Molecular Docking Studies of Bitter Gourd Compounds against P53 Drug Target

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A B S T R A C T

Momordica charantia L common name is bitter gourd and widely distributed throughout tropical and subtropical regions in all continents belonging to the family *cucurbitaceae*. *Momordica charantia* has antioxidant, antihypoglygemic, antifungal, anticancer, antitumour, antidiabetic, antimicrobial, antibacterial, and antiparasitic activity. The compounds with anticancer activity present in *Momordica charantia* are Triterpene, Carotenoid, Cucurbitacin, and Momordin. Lung cancer is one of the most common disease in the world.p53 involves in the regulation of cell cycle and apoptosis. Smoking leads to uncontrolled p53 mechanism of regulation of cell cycle and apoptosis this leads to overexpression of p53 in lung cancer.p53 Human p53 core domain structure was downloaded from PDB database which was docked with compounds from *Momordica charantia* using autodock software. Docked structure visualized using PyMOL molecular viewer. From the four compounds, Momordin demonstrated drug like properties endowed with higher binding affinity and can be further complemented by *in vitro* drug testing against lung cancer.

Introduction

Momordica charantia L, is a medicinal plant it is also known as bitter melon, bitter gourd, bitter squash, or balsam-pear is a tropical and subtropical vine of the family *Cucurbitaceae*, widely grown in Asia, Africa, and the Caribbean for its edible fruit (Tritten and Travis, 2011) has long been frequently used in various Asian traditional medicine systems and commonly consumed as a vegetable (Huang HL *et al.,* 2008).

This herbaceous, tendril-bearing vine grows up to 5 m (16 feet) in length and bears male and female flowers that are yellow in color and grow at the axils of the leaves. Traditionally the plant is used in treatment of diabetes, to prevent measles, hepatitis, to get rid of worms and parasites and the topical applications are used for healing wounds, treatment of cancer. In traditional medicine of India different parts of the plant are used as claimed treatments

for diabetes (particularly Polypeptide-p, an insulin analogue), and as a stomachic, laxative, emetic, for the treatment of cough, respiratory diseases, skin diseases, wounds, ulcer, gout, and rheumatism (Wang *et al.,* 2014). Figure 1 shows the plant *momordica charantia*

Extracts have been reported to possess anti-cancer activity against lymphoid leukemia, lymphoma, choriocarcinoma, melanoma, breast cancer, skin tumor, prostatic cancer, squamous carcinoma of the tongue and larynx, human bladder carcinomas and Hodgkin's disease (Licastro, 1980). *Momordica charantia* has a number of purported uses including cancer prevention, treatment of diabetes, fever, HIV and AIDS, and infections (Grover and Yadav., 2004). Bitter gourd are rich in Vitamin A, Vitamin C, carbohydrates, and iron (Trivedi Lakshmi *et al.,* 2011).

Momordica charantia has antioxidant (Jittawan Kubola *et al.,* 2008), anti-inflammation (Raish *et al.,* 2016), antihypoglygemic, antifungal (Zhu *et al.,*1991), anticancer (Pornsiri *et al.,* 2010), antitumour (Hlin *et al.,* 2014), antidiabetic (Güdr, Wu SB *et al.,* 2017), antimicrobial (Rashid *et al.,*2004), antibacterial (Chang *et al.,*2017), antiviral and antiparasitic activity. Bitter gourd seed can be potentially used to destroy the cancer cells. The compound with anticancer activity present in *momordica charantia* are triterpene, carotenoid, cucurbitacin, and momordin.

Lung cancer is most common disease in the world. Lung cancer is the most prevalent type of cancer which causes greater than millions worldwide cancer-related death (*Herbst RS et al., 2008*).About 85−90% of lung cancer is caused due to tobacco smoking resulting in bronchogenic carcinoma (Hackshaw *et al.,* 1997). Lung cancer also known as lung carcinoma, is a malignant lung tumour characterized by uncontrolled cell growth in the tissue of the lung (Falk and Williams *et al.,* 2010).

