Biolife 7(4):7-13
AN INTERNATIONAL QUARTERLY JOURNAL OF BIOLOGY & LIFE SCIENCES
ISSN (online): 2320-4257
www.biolifejournals.com
BIOLIFE ORIGINALARTICLE

Molecular docking of flavonoids from *Rumex vesicarius*with FOXO1 target related to Diabetes mellitus

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ABSTRACT

Rumex vesicarius flavonoids were taken as ligands for molecular docking. The molecular target, FOXO1 whose crystallographic structures is available on the PDB database as 3CO7, 3CO6 and 3CO7 were used for the docking analysis using the Autodock software. The objective of this study is the evaluation of *Rumex vesicarius* flavonoids for anti-T2DM activity. The docking studies of the ligands of *Rumex vesicarius* flavonoids with FOXO1 target showed that *Rumex vesicarius* flavonoids are good molecules which dock well with FOXO1 target related to diabetes mellitus. Isoorientin was found to be a lead with better docking score. In the present study, 9 compounds (apigenin, Catechin, Epicatechin, Isoorientin, Isovitexin, Luteolin, Orientin, quercetin, Vitexin) of *Rumex vesicarius* were docked into FOXO1 and out of nine, one compound, Isoorientin showed high binding score (-6.38 kcal/mol) and the residues SER:164, 205, 212, 206, ASN:158, GLY:208, ALA:207, 159, TRP:160, 209, TYR:165, 196 PHE:197, ARG:157, LYS:200 were might play important roles in binding with this compound. The above results demonstrate that *Rumex vesicarius* flavonoids might be potentially used for blood glucose regulation..

Key words: Docking, FOXO1, Rumex vesicarius, Diabetes mellitus.

INTRODUCTION

Diabetes mellitus (DM) and its complications are main causes of deaths in most countries. Type 2 DM has also been known as another terms “Non-insulin dependent diabetes mellitus (NIDDM)” which accounted for more than 90 % of diagnosed cases of DM in adults (International Diabetes Federation 2015). In accordance with (Ford et al. 2002), the statistics of patients suffering Type 2 DM and metabolic syndromes were estimated about 50 million in the US and 314 million around the world and this number was predicted to increase dramatically in the next decades. The feature of Type 2 DM is the partial or complete failure in using insulin (insulin resistance) even though the functional insulin is available and then causes hyperglycemia.To overcome this resistance, the pancreatic β cells produce extra mount of insulin to maintain glucose in the normal range.

HowtoCite thisArticle:
Rakesh Davella and EstariMamidala(2019).Molecular docking of flavonoids from *Rumex vesicarius*with FOXO1 target related to Diabetes mellitus*Biolife*.7(4), xxxx.
DOI: 10.5281/zenodo.7404151

Received: 2 October 2029; Accepted : 18 November 2019; Published online: 27 November 2019

Compared with synthetic compounds, natural small molecules with special bioactivity have become the major resource of bioactive agents and played a key role in diabetes therapy (Liu et al., 2010). Therefore, management of diabetes without any side effects is still a challenge to the medical system. This leads to increasing demand for natural products with antidiabetic activity with less side effects.

A mechanism that is thought to play an important role in the regulation of pancreatic β cell regeneration is the FOXO1 (Forkhead box protein O1) transcription factors. One of the mechanisms to prevent the occurrence of apoptosis and to increase pancreatic β cells proliferation is the prevention FOXO1 transcription factors migration to the nucleus or the FOXO1 inactivation in the nucleus (Martinez et al. 2006; Gross et al. 2008).

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) (Gross et al. 2008).

Rumex vesicarius L. (Polygonaceae), known as Chukra or Bladder dock, is an annual, monoecious, glabrous, dichotomously branched, succulent pale green herb. It is

a native to south western Asia and northern Africa; cultivated as a leafy vegetable in many parts of India. Previous phytochemical investigation revealed the presence of anthraquinones, flavonoids (Saleh et al. 1993; Khare 2007) and minerals (Al-Rumaih 2003).

