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Molecular Docking Studies of *Moringa concanensis* Nimmo Leaf Phytocompounds for Brain Cancer

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Abstract

Phytochemicals are the secondary metabolites of medicinal plants and are considerably used in traditional cancer research. Computational methods involving virtual screening, shape and pharmacophore analysis and molecular docking have been used to select chemicals that target a particular protein or enzyme and to determine potential protein targets for well characterized as well as for novel phytocompounds. Objective of the present study is, in silico approach to identifying the anticancer activity of phytochemicals from Moringa concanensis Nimmo plant against the brain cancer target proteins. The structures of the target receptor binding sites of all four GC-MS compounds and brain cancer protein structure (PDB ID: 1QH4 Crystal structure of brain-type creatine kinase at 1.41 A resolution) were obtained from the RCSB Protein Data Bank. The docking analysis of M. concanensis Nimmo leaf compounds were carried out by means of the Autodock tools and Autodock v4.2 program. The results of docking analysis show the binding affinity of legend molecules (Phytocompounds) towards the brain cancer receptors. Docking studies of the M. concanensis Nimmo leaf contains four phytocompounds which can be considered for developing into a potent brain cancer drug.

Keywords: *Brain cancer, Moringa concanensis, phytocompounds, molecular docking*

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INTRODUCTION

Cancer has been seriously threatening the health and life of human beings for a long period and has become the leading disease related to cause of the deaths for human population. The World Health Organization estimates that approximately 80% of the world's inhabitants rely on traditional medicine for their primary health care [1]. It was estimated that worldwide, there were approximately 12 million deaths in 2030 [2]. Brain cancer types include adult brain tumor, brain stem glioma, and cerebellar astrocytoma. Glioma is a type of tumor that starts in the brain or spine. It is called a glioma because it arises from glial cells. The most common site of gliomas is the brain. Gliomas make up about 30% of all brain and central nervous system tumors and 80% of all malignant brain tumors [3]. Plant based drugs have a long history in both traditional and modern societies as herbal remedies or crude drugs, or as purified compounds approved by the Food and Drug Administration and similar regulatory agencies [4, 5]. Drug discovery from plants still provides new important drugs, many of which are approved or have undergone trials for clinical uses against cancer, malaria, Alzheimer's disease, HIV/AIDS, pulmonary pathologies and other diseases [6]. However, plant-based drugs present many challenges, including legal and logistic difficulties involved in the procurement of plant materials [7, 8].

Evaluation of Phytochemical, Pharmacognostical and Antimicrobial Studies [9, 10] Apoptosis inducing effects by using HepG2 cell lines [11], and GC-MS analysis of leaf and bark [12], were reported in *M. concanensis.*

Even whole plant extracts are used to prevent, arrest, or reverse the cellular and molecular processes of carcinogenesis due to its multiple intervention strategies [13]. Natural phytochemicals derived from medicinal plants have gained significant recognition in the

potential management of several human clinical conditions, including cancer. Plants have long been used in the treatment of cancer [14]. The National Cancer Institute collected about 35,000 plant samples from 20 countries and has screened around 114,000 extracts for anticancer activity [15]. Of the 92 anticancer drugs commercially available prior to 1983 in the United States, and among worldwide approved anticancer drugs between 1983 and 1994, 60% are of natural origin [16].

Computational biology and bioinformatics have the potential not only of speeding up the drug discovery process thus reducing the costs, but also of changing the way drugs are designed. Rational drug design helps to facilitate and speedup the drug designing process, which involves variety of methods to identify novel compounds [17, 18]. One such methods is the docking of drug molecule with the receptor (target). The site of drug action, which is ultimately responsible for the pharmaceutical effect, is a receptor. Docking is the process by which two molecules fit together in 3D space [19].

In recent research, computational techniques have enabled researchers to estimate the binding affinity of different molecules before their synthesis and evaluation in lab. Molecular docking is used to find out the binding orientation of the small molecules against their targets. Thus, molecular docking is considered as important technique in drug designing and screening of novel compounds against this dreadful and challenging diseases [20]. The present investigation is focused on the docking of the plant *M. concanensis* Nimmo leaf. Phytocompounds are used 1, 3-Dioxolane, 2-(3-bromo-5, 5, 5-tricloro-2, 2-dimethylpentyl)-, Butanoic acid, 2-hydroxy-2-methyl-, methyl ester, DL-3,4-Dimethyl-3,4-hexanediol, Pantolactone against 1QH4, proteins.