It has been classified into four distinct histological types, namely, small cell lung carcinoma (SCLC) and three non-small cell lung carcinoma (NSCLC) types adenocarcinoma (ADC), squamous cell carcinoma (SQC), and large cell carcinoma (LCC) (Kohno *et al.,2014)*. This type of cancer develops its proliferation through alterations in oncogenes, such as EGFR and tumor suppressor genes, such as *TP53, RB1, CDKN2A/p16* (Herbst *et al.,* 2008).

Smoking is the most important root of all lung cancer types but small-cell lung cancer and squamous-cell carcinoma are more strongly caused by tobacco smoke. However, in patients who have never smoked in their life, adenocarcinoma is the most frequent type most cancers that start in the lung, known as primary lung cancers, are carcinomas.

The two main types are small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC). The most common symptoms are coughing (including coughing up blood), weight loss, shortness of breath, and chest pains. (Horn *et al.,* 2015).

The vast majority of (85%) of cases of lung cancer are due to long term tobacco smoking (Alberg *et al.,* 2016) 10-15% of cases occur in people who never smoked(Thun MJ *et al.,*2008).

These cases often caused by the combination of genetic factors and exposure to radon gas, second-hand smoke & air pollution (Carmona, 2006). Tobacco smoking is by far the main contributor to lung cancer (Alberg *et al.,* 2016).p53 is a tumour suppressor gene

which plays a major role in regulating or controlling cell cycle or apoptosis.p53 has been described as "the guardian of the genome" referring to its role in conserving stability by preventing genome mutation (Strachan, 1999) and it was First discovered in 1979.

The TP53 tumor suppressor gene is located at the short arm of chromosome 17 (17p13). It contains 11 exons spanning 20 kilobases and encodes a nuclear phosphoprotein of 53 kDa. The TP53 protein contains distinct functional domains: the N-terminus transactivation domain, the sequence-specific DNA-binding domain, the oligomerization domain, and the C-terminus negative regulatory domain (McKinney2005). p53 play a major role in lung cancer. It has been overexpressed and leads to cell death causes tumour. Smoking leads to uncontrolled p53 mechanism of regulation of cell cycle and apoptosis (Mraz M *et al.,* 2009).

In normal p53 level in the cell will be very low and it is quite unstable, degraded quickly DNA damage and other stress signals may trigger the increase of p53 proteins, which have three major functions: growth arrest, DNA repair and apoptosis (cell death) (Gilbert *et al.,*2008*).* The growth arrest stops the progression of cell cycle, preventing replication of damaged DNA. During the growth arrest, p53 may activate the transcription of proteins involved in DNA repair. Apoptosis is the "last resort" to avoid proliferation of cells containing abnormal DNA (Blagosklonny *et al.,* 2002). In cell cycle arrest the G1 phase has been arrest (Han ES *et al.,* 2008). In normal function phosphorylated p53 and mdm2 gene to form a p53 complex and p53 has been degraded if p53 has not form the p53 complex leads to overexpression and increasing the level of p53

The cellular concentration of p53 must be tightly regulated. While it can suppress tumors, high level of p53 may accelerate the aging process by excessive apoptosis. The major regulator of p53 is Mdm2, which can trigger the degradation of p53 by the ubiquitin system (Blagosklonny *et al.,* 2002). The mechanism of p53 in lung cancer has been changed due to exposure of UV and smoking leads to damage in the cell.

Molecular docking is one of the method used in structure based drug design due to its ability to predict the binding-conformation of small molecule ligands to the appropriate target binding site. Characterisation of the binding behaviour plays an important role in rational design of drugs as well as to elucidate fundamental biochemical processes (Kitchen DB *et al.,*2004).The phytochemical constituents extracted from the Momordica *charantia* are Triterpene, Carotenoid,Cucurbitacin, Momordin shows the anti-cancer activity.

Materials and Methods

Protein Preparation

Uniprot

UniProt is a freely accessible database of protein sequence and functional information, many entries being derived from genome sequencing projects. It contains a large amount of information about the biological function of proteins derived from the research literature.The UniProt consortium comprises the European Bioinformatics Institute (EBI), The Swiss Institute of Bioinformatics (SIB), and the Protein Information Resource (PIR). UniProt KB is the central access point for extensive curated protein information, function, classification, and cross-reference (http://www.uniprot.org/) (dayhoff,1965).

