ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES Knowledge to Innovation

Vol 7, Suppl 2, 2014

ISSN - 0974-2441

Research Article

MOLECULAR DOCKING STUDIES OF ANTIDIABETIC ACTIVITY OF CINNAMON COMPOUNDS

JAYASREE GANUGAPATI* AND SRUTHI SWARNA

Sreenidhi Institute of Science and Technology, Yamnampet, Ghatkesar, Hyderabad, 501301

Email: gpljayasree@sreenidhi.edu.in

Received: 23 March 2014, Revised and Accepted: 29 April 2014

ABSTRACT

Objective: Diabetes mellitus is a prevailing problem in most of the countries. It occurs due to the lack of insulin or production of insufficient amount by pancreatic islets. Insulin is essential for maintaining blood glucose levels and hence is essential in the body. When inadequate amount of insulin is produced it has to be compensated by administration of insulin injections which is a painful procedure. To supplement the insulin needs, small molecules that can be administered through oral route and can mimic insulin action are considered in the present study. The objective of the present study is to perform In-silico analysis of Cinnamon compounds to understand their insulin mimetic activity.

Methods: Docking studies are essential to understand the interaction between the protein and the ligands. In our study we have selected the insulin receptor as the crucial protein and ligands from Cinnamon. QSAR, Toxicity and ADMET properties of these compounds are calculated using Osiris property calculator, Molinspiration, and preADMET calculator. Docking studies were performed using Autodock 4.0 and Argus Lab 4.0.

Results: Based on these properties out of 10 compounds- we have selected 2 best compounds which had no side effects and were docked with insulin receptor. The energy values obtained for 3, 4, 5-trimethoxy cinnamic acid is -6.6 and for 2-chloro cinnamic acid is -8.3 kcal /mol. Autodock results indicate that these ligands interact with crucial residues in the active site region.

Conclusion: From the Argus lab and Autodock studies, the best pose was obtained with least energy value from which it can be hypothesized that these 2 compounds can be considered as potential activators of insulin receptor. Further wet lab studies have to be performed to confirm the properties of these 2 compounds.

Keywords: Cinnamon, Diabetes, Docking, Insulin mimetics, Insulin receptor.

INTRODUCTION

Diabetes mellitus is most common metabolic disease all over the world and number of diabetic patients is still on rise. Reports of 2011 indicate that about 366 million people are diagnosed with diabetes globally, and this may rise to 552 million by the year 2030 [1]. Diabetes mellitus is characterized by abnormally high levels of glucose in the blood. Majority of diabetic people are insulin dependent and depend on insulin injections. Instead of injections or pump which is a painful procedure oral consumption of insulin is preferable choice. To supplement the insulin needs, metabolites that can be administered orally and mimic insulin action are to be considered.

One such plant that has anti diabetic activity is cinnamon [2]. Spices such as cinnamon, bay leaves, turmeric and cloves exhibit insulin like activity. Cinnamon generally has been shown to be safe when ingested and have many pharmacological activities like antioxidant and antimicrobial effects. Cinnamon is small ever green tree approximately 10-15m tall, native to Southern India and Srilanka.

Many in vitro and in vivo data have been accumulated which support the role of cinnamon in control of diabetes. Cinnamon (10.3%) reduces fasting glucose. Cinnamon is known to stimulate glucose uptake, increase glycogen synthesis in 3T3-L1 adipocytes [3].

Molecular docking of a small molecule with the receptor is well known computational method used to predict the interactions between two molecules [4].

MATERIALS AND METHODS

Tools and materials

In our present study we retrieved the data from biological databases like Protein Data Bank (PDB), PubChem. In silico studies were carried out using softwares and online tools like Swiss–Pdb Viewer (SPDBV), Osiris Property Calculator and Molinspiration and ADME prediction, Argus Lab, Auto Dock and Accelrys Discovery Studio Client 3.5. Protein Data Bank (PDB) is a repository for the 3-D structural data of large biomolecules, such as protein, DNA and RNA [5]. NCBI PubChem is a chemical compound database that provides information on biological activities of small molecules. Swiss PDB viewer (SPDBV) is a molecular modeling and structure analysis tool [6]. Osiris property calculator is chemical structural database that calculates various drug related properties like Mutagenic, Tumorigenic, Irritant, Reproductive effective, clop, Solubility, Mol weight, Drug likeness, Drug-score prediction based on chemical structure. Molinspiration offers broad range of cheminformatics software tools that support molecule manipulation, tautomer generation, molecule fragmentation, calculation of various molecular properties such as QSAR, molecular modeling and drug design [7]. ADME is used in pharmacokinetics and pharmacology for absorption, distribution, metabolism and elimination. These properties describe the disposition of a drug like compound within the body of an organism [8]. ArgusLab is a molecular modeling, graphics, and drug design program [9]. AutoDock uses Genetic Algorithm for molecular docking.