MATERIAL AND METHODS

Isolation and Identification of *M. concanensis* Nimmo Leaf Phytocompounds

The *M. concanensis* leaf samples were air-dried and powdered. Required quantity of powder was weighed and transferred to stopper flask and treated with ethanol until the powder was fully immersed. The flask was shaken at every 1 h interval for the first 6 h and it was kept aside and again shaken after 24 h. This process was repeated for 3 days and the extract was filtered. The extract was collected and evaporated to dryness by using a vacuum distillation unit. The final residue was obtained and subjected to GC-MS analysis. Interpretation on mass spectrum GC-MS was conducted using the database of National Institute of Standard and Technology (NIST) having more than 62,000 patterns. The spectrum of the unknown component was compared with the spectrum of the known components stored in the NIST library. The name, molecular weight and structure of the *Moringa concanensis* Nimmo leaf Phytocompounds 1, 3-Dioxolane, 2-(3-bromo-5, 5, 5-tricloro-2, 2-dimethylpentyl)-, Butanoic acid, 2-hydroxy-2-methyl-, methyl ester, DL-3,4-Dimethyl-3,4-hexanediol, Pantolactone of the test materials were ascertained.

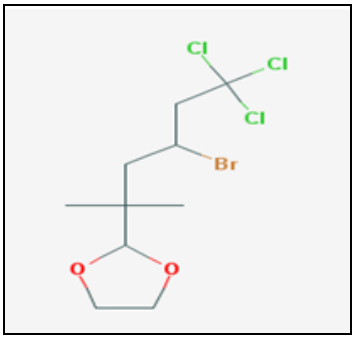
Retrieval of the Three-Dimensional Structure of Target Proteins

The structures of the target receptor binding sites of all four GC-MS compounds and brain cancer protein structure **(**PDB ID: 1QH4 Crystal structure of brain-type creatine kinase at 1.41 A resolution) were obtained from the RCSB Protein Data Bank. Then the possible binding sites of selected target receptors were searched using Q-site Finder to predict the ligand binding site and also whole protein structure assumed as a binding site. It works by binding hydrophobic probes to the protein and finding clusters of probes with the most favorable binding energy.

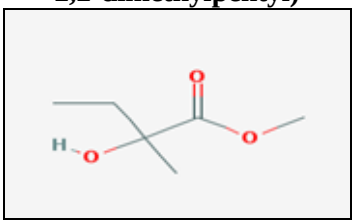
Ligand Selection

Four phytocompounds namely 1,3-Dioxolane, 2-(3-bromo-5, 5, 5-tricloro-2, 2-dimethylpentyl)-, Butanoic acid, 2-hydroxy-2-methyl-, methyl ester, DL-3,4-Dimethyl-3,4-hexanediol, Pantolactone isolated from *M. concanensis* Nimmo leaf were screened against the brain cancer protein. The drugs were chosen from the National Centre for Biotechnology Information (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

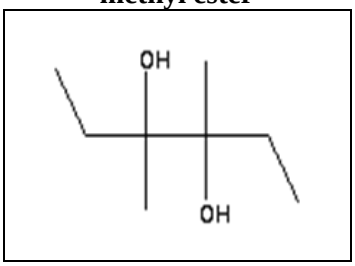
(http://openbabel.org) converter. All the chemical structures of ligand compounds used in the study were shown in Figure 1.



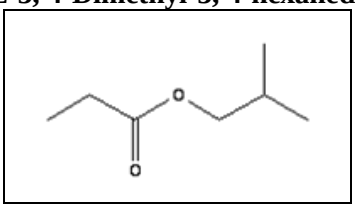
1, 3-Dioxolane, 2-(3-bromo-5,5,5-tricloro-2,2-dimethylpentyl)



Butanoic acid, 2-hydroxyl-2-methyl-, methyl ester



DL-3, 4-Dimethyl-3, 4-hexanediol



Pantalactone

Fig. 1: *The Chemical Structures of Moringa concanensis Nimmo Leaf Phytocompounds.*