PDB

The protein data bank (PDB) is a crystallographic database for three dimenstional structure data for biological molecule, such as protein and nucleic acid (Laskowski *et al.,* 1997). The data obtained by x-ray crystallography, NMR spectroscopy and submitted by biologists and biochemicals from around the world, are freely accessible on the internet via the websites of its member organization. (https://www.rcsb.org/pdb/home/home.do) (berman, 2008).

PFAM

Pfam is a database of protein families that includes their annotations and multiple sequence alignments generated using hidden Markov models. (Finn RD *et al.,* 2008). The most recent version, Pfam 31.0, was released in March 2017 and contains 16,712 families (Finn *et al.,* 2017). The general purpose of the Pfam database is to provide a complete and accurate classification of protein families and domains(Sammut *et al.,* 2008).Originally, the rationale behind creating the database was to have a semi-automated method of curating information on known protein families to improve the efficiency of annotating genomes (Sonnhamme *et al.,* 1997) The Pfam classification of protein families has been widely adopted by biologists because of its wide coverage of proteins and sensible naming conventions(Xu *et al.,* 2012).

RASMOL

RasMol is a computer program written for molecular graphics visualization intended and used mainly to depict and explore biological macromolecule structures, such as those found in the Protein Data Bank. It was originally developed by Roger Sayle in the early 1990s (Roger Sayle *et al.,* 1995)

Ligand Preparation

ACD Chemsketch

ACD/ChemSketch is a molecular modeling program used to create and modify images of chemical structures. Also, there is a software that allows molecules and molecular models displayed in two and three dimensions, and 2Dstucture cleaning 3d optimization to understand the structure of chemical bonds and the nature of the functional groups (utlizandochemsketch, 2014).

Openbabel

Open Babel is computer software, a chemical expert system mainly used to interconvert chemical file formats. Due to the strong relationship to informatics this program belongs more to the category cheminformatics than to molecular modelling. (http://openbabel.org/) (O'Boyle *et al.,* 2011).

Autodock

AutoDock is a molecular modeling simulation software. It is especially effective for protein-ligand docking. Auto dock is a automate docking tools. AutoDock 4 is available under the GNU General Public License. AutoDock Vina is available under the Apache license. The software is used for modelling flexible small molecule such as drug molecule binding to receptor protein of known three dimenstional structures. It is designed to predict how small molecules, such as substrates or drug candidates bind to a receptor of known 3D structures (Trott *et al.,* 2010). AutoDock 4 actually consists of two main programs. Autodock performs the

docking of the ligand to a set of grids describing the target protein autogrid pre calculates these grids. (Gauet Morris *et al.,* 2013)

It uses Genetic Algorithms for the conformational search and is a suitable method for the docking studies. After the grid generation, the processed ligand was docked with the protein to evaluate the interaction between each target protein and the ligand. Interactions were hydrophilic, Vander Waals and hydrophobic. The interaction strength varies from protein to protein based on its affinity for the ligand.

PyMOL

PyMOL is computer software, a molecular visualization system created by Warren Lyford DeLano. PyMOL is one of a few open-source model visualization tools available for use in structural biology. private software company dedicated to creating useful tools that become universally accessible to scientific and educational communities.

It is currently commercialized by Schrödinger, Inc. PyMOL can produce high-quality 3D images of small molecules and biological macromolecules, such as proteins. According to the original author, by 2009, almost a quarter of all published images of 3D protein structures in the scientific literature were made using PyMOL.

Results and Discussion

Sequence retrieval and domain

The sequence of human P53 (*Homo sapiens*) was retrieved from UNIPROT database, its sequence accession number is P04637 and domain performed using pfam core region.

Structure Retrival: P53 Human p53 core domain

The three dimensional structure of p53 core domain has retrieved and protein id-3D08 from protein data bank (PDB) database (http://www.rcsb.org/pdb/home.do). The structure has visualized in rasmol the final structure of protein. This structure was determined using x-ray diffraction with resolution 1.40 chain A. Protein information in Table 1. 3D structure of protein was shown in the figure 2.