MATERIALS AND METHODS

Lipinski's rule of five

During the initial stages of drug discovery, it is crucial to assess the drug-likeness of each potential candidate to minimize cost by removing hits presenting false positive results. An ideal drug candidate should not violate more than one of the criteria, as defined by the "Lipinski's rule of five" (RO5). These parameters include molecular weight (no greater than 500 Da or g/mol), octanol-water partition coefficient (Logp of 5 or less), as well as hydrogen bond donors (5 or less) and acceptors (10 or less). In the current study, these characteristics were determined with the Drug Likeness Tool (Lipinski CA et al. 2001).

Table -1. Examination of the "Lipinski's rule of five" parameters

"Lipinski's Rule of Five" Parameters (Ideal Drug Value)					
S No	**Ligand**	**Mol. Wt (≤ 500)**	**Log p (≤ 5)**	**H-Donors (≤ 5)**	**H-rcceptors (≤ 10)**
1	Apigenin	270.24	2.46	3	5
2	Catechin	290.08	1.88	5	6
3	Epicatechin	290.08	1.88	5	6
4	Isoorientin	257.11	1.93	1	3
5	Isovitexin	432.38	0.52	7	10
6	Luteolin	286.05	2.68	4	6
7	Orientin	448.38	0.03	8	11
8	Quercetin	302.04	2.11	5	7
9	Vitexin	432.38	0.52	7	10

Preparation of the target

The three dimensional structure of the target (forkhead box protein O1) FOXO1 (PDB ID: 3CO7).was obtained from Protein data bank database (https://www.rcsb.org/) and downloaded in PDB format. The ligands and water molecules were removed from the protein and the chemistry of the protein was corrected for the missing hydrogen followed by the energy minimization of the protein.

Preparation of the ligands

Rumex vesicarius L. (Polygonaceae) flavonoids (i.e. apigenin, Catechin, Epicatechin, Isoorientin, Isovitexin, Luteolin, Orientin, quercetin, Vitexin) were chosen from the National Centre for Biotechnology Informaton (NCBI) PubChem compound database. These molecules were downloaded in Structure Date File (SDF) format and converted to Protein Data Bank (PDB) coordinates by using Open Babel (http://openbabel.org) converter.

Protein and ligand docking

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. The prepared file was saved in the PDBQT format. Ligand-binding affinities were predicted as negative Gibbs free energy (ΔG) scores (kcal/mol), which were calculated on the basis of the AutoDock scoring function (Trott O et al.2010). 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.

RESULTS AND DISCUSSION

Protein and ligand docking

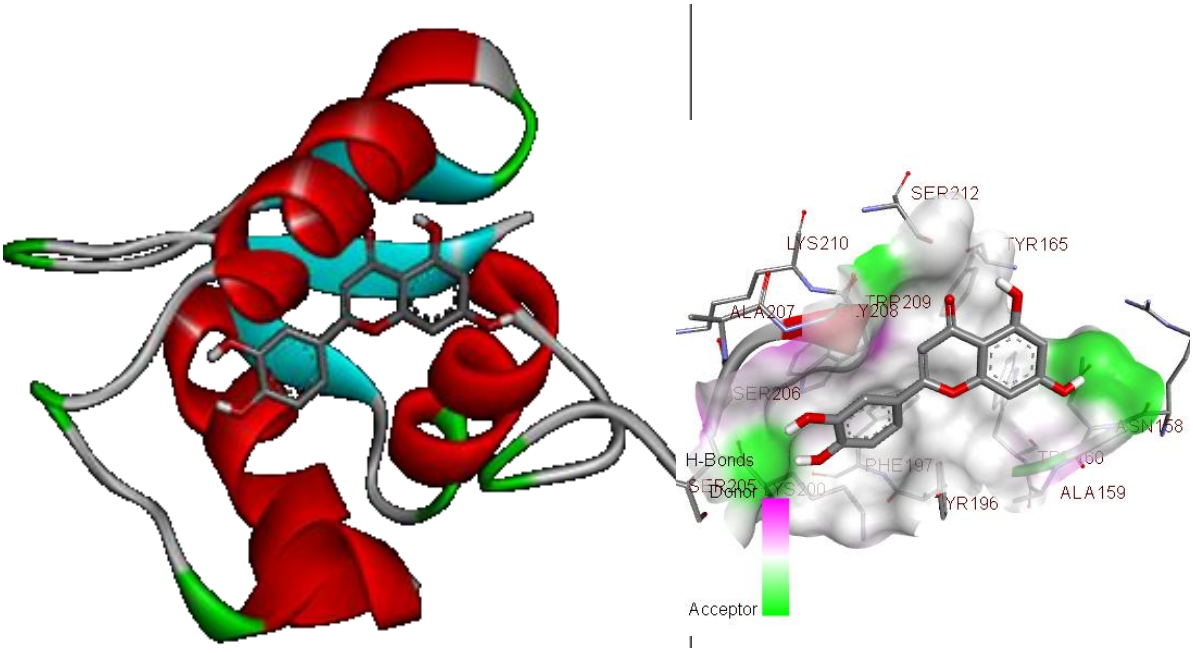
To identify the potential antidiabetic lead molecule, we have subjected the docking analysis of the active flavonoids of *Rumex vesicarius* (L.) to the active site of FOXO1. In order to study the interaction of the compounds with FOXO1 (PDB ID: 3CO7). The docking studies of the ligands of *Rumex vesicarius* flavonoids with FOXO1 target showed that *Rumex vesicarius* flavonoids are good molecules which dock well with FOXO1 target related to diabetes mellitus. Isoorientin was found to be a

