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In silico Molecular docking study on the interaction between adenosine monophosphate-activated protein kinase (AMPK) and bioactive compounds of *Moringa concanensis* Nimmo as a cure for Diabetes Mellitus

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KEYWORDS

Type2 diabetes, AMPK, *Moringa concanensis* Nimmo, Alkaloids, Molecular docking

A B S T R A C T

Type2 diabetes is characterized by abnormal metabolism of glucose and fat, this is due to the resistance of insulin action in peripheral tissues. If untreated, it leads to several complications such as blindness, kidney failure, neuropathy and amputations. The benefits of exercises in diabetic patients are well known and that AMPK (adenosine monophosphate-activated protein kinase (AMPK) plays a major role in this exercise related effect.AMPK is considered as a master switch, regulating glucose and lipid metabolism. The traditional medicinal plants contain more bioactive constituents and are the best source to obtain a variety of drugs to cure ailments. *Moringa concanensis* Nimmo is a medicinal plant, which possesses anticancer, antidiabetic and anti-inflammatory properties. Phytochemical studies on the leaves of this plant have shown the presence of large concentration of alkaloids and phenolic compounds. The crystal structure of AMPK was retrieved from the PDB. Molecular docking experiments were performed using AutoDock4.2. Allyliponitrite, 2-prpanoic, 2-propanyl ester, 2, 2'-Bioxirane, DL-3, 4,-dimethyl 3, 4-hexanediol showed high docking score with low binding energy of-5.98was estimated. Molecular interactions of 2, 2'-Bioxirane, and pantolactone with AMPK suggested that these compounds may act as potent anti-diabetic agent. Hence, compounds that augment insulin receptor activated protein kinase activity would be useful in the treatment of diabetes mellitus.

Introduction

Diabetes mellitus is a common and prevalent disease affecting the citizens of both developed and developing countries. It is estimated that 25% of the world population is affected by this disease. Diabetes mellitus is caused by the abnormality of carbohydrate metabolism which is linked to low blood insulin level or intensitivity of target organs to insulin (Paari *et al.*, 2013). Diabetes Mellitus is characterized by constant high levels of blood glucose (sugar). Human body has to maintain the blood glucose levels at very narrow range which is done with insulin and glucogon. The function of

glucogon is to release glucose from liver cells into the blood for the production of energy (Yanling wu *et al.,* 2014]. There are two primary forms of diabetes, insulin – dependent diabetes mellitus (type IDM) and non-insulin dependent diabetes Mellitus (type II DM). Type 2 Diabetes Mellitus mostly results from the interaction among genetic, environmental and other risk factors (Abdulfatai *et al.,* 2012). Diabetes leads to the development of chronic complications such as retinopathy, neuropathy and nephropathy, etc.., AMPK (adenosine monophosphate activated protein kinase) plays a major role in master switch regulating glucose and lipid metabolism. The AMPK belongs to the family of energy sensing enzymes that are activated by cellular stresses in ATP depletion, thus acting like a fuel gauge. AMPK functions to restore cellular ATP by both inhibiting ATP consumption process. AMPK regulates the coordination of anabolic (synthesis and storage of glucose and fatty acids) and catabolic (oxidation of glucose and fatty acids). AMPK improves blood glucose homeostasis, lipid profile and blood pressure in insulin – resistant (Parimal misra *et al.*, 2007). It exists as a heterotrimer, consisting of a catalytic is α- Subunit and regulatory β – and γ - Subunits. Each subunit has multiple isoforms (α1, α2, β1, β2, γ1, γ2, γ3), making a total of 12 possible heterodimer combinations. AMPK activation stimulates glucose uptake, fatty acid oxidation and glycolysis. AMPK stimulate glucose uptake and fatty acid oxidation in liver while inhibiting gluconeogenesis, as well as cholesterol, fatty acid and protein synthesis. It inhibits insulin secretion from pancreatic β-Cells, and it signals to increase food intake in the hypothalamus (Kimberly *et al.,* 2014). Increased AMP levels activate Adenosine Monophosphate-Activated Protein Kinase (AMPK), which contributes to lowering of glucose production by at least 2 pathways: i) increased AMPK phosphorylates CBP & CRTC2 transcription factors, which inhibits genes involved in the production of glucose ("gluconeogenic genes"); ii) increased AMPK also inhibits mitochondrial glycerol-3-phosphate dehydrogenase (mGPD), leading to an increase in cytosolic NADH, which both stimulates the conversion of pyruvate to lactate, and simultaneously decreases gluconeogenesis. An accumulation of lactate to dangerous levels **(**lactic acidosis**)**. (Ferranni *et al.,* 2015)The plant M*oringa concanensis* Nimmo (Moringacea) has a single genus with 13 species have been recorded in India. It is an evergreen tree, widely distributed on dry lands. Commonly known as kattumurungai or peyimurungai in Tamil. The entire plant is contains different types of ailments and various human diseases such as anti-inflammatory, antifertility agent, analgesic, antimicrobial, reduce cholesterol, skin tumor diabetes and eye care (Shanthi *et al.,*2017). Phytochemical studies on the leaves, stem, bark and root of this plant have shown the presence of large concentration of alkaloids, phenolic compounds, some of the compounds such as Butanic acid, 3,3, Dimethyl (E)and 2 – Propanoic acid, 2 Propanyl ester,Pantalactone, Allyliponitrite, 2,2'- Bioxirane (Vadivel Balamurugan *et al.*, 2015). Various bioactive compounds justifies *M. concanensis* is an excellent phytocomponents and to treat various disease and complications in human beings. Although insulin has become one of the most important therapeutic agents known to medicine, there is a continuing effort to find insulin substitutes, or sensitizers from synthetic or plant sources for the treatment of diabetes mellitus [Pushparaj PN *et al.*,]. In the present study we have attempted to dock the bioactive compound of Moringa *concanensis* Nimmo with AMPK (adenosine monophosphate activated protein kinase) to