The direct functional and structural determination of all the proteins in an organism is prohibitively costly and time consuming because of the relative scarcity of 3D structural information therefore primary sequence analysis is preferred to identify majority of protein domain families (Sonnhammer *et al.,* 1998).p53 human core domain was predicted using Pfam domain analysis. The predicted domain is PCI domain (95-289) and shown in Figure 3

Lig and Preparation

The compounds from *momordica charantia* were retrieved from NCBI PubChem Compound database (https://pubchem.ncbi.nlm.nih.gov). The ligands were drawn using ACD/ chemsketch then structure was saved as a molecular file format (mol format).The MDL mol structure was converted to pdb format using open babel tool. The structure and molecular formula of anticancer compound was shown in Table 2. Lipinski's rule of the Ligands are shown in Table.3. Lipinski's rule of five also known as the Pfizer's rule of five or simply the rule of five (RO5) is a rule of thumb to evaluate drug likeness or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a

likely orally active drug in humans. The rule was formulated by Christopher A. Lipinski in 1997, based on the observation that most orally administered drugs are relatively small and moderately lipophilic molecules (Lipinsk *et al.,* 2001)

Table.1 p53 human core domain

S.NO	PROTEIN NAME	QUERY COVERAGE	PDB ID	CHAIN	RESOLUTION
1.	*P53 human core domain*	94-293	3D08	A	1.40

Table.2 Compound properties and 2D and 3D structure
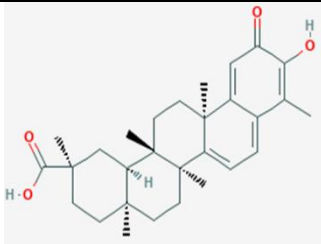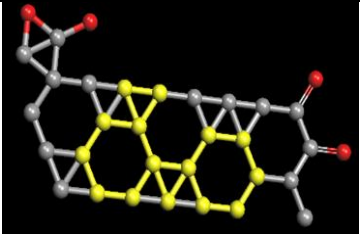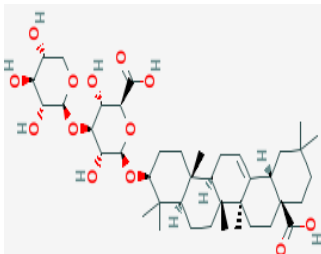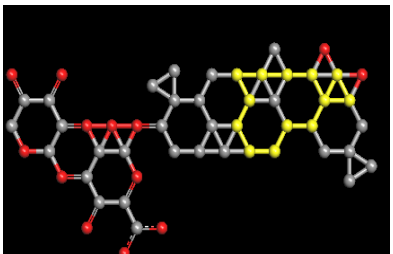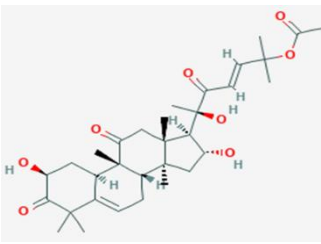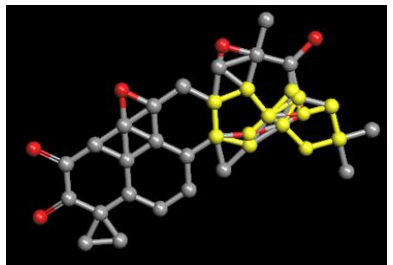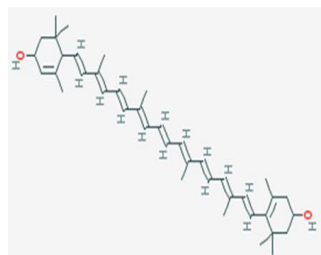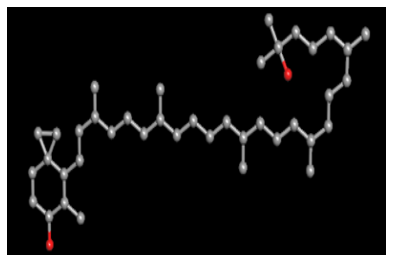
S.NO	COMPOUND NAME	MOLECULAR FORMULA	2D STRUCTURE	3D STRUCTURE
1.	TRITERPENE	$C_{29}H_{38}O_4$		
2.	MOMORDIN	$C_{41}H_{64}O_{13}$		
3.	CUCURBITACIN	$C_{32}H_{46}O_8$		
4.	CAROTENOID	$C_{40}H_{56}O_2$		