lead with better docking score. In the present study, 9 compounds (apigenin, Catechin, Epicatechin, Isoorientin, Isovitexin,

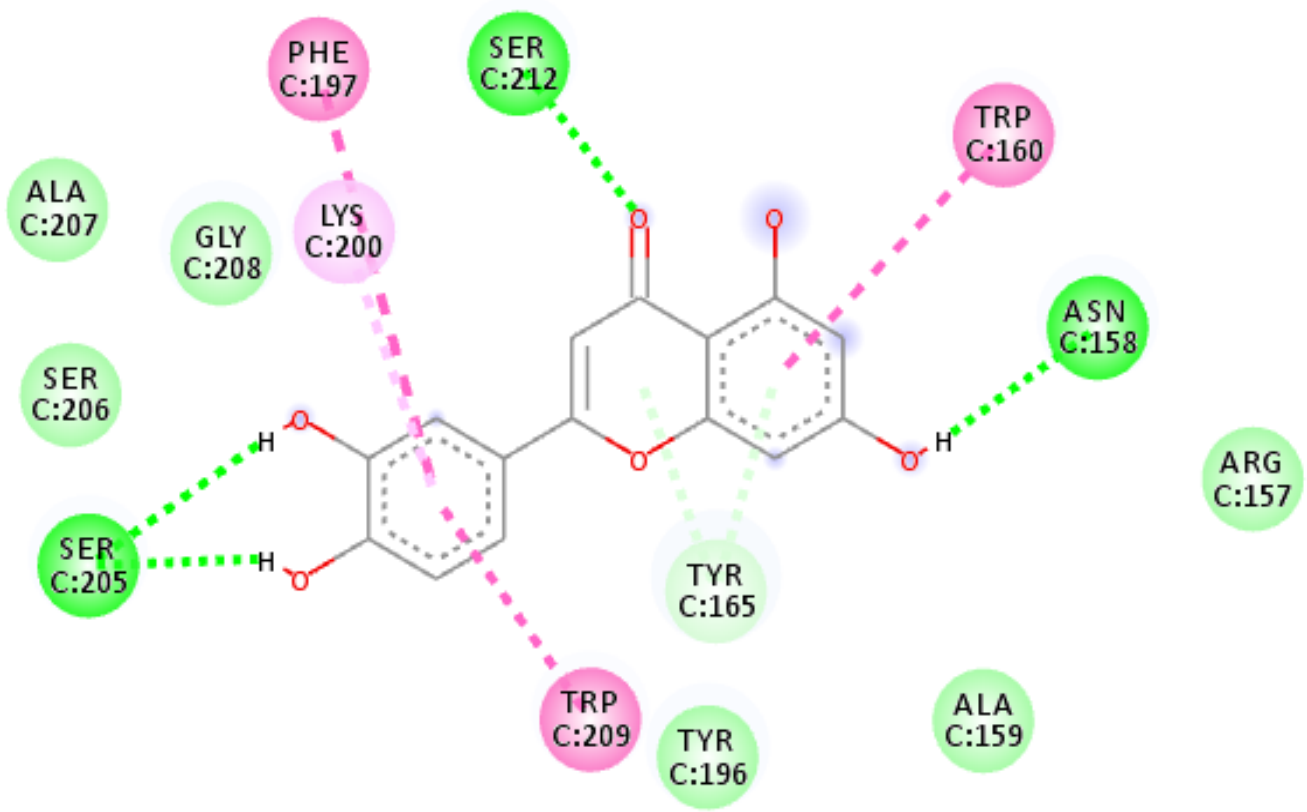
Table 2.Comparative parameters for selected nine different ligands and a common target (FOXO1).*Rumex vesicarius* flavonoids docked against T2DM- FOXO1