Docking Analysis

The docking analysis of *Moringa concanensis* Nimmo leaf-compounds were carried out by means of the Autodock tools [21] (ADT) v1.5.4 and Autodock v4.2 program; (Autodock, Autogrid, Autotors, Copyright-1991-2000) from the Scripps Research Institute. To run Autodock, searching grid extended over the selected target proteins was used and polar hydrogen was added to the ligand moieties. Kollman charges were assigned and atomic salvation parameters were added. Polar hydrogen charges of the Gasteiger-type were assigned and the nonpolar hydrogen was merged with the carbons and the internal degrees of freedom and torsions were set. *M. concanensis* Nimmo leaf-compound was docked to the entire target protein complexes with the molecule considered as a rigid body and the ligands being flexible. The search was extended over the whole receptor protein used as blind docking. Affinity maps for all the atom types present, as well as an electrostatic map, were computed with a grid spacing of 0.375 E. The search was carried out with the Lamarckian Genetic Algorithm [22]. Populations of 150 individuals with a mutation rate of 0.02 have been evolved for 10 generations. Evaluation of the results was done by sorting different complexes with respect to the predicted binding energy. A cluster analysis based on root mean square deviation values, with reference to the starting geometry was subsequently performed and the lowest energy conformation of the more populated cluster was considered as the most trustable solution. The hydrophobic effect of ligand was retrieved by ALOGPS 2.1. This Applet provides interactive online prediction of logP, water solubility and pKa(s) of compounds for drug design (ADME/T and HTS) and environmental chemistry studies [23].

RESULTS

The target protein and inhibitors were geometrically optimized. Given the three dimensional structure of a target receptor molecule usually a protein; chemical compounds having potential affinity toward site are designed rationally, with the aid of computational methods. Detailed bioinformatics analysis offers a convenient methodology for efficient *in silico* preliminary analysis of possible function of new drug.

The docking simulations in the active sites of 1QH4 proteins were performed by the Autodock program, which has been shown to successfully reproduce experimentally observed binding modes in terms of lowest docking energy. The target protein structures of 1QH4 proteins were docked with *M.concanensis* Nimmo leaf Phytocompounds (1, 3-Dioxolane, 2-(3-bromo-5, 5, 5-tricloro-2,

2-dimethylpentyl)-, Butanoic acid, 2-hydroxy-2-methyl-, methyl ester, DL-3,4-Dimethyl-3,4-hexanediol, Pantolactone which provided excellent results as were seen by the least values of the binding energy.

The best possible binding modes of *Moringa concanensis* Nimmo leaf Phytocompounds 1, 3-Dioxolane, 2-(3-bromo-5, 5, 5-tricloro-2, 2-dimethylpentyl)-, Butanoic acid, 2-hydroxy-2-methyl- methyl ester, DL-3,4-Dimethyl-3,4-hexanediol, Pantolactone ligands at target proteins active sites are displayed in Figures 2–9 by using PYMOL tool v1.1. Ligands hydrogen-bonding to four target proteins and their corresponding energy values are listed in Table 1.

The results of docking analysis show the binding affinity of ligand molecules (Phytocompounds) towards the brain cancer receptors. Ligand molecules that possess strong binding affinity towards Pantolactone (–4.15 kcal/mol) are shown in Figures 8 and 9; followed by compounds with moderate binding affinity 1,3-Dioxolane, 2-(3-bromo-5,5,5-tricloro-2,2-dimethylpentyl)- (–3.90 kcal/mol), shown in Figures 2 and 3; and DL-3, 4-Dimethyl-3, 4-hexanediol (–3.05 kcal/mol), shown in Figures 6 and 7. The compounds that has less binding affinity were Butanoic acid, 2-hydroxy-2-methyl-, methyl ester (–2.75 kcal/mol) (Figures 4 and 5).