Table.3 Lipinski rule of the Ligands

COMPOUNDS	MOLECULAR WEIGHT	HYDROGEN BOND DONOR	HYDROGEN BOND ACCEPTOR	LOGP
TRITERPENE	450.619 g/mol	2	4	5.9
MOMORDIN	764.95 g/mol	7	13	4.6
CUCURBITACIN	558.712 g/mol	3	8	12.2
CAROTENOID	568.886 g/mol	1	2	2.6

Table.4 Interaction between atoms of the ligands from *MOMORDICA CHARANTIA* and the amino acid residues of P53 HUMAN CORE DOMAIN protein along with the hydrogen bond distance and docking score

Ligand	P53HUMAN CORE DOMAIN protein		Ligand Atom	Distance (Å)	Docking Score
	Residue	Atom			
TRITERPENE	PHE113	HH	O	3.1	
	SER259	HN	O	2.9	
	SER259	HN	O	2.6	
	SER259	HN	O	2.4	-9.52
	ASN131	HD	O	3.2	
	ASN131	HD	O	3.4	
MOMORDIN	VAL97	HN	O	3.2	
	VAL97	HN	O	3.3	
	VAL97	HN	O	3.2	
	SER99	HG	O	2.5	-11.63
	SER99	HG	O	2.5	
	ARG267	HH	O	3.3	
	ARG267	HH	O	2.9	
CUCURBITACIN	ARG110	HE	O	2.9	-10.72
CAROTENOID	ARG110	HE	O	3.3	-3.91
	GLU104	HE	O	3.1	

Fig.1 *Momordica charantia*

Fig.2 3D Structure of p53 Core Domain [3D08]

Fig.3 Pfam Result page

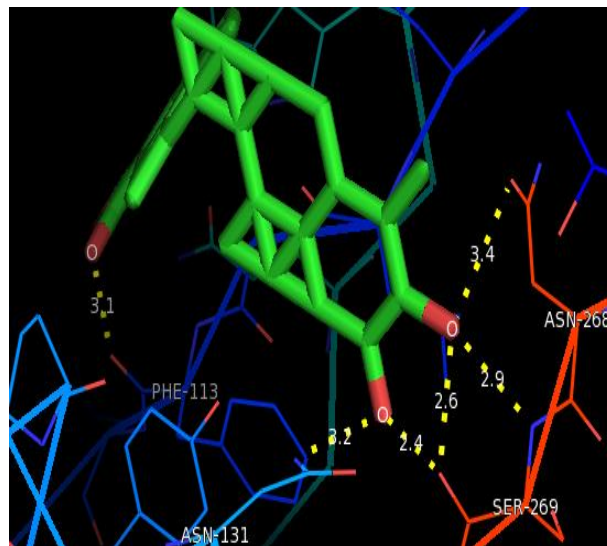**Fig.4** Interaction between triterpene and p53 core domain and formation of hydrogen bond