Sl.No	Compound Name	Binding energy	Inhibition constant	Intermolecular energy	Residue involving interaction	No. of H bonds	Interaction of residues forming H_2 bonds
1	Apigenin	-6.02 kcal/mol	38.51 uM	-7.22 kcal/mol	SER:205,206,212, LYS:200, TRP:160,20, ARG:157, GLY:208 TYR:165,196 ASN:158, PHE:197, ALA:159	3	SER:205,212 ASN:158
2	Catechin	-5.95 kcal/mol	43.49 uM	-7.74 kcal/mol	ALA:172,177, SER:175,176, LEU:181, LYS:179 GLU:178,188, ARG:180, RP:189,236, ILE:186, GLN:185	4	ALA:172 SER:175,176 GLN:185
3	Epicatechin	-5.92 kcal/mol	45.84 uM	-7.71 kcal/mol	SER:175,176, ALA:172,177, GLN:185, ARG:180, TRP:189,236, GLU:178,188, LEU:181, LYS:179	4	ALA:172 SER:175,176 GLN:185
4	Isoorientin	-6.38 kcal/mol	21.19 uM	-9.66 kcal/mol	SER:164,205,206,212, ASN:158, ALA:207,160, TYR:165,196, PHE:197, ARG:157, LYS:200	5	SER:205,212, ASN:158 ARG:157
5	Isovitexin	-5.78 kcal/mol	58.38 uM	-8.76 kcal/mol	ARG:157, SER:164,205,206,212, ASN:158,216, TRP:160,209, TYR:165,196, LYS:200, GLY:208, PHE:197	5	ARG:157,158 SER:205,212
6	Luteolin	-6.36 kcal/mol	21.83 uM	-7.85 kcal/mol	SER:205,206,212, ASN:158, ALA:159,207, GLY:208, LYS:200, TRP:160, ARG:157, TYR:165,196, TRP:209	3	SER:205,212 ASN:158
7	Orientin	-3.95 kcal/mol	1.28 mM	-7.23 kcal/mol	GLU:188, LYS:192, SER:175,176,193, TRP:189, LEU:181, GLN:185, VAL:191	3	GLU:188 LYS:192
8	Quercetin	-5.76 kcal/mol	59.76 uM	-7.55 kcal/mol	SER:205,206,212, ARG:157, ASN:158, PHE:197, TYR:196,165, ALA:159,207, TRP:160,209, GLY:208, LYS:200	4	SER:205 ARG:157 ASN:158
9	Vitexin	-5.78 kcal/mol	57.73 uM	-8.77 kcal/mol	SER:212, TYR:165,196, ASN:158, TRP:160,209, GLY:208, ALA:159, ARG:157, LYS:200, PHE:197	5	SER:212 ASN:158 TYR:196

Figure-1.Schematic representation of the interactions between the luteolin selected from *Rumex vesicarius* L. with FOXO1 (PDB ID: 3CO7).