Table 1: *Summary of Molecular Docking Results of Moringa concanensis Nimmo Leaf Phytocompounds with Drug Target Protein of Brain Cancers.*

Type of Cancer	Protein (PDB ID)	Phytochemical Compounds	Binding Amino Acids	Binding Energy (kcal/mol)
Brain cancer	1QH4	1,3-Dioxolane, 2-(3-bromo-5,5,5-tricloro-2,2-dimethylpentyl)-	ASP 195/3.00 Å 12 ATOMS	–3.90
Brain cancer	1QH4	Butanoic acid, 2-hydroxy-2-methyl-, methyl ester	LEU 193/HN 19 ATOMS 2.91 Å, PHE 192/HN 39 ATOMS 3.02 Å, HIS191/HN 56 ATOMS 3.09 Å, ILE 188/O 75 ATOMS, LEU 187/O 94 ATOMS 2.76 Å	–2.75
Brain cancer	1QH4	DL-3,4-Dimethyl-3,4-hexanediol	HIS 305/O 18 ATOMS 2.72 Å, PHE 308/HN 38 ATOMS 2.76 Å, GLY 309/HN 45 ATOMS 2.72 Å	–3.05
Brain cancer	1QH4	Pantolactone	GLY 73/HN 23 ATOMS 2.71 Å, CYS 74/HN 33 ATOMS 3.17 Å, CYS 74/O 23 ATOMS 2.46 Å	–4.15

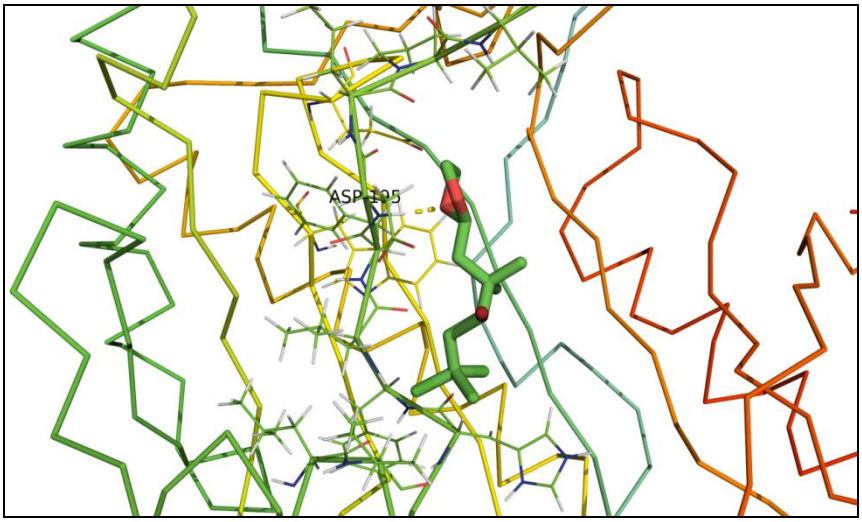


Fig. 2: *Docked Orientation of 1,3-Dioxolane, 2-(3-Bromo-5,5,5-Tricloro-2,2- Dimethylpentyl) with Hydrogen Bond Interaction of Corresponding Amino Acid Residues of Brain Cancer Protein (PDB ID: 1QH4).*