understand the interactions. This insilico approach can be further investigated to generate more effective and potential AMPK (adenosine monophosphate activated protein kinase) activators through ligand based drug designing approaches.

Materials and Methods

UNIPROT

Uniprot is a universal protein resource, a central repository of protein data created by combining the swiss-prot, TrEMBL and PIR-PSD databases. It provides comprehensive, high quality and freely accessible resources of protein sequence and functional information. The uniprot databases are the Uniprot knowledgebase (UniProtKB), the Uniprot reference clusters (UniRef) and the Uniprot Archive (UniParc) (www.uniprot.org/). The primary sequence of AMPK (Adenosine monophosphate activated protein kinase) has been retrieved and the accession number is Q13131.

PDB

The protein data bank PDB (http//www.rcsb.org/pdb/) is the single worldwide archive of structural data if biological macromolecules. It was established at Brookhaven national laboratories (BNL). PDB have varying expertise in the techniques of X-ray crystal structure determination, NMR, Cryoelctron microscopy and theoretical modelling. The PDB Id of AMPK is 4RED.

PUBCHEM

Pubchem is a database of chemical molecules and their activities against biological assays. It is a product of NCBI database. Useful for collecting the information about the specified chemical compounds. It is an online archive containing the information of all the known chemical compounds and their biological properties. The 2D structure of compounds such as Pantolactone, Allyliponitrite, 2-propanoic, 2-propanyl ester, 2, 2'-Bioxirane, DL,-3, 4dimethyl, and 3, 4-hexanediol are obtained from the pubchem. (http://pubchem.ncbi.nlm.nih.gov/)

ACD Chemsketch

ACD/Chemsketch is the powerful chemical drawing and graphics package from ACD/labs software, which will draw molecular structures, reactions and calculate chemical properties very quickly and easily.

The three dimensional structures of bioactive constituents of *Moringa concanesis* Nimmo were drawn by ChemSKetch. The 2D structure of compounds are converted into 3D structure and saved in MDLMOL format.

Open Babel

Open Babel is software used to interconvert chemical file formats. It as an open collaborative project allows to search, convert analysis or stored data from molecular modelling, chemistry, solid-state materials or related areas. The mol format of 3D structure compounds are converted into pdb format using Open Babel.

Autodock

Autodock is molecular simulation software.it is a widely used docking program developed at the Scripps research institute. Docking is an important tool for gaining understanding of the binding interactions between a ligand (small molecule) and its target receptor (enzyme) (Anderson, 2003). The autodock requires

several separate pre-docking steps such as ligand preparation, receptor preparation, and grid map calculation.