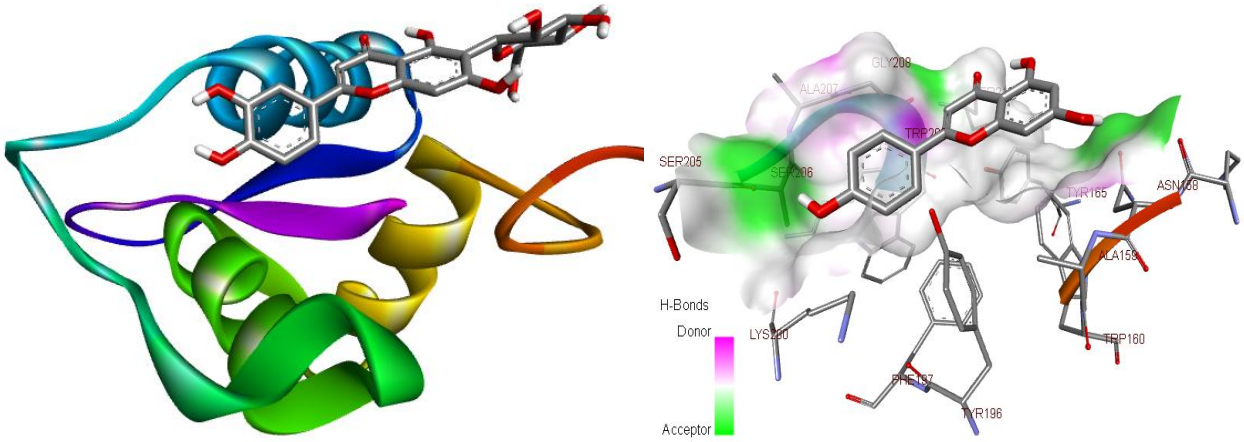


2.a) **3D images of Luteolin and FOXO1 complex file**

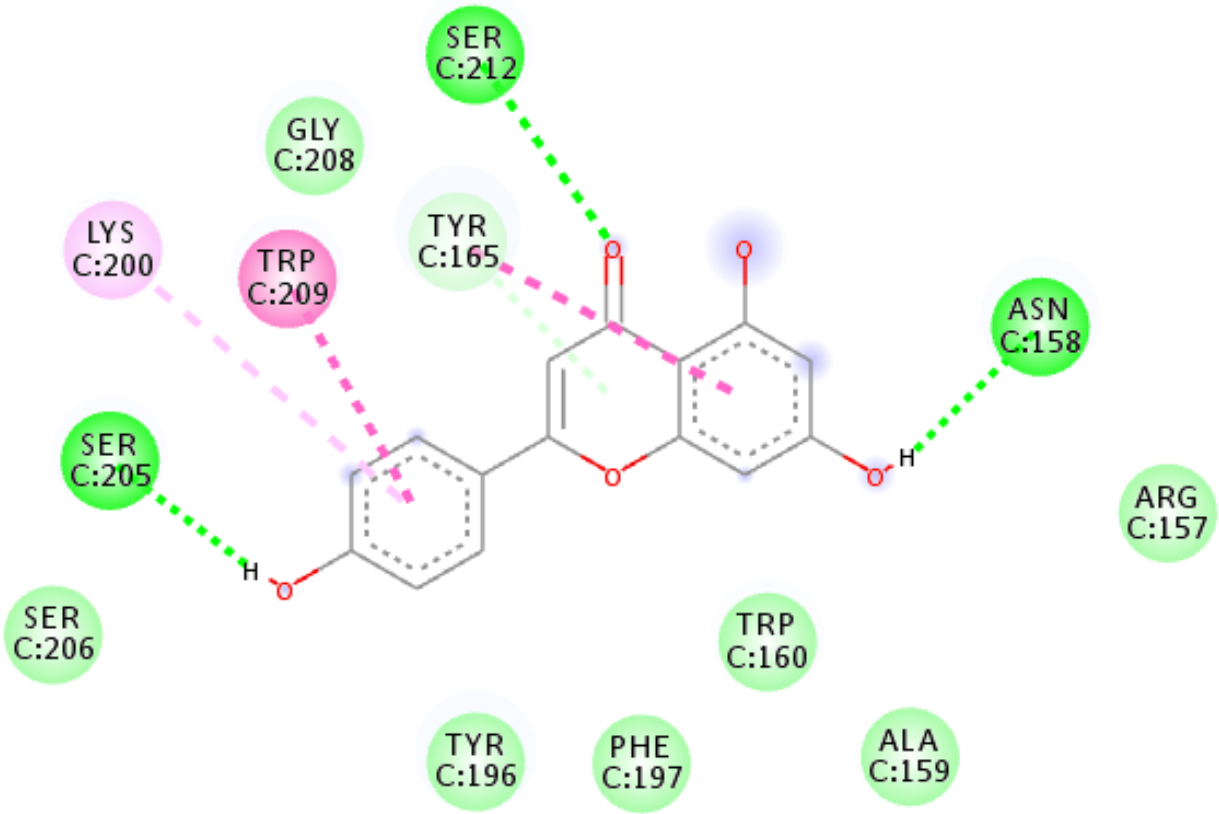


3.b) **2D Image of interaction between Luteolin and FOXO1**

Figure-2.Schematic representation of the interactions between the Isoorientin selected from *Rumex vesicarius* L. with FOXO1 (PDB ID: 3CO7).