Preparation of Protein

The crystal structure of protein insulin receptor 1IR3 used in this study was retrieved from RCSB Protein Data Bank (http://www.rcsb.org/pdb). The PDB files were energy minimized using ArgusLab and Autodock. Hydrogen was added and the protein was prepared as PDBQT in Autodock and was used further for docking studies.

Ligands

Ligands are selected compounds from Cinnamon namely 3,4,5-Trimethoxy Cinnamic Acid, Alpha-methyl Cinnamic Acid, 4-Fluoro Cinnamic Acid, p-Methoxy Cinnamic Acid, Octyl Methoxy Cinnamate,

Ethyl p-Methoxy Cinnamate, p-Hydroxy Cinnamic Acid, Methyl 4-Hydroxy Cinnamate, 4-Bromo Cinnamic Acid, 2- Chloro Cinnamic Acid. The SDF files were retrieved from NCBI Pubchem and prepared for docking using SPDBV. Optimization of the ligands was carried out in Argus Lab 4.0 (http://www.arguslab.com) and Auto dock 4.0.

Toxicity Studies

The toxicity analyses of ligands were carried out by Osiris property explorer, Molinspiration and PreADMET. Based on these properties out of 10 compounds 2 compounds namely 3, 4, 5-trimethoxy cinnamic acid and 2-chloro cinnamic acid were selected further to perform docking studies since they had no side effects.

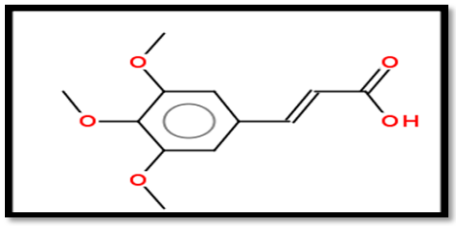

Fig. 1: Structure of 3, 4, 5-Trimethoxy Cinnamic Acid

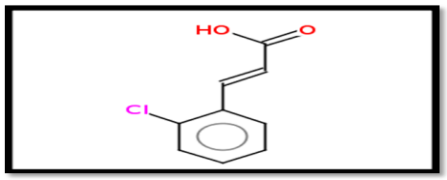

Fig.2: Structure of 2-Chloro Cinnamic Acid

Docking Studies

The docking analysis of insulin receptor and ligands were carried out by Argus Lab and Auto dock softwares [10].

RESULTS AND DISCUSSION

Osiris Property Results

Osiris Property values of ligands of cinnamon are shown in Table 1 which indicates the values of clogp, solubility, molecular weight, drug likeness, drug score, mutagenic, tumoric, irritant, reproductive effect. Of the 10 compounds of cinnamon, 3, 4, 5-trimethoxy cinnamic acid and 2-chloro cinnamic acid has no toxic effects and remaining compounds have drug likeness, drug score, mutagenic and reproductive effect.

QSAR Property Results

Quantitive structure-activity relationship of the compounds was obtained by Molinspiration. The QSAR property values are shown in

Table 2. Of the 10 compounds 9 compounds has shown zero violations except octyl methoxy cinnamate.

PreADMET Results

ADME properties of ligands were obtained by using PreADMET **(Table 3).** Caco- 2 cell permeability, plasma protein binding, blood brain barrier Skin permeability, human intestinal penetration properties of compounds were calculated. All the compounds have medium permeability to invitro MDCK cell permeability, invitro caco-2 cell permeability and to the central nervous system. Only 3, 4, 5 trimethoxy cinnamic acid and 2-chloro cinnamic acid have strong plasma protein binding.

Based on Toxicity evaluation, QSAR properties and ADMET properties 3, 4, 5-trimethoxy cinnamic acid and 2-chloro cinnamic acid were selected as potential targets and were assessed for insulin mimetic activity by molecular docking studies and binding interactions

Table 1: Toxicity evaluation of cinnamon compounds using Osiris property calculator

Compound	Drug likeness	Drug score	Mutagenic	Tumoric	Irritant	Repro-ductive effect
3,4,5 trimethoxy cinnamic acid	-10.7	0.12	Normal	Normal	Normal	Normal
Alpha methyl cinnamic acid	-1.02	0.29	Toxic	Normal	Normal	Slightly toxic
4-fluoro cinnamic acid	-1.02	0.29	Normal	Normal	Normal	Slightly toxic
p-methoxy cinnamic acid	-0.42	0.53	Normal	Normal	Toxic	Normal
Octyl methoxy cinnamic acid	-1.1	0.36	Normal	Normal	Toxic	Normal
Ethyl p-methoxy cinnamic acid	-9.36	0.13	Normal	Normal	Toxic	Normal
p-hydroxy cinnamic acid	-7.65	0.28	Slightly toxic	Normal	Normal	Toxic
Methyl 4-hydroxy cinnamic acid	0.58	0.38	Slightly toxic	Normal	Normal	Toxic
4-bromo cinnamic acid	-1.65	0.52	Normal	Normal	Normal	Normal
2-chloro cinnamic acid	1.16	0.81	Normal	Normal	Normal	Normal