Pymol

PYMOL is an open source tool to visualize molecules available from (www.pymol.org). It runs on windows, linux and MacOS equally well.

The target protein was docked against the bioactive compounds and the results were visualized using "PYMOL" software.

Results and Discussion

Preparation of ligand

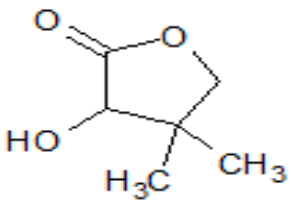
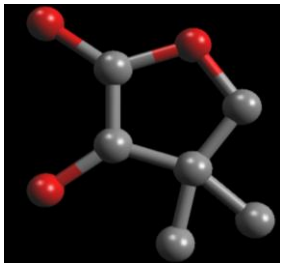
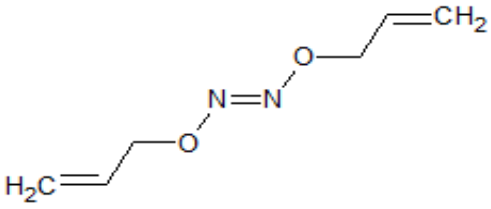
The bioactive compounds such as pantolactone, Allyliponitrite, 2-propanoic-2-propanyl ester, 2,2'-Bioxirane, DL-3,4, Dimethyl 3,4-hexanedol from *Moringa concanesis* Nimmo leaves are subjected for docking analysis.

The two dimensional structure of the ligands were generated using the ACD/CHEMSKETCH tool. This software contains tools for 2D cleaning, 3D optimization, and viewing. These data are saved as a molecular format file (MDL MOL format). The molecular format converter tool (open babel) is used to convert this file into the PDB format and is used during docking analysis. The structure and molecular formula of compounds was shown in. Table 1.

Preparation of Protein

PDB have varying expertise in the techniques of X-ray crystal structure determination, NMR, Cryoelctron microscopy and theoretical modelling. The PDB Id of AMPK is 4RED.

Table.1 2D structure and 3D structure of ligands

COMPOUNDS	MOLECULAR FORMULA	2D STRUCTURE	3D STRUCTURE
Pantolactone	$C_6H_{10}O_3$		
Allyliponiirite	$C_6H_{10}N_2O_2$		