Fig.5 Momordin Interaction between p53 with momordin and formation of hydrogen bond
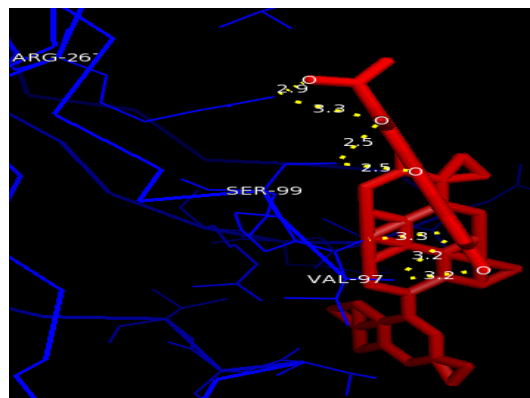
Fig.6 Cucurbitacin Interaction between p53 with cucurbitacin and formation of hydrogen bond
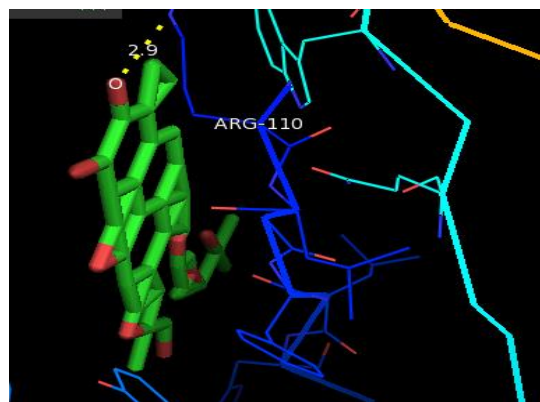
Fig.7 Carotenoid Interaction between p53 with carotenoid and formation of hydrogen bond
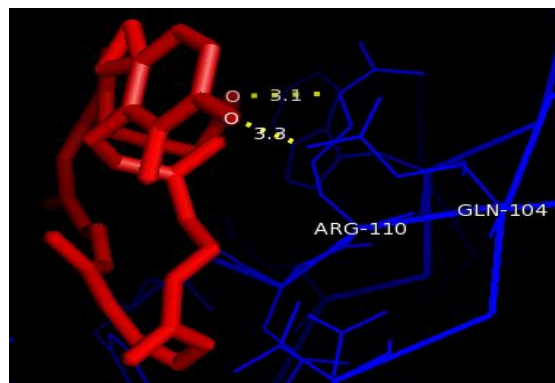
Molecular docking studies of p53 and compounds from *momordica charantia*

Docking studies were performed with compounds from *Momordica charantia* and p53 core domain. After docking, the ligands were ranked according to their protein-ligand affinity. AutoDock results were analyzed based on the interactions between p53 human core domain proteins and compounds from *Momordica charantia* and the binding energies of the complexes. The

accuracies of the AutoDock results were confirmed by considering the lowest binding energy and the hydrogen bonds between the p53 and compounds from *Momordica charantia*. Momordin demonstrated good affinity with p53.

The docking results are ranked according to the binding energies with triterpene, momordin, cucurbitacin, carotenoid. The docking studies of p53 with Triterpene shows four hydrogen bond with binding energies of -9.52 kcal/mol has shown in figure 4.p53 with Momordin shows two hydrogen bond with binding energies of -11.03 kcal/mol has shown in figure5.p53 with Cucurbitacin shows two hydrogen bond with binding energies of -10.72 kcal/mol has shown in figure 6.p53 with Carotenoid shows one hydrogen bond with binding energies of -3.91 kcal/mol has shown in figure7.

Interaction between atoms of the ligands from *Momordica charantia* and the amino acid residues of p53 human core domain with the hydrogen bond distance and docking score was shown in the Table 3. From the result, Momordin were found to have a good binding affinity with p53 and more hydrogen bond interactions.

The interaction of proteins with ligand molecules plays a major role in structural based drug designing. *Momordica charantia* has been used as a valuable oriental medicine for thousands of years. Recently, many studies have focused on the identification of cancer inhibitors from natural sources, and clinical trials with such chemicals have begun. In the present study, bioactive compounds from *Momordica charantia,* namely, triterpene, momordin, carotenoid, and cucurbitacin were docked against P53 human core domain which was over expressed in lung cancer. Analysis of

docking studies showed that the compound momordin were showed best inhibition p53 core domain with least binding energy and shows seven hydrogen bond interactions. Hence, through *in silico* analysis momordin from *Momordica charantia* can be used as an anticancer agent for lung cancer which could be further confirmed by *in vivo* and *in vitro* studies. Therefore, these results may offer therapeutic advantages in the treatment and prevention of human lung cancer.

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