Table 2: Molinspiration property values of cinnamon compounds

Compound	Milogp	TPSA	Mol.wt	No.N	N.OHNH	violations	Nrotb
3,4,5 trimethoxy cinnamic acid	1.541	65	238.2	5	1	0	5
Alpha methyl cinnamic acid	2.457	37.29	162.18	2	1	0	2
4-fluoro cinnamic acid	2.073	37.29	166.18	2	1	0	2
p-methoxy cinnamic acid	1.966	46.53	178.18	3	1	0	3
Octyl methoxy cinnamic acid	5.775	35.53	290.4	3	0	1	10
Ethyl p-methoxy cinnamic acid	2.959	35.53	206.2	3	0	0	5
p-hydroxy cinnamic acid	1.43	57.52	164.1	3	2	0	2
Methyl 4-hydroxy cinnamic acid	2.04	46.53	178.1	3	1	0	3
4-bromo cinnamic acid	2.71	37.29	227.05	2	1	0	2
2-chloro cinnamic acid	2.36	37.29	182.6	2	1	0	2

Table 3: ADMET property values of cinnamon compounds using preADMET

Compound	ABSORPTION				DISTRIBUTION	
	Human intestinal absorption (HIA%)	In vitro CaCo-2 cell permeability (nm/sec)	In vitro MDCK cell permeability (nm/sec)	In vitro skin permeability (logkp,cm/hour)	In vitro plasma protien binding (%)	In vitro blood-brain penetration (c.brain/c.blood)
3,4,5 trimethoxy cinnamic acid	94.67	25.71	325.5	-2.33	99.98	1.157
Alpha methyl cinnamic acid	98.11	21.08	72.6	-1.37	83.29	1.92
4-fluoro cinnamic acid	97.86	20.56	99.66	-1.78	37.06	1.91
p-methoxy cinnamic acid	96.72	21.42	131.26	-1.65	78	1.74
Octyl methoxy cinnamic acid	98.76	55.98	1.044	-0.95	94,07	1.635
Ethyl p-methoxy cinnamic acid	99.16	52.09	84.5	-1.53	78.82	0.05
p-hydroxy cinnamic acid	92.05	21.1	75.05	-1.7	63.05	0.694
Methyl 4-hydroxy cinnamic acid	94.35	21.4	66	-1.628	68.59	0.624
4-bromo cinnamic acid	98.44	9.32	4.16	-1.45	99.87	1.84
2-chloro cinnamic acid	98.44	20.82	280.4	-1.5	96.26	1.873

Docking Results

Docking was performed between insulin receptor and 3, 4, 5-trimethoxy cinnamic acid as well as with 2-chloro cinnamic acid using Argus Dock and Auto Dock and binding energy values are indicated in **Table 4** and interactions are indicated in **Fig 3 and 4.** The Argus dock binding energy of 3, 4, 5-trimethoxy cinnamic acid is **-6.6 kcal/mol** and 2-chloro cinnamic acid is **-8.3 kcal / mol** and Auto Dock binding energy of 3, 4, 5-trimethoxy cinnamic acid is **-10.6 kcal/mol** and 2-chloro cinnamic acid is **-16.3 kcal / mol**

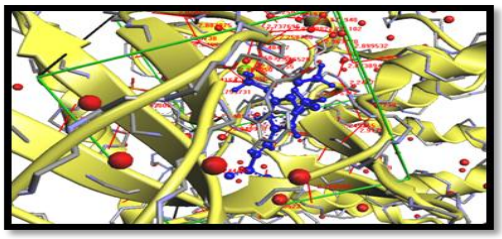

Fig. 3: Docking of 3, 4, 5-Trimethoxy Cinnamic Acid (blue) with insulin receptor (yellow)

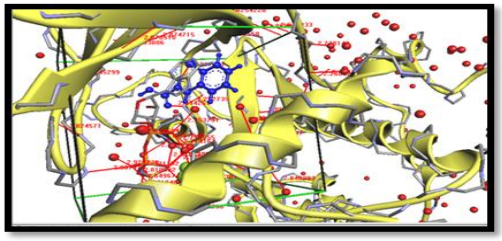

Fig. 4: Docking of 2-Chloro Cinnamic Acid (blue) with insulin receptor (yellow)

INTERACTIONS WITH ACTIVESITE RESIDUES

Active site analysis of the Insulin Receptor was performed using Swiss PDB Viewer (SPDBV) V.4.02 and PDB ligand Explorer. The active site consists of residues: **SER 1006**, LYS 1030, GLU 1077, ASP 1083, ASN 1137, and ASP 1150, MET 1079. 3, 4, 5-trimethoxy cinnamic acid and 2-chloro cinnamic acid were found to interact with the active site residue Ser 1006 **(Fig 5 and Fig 6)**