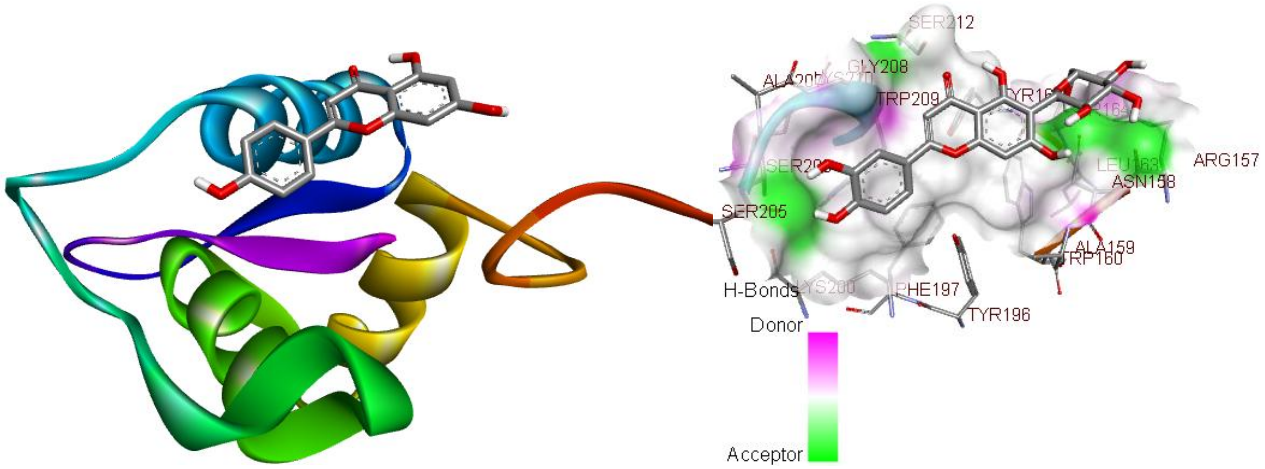


2.a) **3D images of** Isoorientin **and FOXO1 complex file**

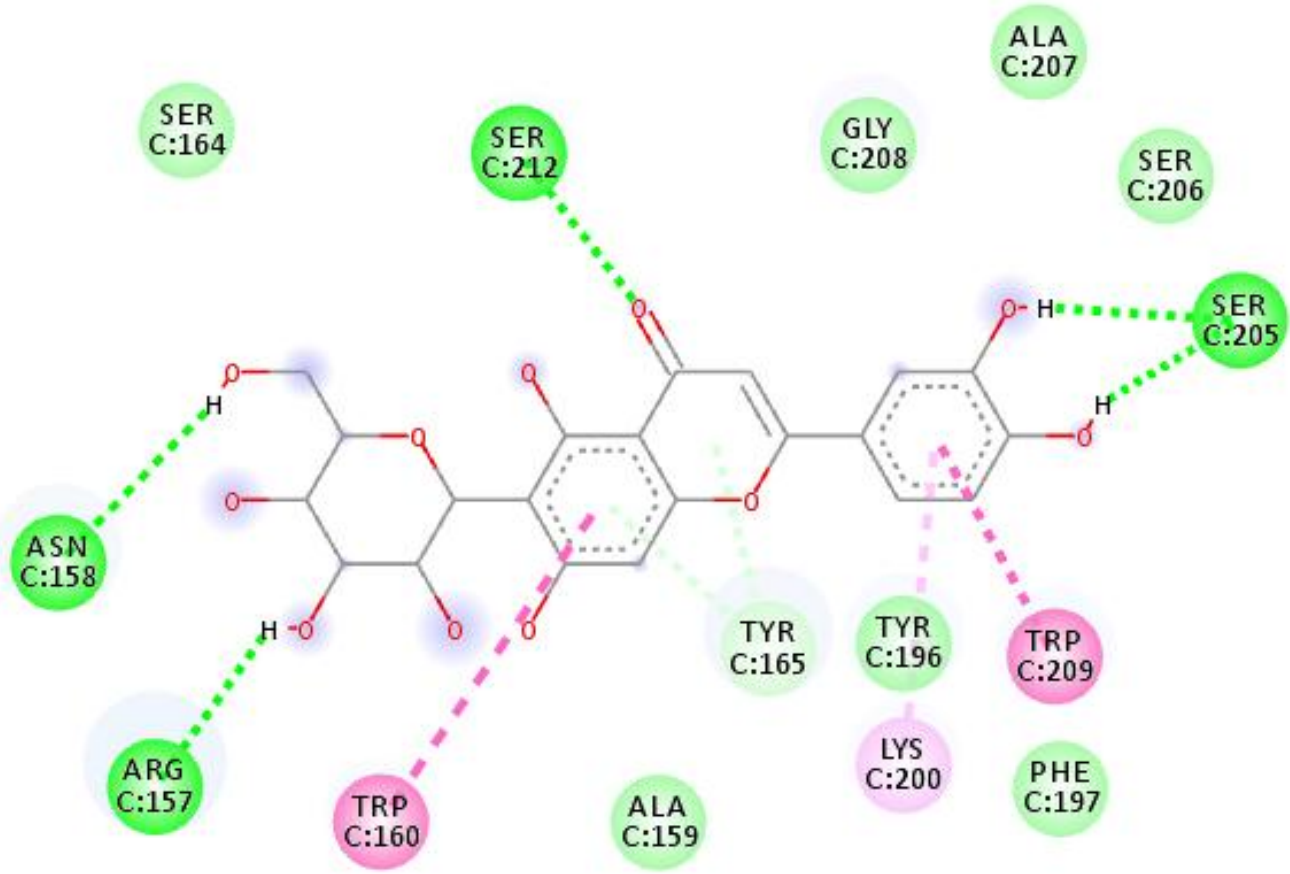


2.b) **2D Image of interaction between** Isoorientin **and FOXO1**

Figure-3.Schematic representation of the interactions between the Apigenin selected from *Rumex vesicarius L.*with FOXO1 (PDB ID: 3CO7).



3.a) **3D images of Apigenin and FOXO1 complex file**



3.b) **2D Image of interaction between Apigenin and FOXO1**

Luteolin, Orientin, quercetin, Vitexin) of *Rumex vesicarius* were docked into FOXO1 and out of nine, one compound, Isoorientin showed high binding score (-6.38 kcal/mol) and the residues SER:164, 205, 212, 206, ASN:158, GLY:208, ALA:207, 159, TRP:160, 209, TYR:165, 196 PHE:197, ARG:157, LYS:200 were might play important roles in binding with this compound.

CONCLUSION

From the study, it was found that ***Rumex vesicarius.****(L.)* could be a great source of new FOXO1 inhibitory activity. In silico model support that all the isolated flavonoids from *Rumex vesicarius.(L.)* might be an FOXO1 inhibitors. Among nine compounds three compounds Luteolin, Isoorientin and Apigenin showed better docking score . The present molecular docking experiments suggest that apigenin, Catechin, Epicatechin, Isoorientin, Isovitexin, Luteolin, Orientin, quercetin, Vitexin are candidate ligands for inhibiting and act through interactions with FOXO1 protein. Further in vitro & in vivo investigation needs to identify the potential inhibitory activity of isolated compounds from *Rumex vesicarius. (L.)*

Conflicts of Interest

Authors declare that there is no conflict of interests regarding the publication of this paper.

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