Table-1. Interactions of meroditerpenoids of *Stypopodium flabelliforme* with FOXO1 receptor sites.

S.N	Compound Name	Binding energy	Inhibition constant	Intermolecular energy	Residue involving interaction	No. of H bonds	Interaction of residues forming H_2 bonds
1	Atomarianone-A	-8.15 kcal/mol	1.05 uM	-8.15 kcal/mol	ARG:180, TRP:189,236, GLN:185, LEU:181, SER:175,176, ALA:177, GLU:178, ASN:228	1	ARG:180
2	Flabellinol	-8.41 kcal/mol	689.97 nM	-9.30 kcal/mol	SER:205,212, TRP:160,209, PHE:197, LYS:200, TYR:165,196, GLY:208, ASN:158	2	SER:205,212
3	Flabellinone	-7.91 kcal/mol	1.58 uM	-8.21 kcal/mol	TYR:165,196, ASN:158, TRP:160,209, LYS:200, GLY:208, SER:205	1	TYR:196
4	isoepitaondiol	-7.57 kcal/mol	2.85 uM	-8.16 kcal/mol	SER:234,235,218, TRP:237, ARG:214,225, ASN:211, HIS:215	2	SER:234 ASN:211
5	Stypodiol	-7.38 kcal/mol	3.90 uM	-7.98 kcal/mol	GLU:178, SER:176,234, LYS:179,233, ALA:177, TRP:236, LEU:181, THR:182, GLN:185, ASN:228, ARG:180	2	ASN:228 SER:176
6	Stypoldione	-7.61 kcal/mol	2.66 uM	-7.91 kcal/mol	SER:176,234, ASN:228, TRP:228, TRP:236, GLU:178,229, ARG:180, ALA:177, GLU:9, ARG:180, ALA:177, GLN:185, GLY:232, LYS:233, THR:182	2	ASN:228 SER:176
7	Stypoquinonic acid	-7.39 kcal/mol	3.84 uM	-9.18 kcal/mol	SER:193, PRO:195, LEU:163,168, TRP:160,189, ARG:156, GLY:161, ASN:162, VAL:194, LYS:171	0	0
8	Stypotriol	-7.15 kcal/mol	5.74 uM	-8.05 kcal/mol	GLU:178,188, SER:175,176,193, ALA:177, GLN:185, LYS:192, TRP:189, LEU:181	2	GLU:188 SER:176
9	Taondiol	-7.83 kcal/mol	1.82 uM	-8.43 kcal/mol	LYS:171, TRP:160,189, GLU:174, SER:175,193, VAL:194, LEU:163,168, GLY:161, PRO:195	2	TRP:160 LYS:171

Atomarianone-A compound shows binding score -8.15 kcal/mol with FOXO1 and forming hydrogen bond with ARG180 amino acid of FOXO1. Atomarianone-A also formed four hydrophobic interactions with FOXO1, involving the amino acid residues ASN228, GLU178, GLN185 and SER175. The docking results of FOXO1 with Atomarianone-A compound was showed in Figure-2.

4. Conclusion

Our results suggest that docking program studied here do a reasonable job in docking and should aid significantly the drug discovery process. However, AutoDock consistently outperformed as compared to other programs and was found to be relatively more useful in blind docking pose prediction.

From the study, it was found that *Stypopodium flabelliforme*. (L.) could be a great source of new FOXO1 inhibitory activity. *In silico* model support that all the isolated compounds from *Stypopodium flabelliforme* might be an FOXO1 inhibitors. The present molecular docking experiments suggest that Atomarianone-A, flabellinol, flabellinone, Isoepitaondiol, stypodiol, stypoldione, stypoquinonic-acid, stypotriol, taondiol are candidate ligands for inhibiting and act through interactions with FOXO1 protein. Further *in vitro* and *in vivo* investigation needs to identify the potential inhibitory activity of isolated compounds from *Stypopodium flabelliforme*.

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Conflicting Interests

The authors have declared that no conflicting interests exist.

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