Table 4: Docking results of insulin receptor with 3, 4, 5-Trimethoxy Cinnamic Acid and 2-Chloro Cinnamic Acid

Compound	Argusdock Binding Energy Kcal/mol	Autodock Binding Energy Kcal/mol
3,4,5 trimethoxy cinnamic acid	-6.6	-10.6
2-chloro cinnamic acid	-8.3	-16.3

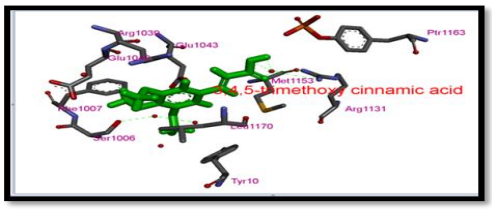

Fig. 5: Hydrogen bond (Green dotted lines) Interaction of 3, 4, 5-Trimethoxy Cinnamic Acid (green) with active site residue Ser 1006 (represented in sticks) of insulin receptor

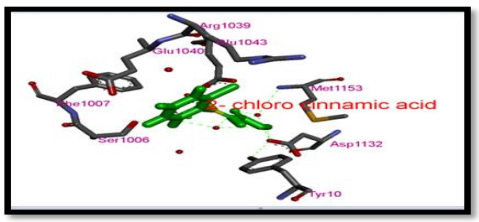

Fig. 6: Interaction of 2-Chloro Cinnamic Acid (green) with active site residue Ser 1006 (represented in sticks) of insulin receptor

CONCLUSION

The aim of present study was to identify small molecules of Cinnamon as insulin mimetics that can mimic the action of insulin and activate insulin receptor. Ten compounds of cinnamon were selected for studies. These compounds were retrieved from Pubchem and their properties were calculated using online tools OSIRIS PROPERTY EXPLORER, MOLINSPIRATION and PREADMET. Based on these analyses two molecules 3, 4, 5-trimethoxy cinnamic acid and 2-chloro cinnamic acid were found to be suitable for docking studies.

Docking studies were performed with insulin receptor using ARGUSLAB and AUTO DOCK 4.0. From the Arguslab and Auto dock studies the best pose was obtained with least energy value.The interaction with active site residue Ser 1006 indicate that these two compounds can be considered as activators of insulin receptor. Further wet lab studies have to be performed to confirm the study.

ACKNOWLEDGEMENTS

We would like to express our thanks to management of Sreenidhi Institute of Science and Technology for providing the necessary infrastructure to carry out this work.

REFERENCES

1. Whiting Dr, Guariguata L, Weil C, Shaw j. IDF Diabetes atlas: Global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011; 94: 311-321.
2. Kim S, et al. Anti-diabetic effect of cinnamon extract on blood glucose in db/db mice. J Ethnopharmacology 2006; 104: 119-123.
3. Jarvill-Taylor K, et al. A hydroxchalcone derived from cinnamon functions as a mimetic for insulin in 3T3-L1 adipocytes. J Am Coll Nutr. 2001; 20(4): 327-336.
4. Christensen JG, Zou HY, Arango ME,et al. Cytoreductive antitumor activity of PF-2341066, a novel inhibitor of anaplastic lymphoma kinase and c-Met, in experimental models of anaplastic large-cell lymphoma. Mol Cancer Ther 2007; 6: 3314-3322.
5. Berman, HM. "The Protein Data Bank: a historical perspective". *Acta Crystallographica Section Foundations of Crystallography* January 2008; A64 (1): 88–95
6. Johansson, MU, Zeote V, Michielin O and Guex N. Defining and searching for structural motifs using deepviews/swiss-pdb viewer BMC Bioinformatics, 13:173
7. Ertl P, Rohde B, Selzer P., Fast calculation of molecular polar surface area as a sum of fragment based contributions and its application to the prediction of drug transport properties. *J. Med. Chem*. 43, 2000, 3714-3717
8. SK Balani, GT Miwa, LS Gan, JT Wu, FW Lee. "Strategy of utilizing in vitro and in vivo ADME tools for lead optimization and drug candidate selection". *Curr Top Med Chem* 2005; 5 (11): 1033–1038
9. Chikhi and A. Bensegueni, "Docking efficiency comparison of Surflex, a commercial package and Arguslab, a licensable freeware," Journal of Computer Science & Systems Biology, vol. 1, pp. 81–86, 2008
10. Srivastava V, Kumar A, Mishra BN, Siddiqi MI. Molecular docking studies on DMDP derivatives as human DHFR inhibitors. Department of Biotechnology, Institute of Engineering and Technology 4: 180-188