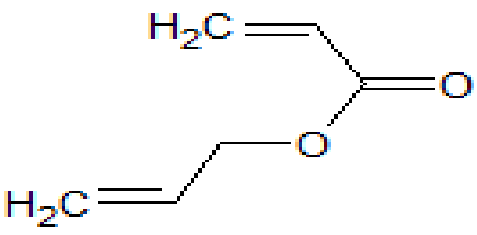
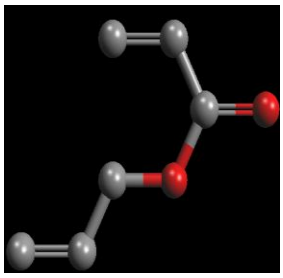
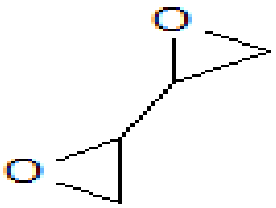
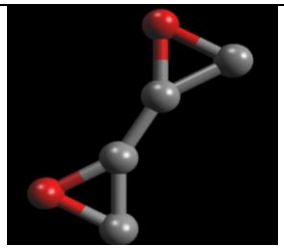
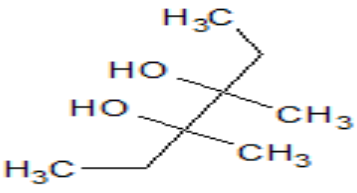
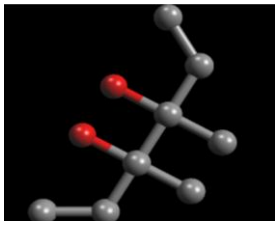
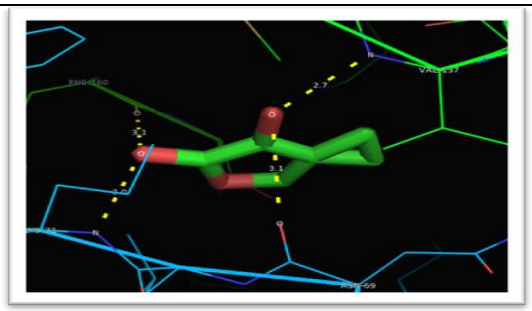
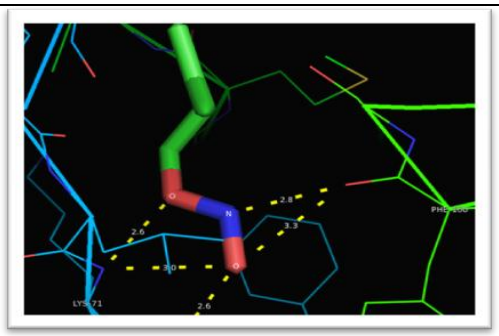
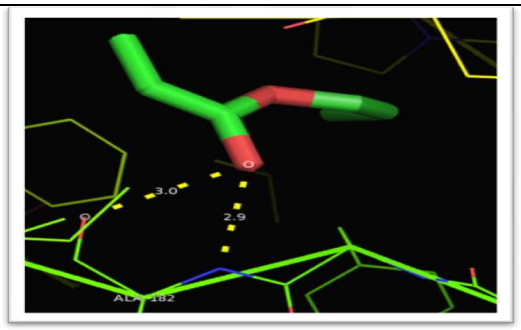
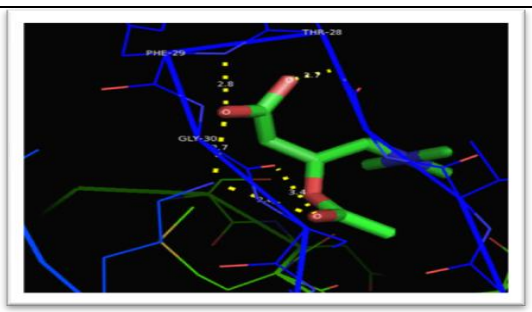
2-propanoic,2-propanyl ester	C6H8O2		
2,2'-BIOXIRANE	$C_4H_6O_2$		
DL,-3,4,Dimethyl 3,4-hexanediol	$C_8H_{18}O_2$		

Table.2 Molecular properties of the ligands

COMPOUNDS	MOLECULAR WEIGHT	NO.OF HYDROGEN ACCEPTORS	NO.OF HYDROGEN DONORS
Pantolactone	146.23	2	2
Allyliponitrite	142.158	4	0
2-propanoic,2-proponyl ester	114.144	2	0
2,2'-bioxirane	86.09	2	0
DL-3,4,Dimethyl 3,4-hexanediol	146.23	2	0

Table.3 HYDROGEN BOND INTERACTION BETWEEN AMPK AND BIOACTIVE COSTITUENTS OF *Moringa concanesis* NIMMO

COMPOUNDS	STRUCTURE	KEY RESIDUES	DISTANCE	NO OF HYDROGEN BOND	DOCKING SCORE (Kcal/mol)
Pantolactone		PHE – 160 LYS – 71 ASN – 69 VAL - 137	3.1 3.0 3.1 2.7	4	-6.07
Allyliponiirite		PHE – 160 LYS - 71	3.0 2.8	2	-7.42
2 - Propanoic, 2 - Propanyl ester		ALA – 182 ALA – 182	3.0 2.9	2	-4.54
2,2'-Bioxirane		PHE – 29 THR – 28 GLY – 30 LYS - 47	2.8 3.7 2.7 3.4	4	-5.98

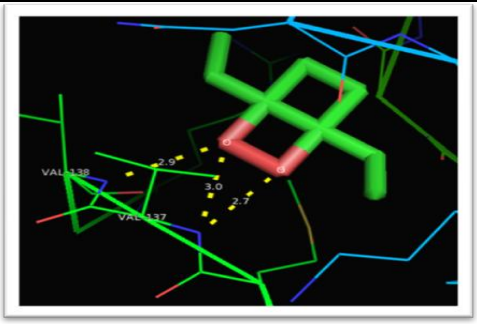
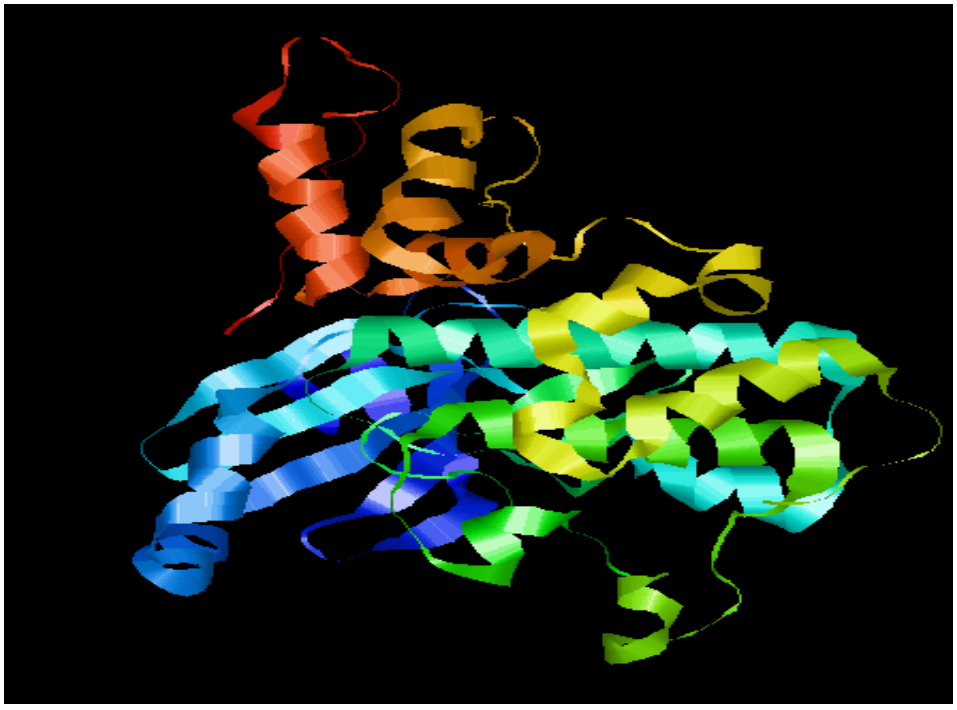
DL, 3,4,Dimethyl 3,4-Hexanediol		VAL – 138 VAL - 137	2.9 3.0, 2.7	2	-7.23

Fig.1 *Moringa concanesis* Nimmo

Fig.2 Crystal Structure of AMPK



Molecular Docking Studies

Molecular docking is an effective tool for Insilco screening. The docking were done to determine the interaction between the AMPK protein and ligands. Autodock tools were used for molecular docking program. Docking studies were performed on developed protein. Autodock tools were used to add kollman charges and polar hydrogen atoms. In autodock, the file is saved in pdbqt format. Auto Grid boxes (x, y, z coordinates126*126*126) were predetermined around the active site of the protein. The Lamarickian genetic algorithm were used in docking calculations. The dock scores were reported in kcal/mol. The Pdbqt format is converted into Pdb format using Open Babel. The best binding mode that fitted well binding activity were checked. The protein ligand hydrogen interaction were viewed and the distance were calculated. The outcome was analysed on the source of ranked clusters of compound conformations and visualized using pymol tool. The binding energy values and molecular interaction of AMPK protein residues and ligands from *Moringa concanesis* Nimmo listed on the Tables2&3. In this study, the compounds Pantolactone, 2, 2'-Bioxirane had 4 interaction with least binding energy.

Type 2 DM is a metabolic disease that can be prevented through lifestyle modification, diet control, and control of overweight and obesity. The lead compounds that activate AMPK in muscles may eventually become novel antidiabetic drug. In this present study, the molecular docking were performed between the AMPK protein and the compounds of *Moringa concanesis* Nimmo leaves like Pantolactone, Allyliponitrite, 2-propanoic, 2-propanyl ester, 2, 2'-Bioxirane, DL-3, 4, Dimethyl 3, 4-hexanediol among these compounds 2,2'bioxirane and pantolactone shows least binding energy and favourable hydrogen bond interaction. The interaction with aminoacid residues indicate that these compounds can be considered as activators of insulin receptor.Further studies are required to understand the molecular interactions of these compounds and structural requirements for their specificity to the various subunits of AMPK or its upstream effectors. Such ongoing efforts may provide a novel class of drugs to treat diabetes and related metabolic abnormalities in the future.

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