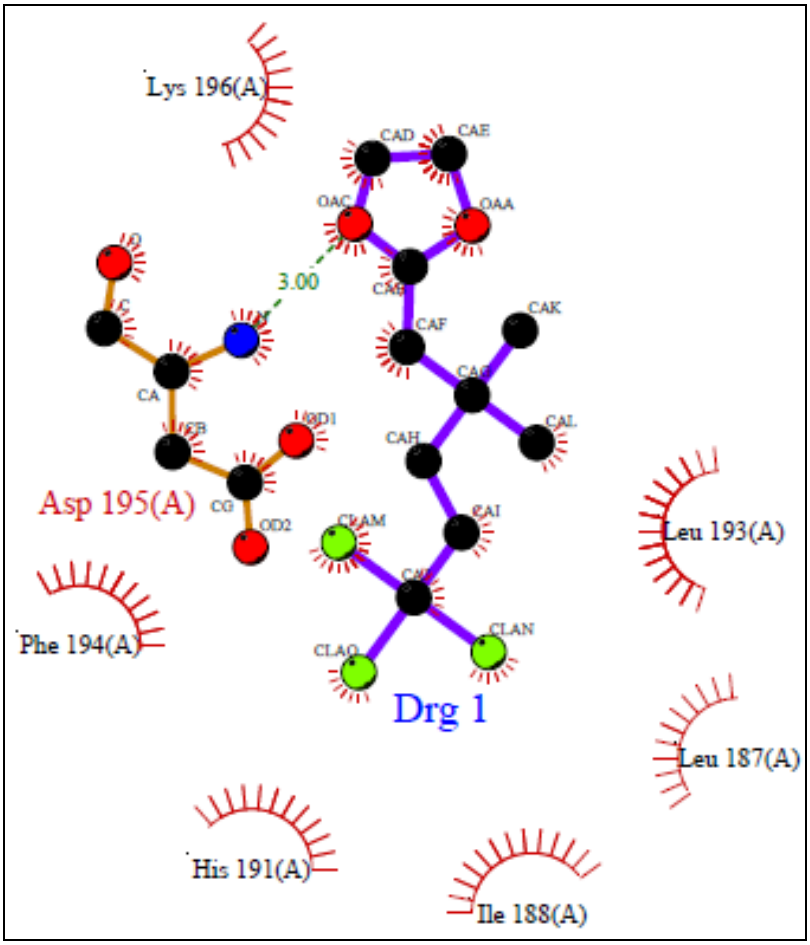


Fig. 3: *Hydrophobic Interactions between 1,3-Dioxolane, 2-(3-Bromo-5,5,5-Tricloro-2,2-Dimethylpentyl) and Brain Cancer Protein (PDB ID: 1QH4).*

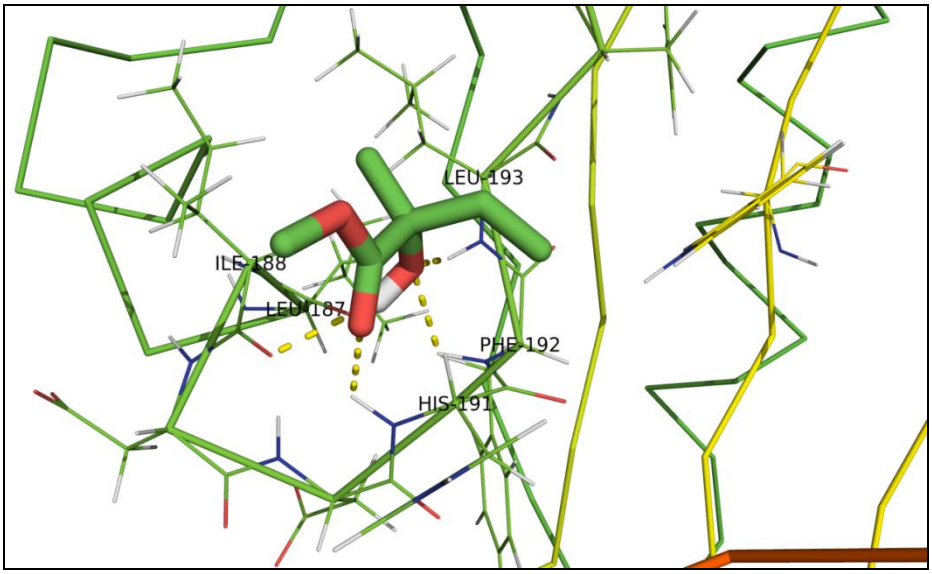


Fig. 4: *Docked Orientation of Butanoic Acid, 2-Hydroxy-2-Methyl-, Methyl Ester with Hydrogen Bond Interaction of Corresponding Amino Acid Residues of Brain Cancer Protein (PDB ID: 1QH4).*

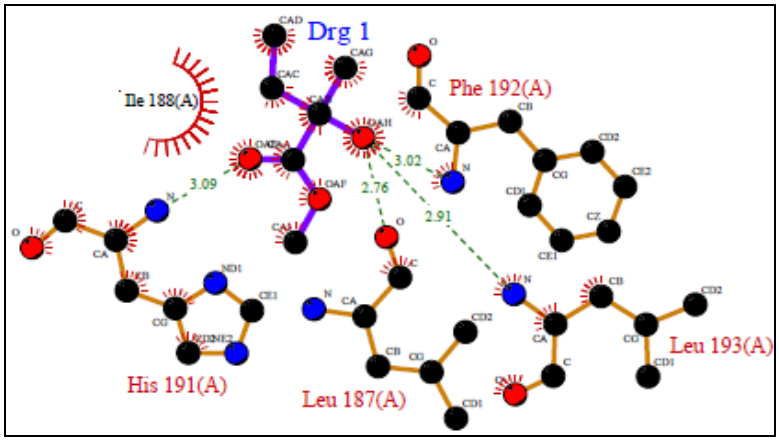


Fig. 5: *Hydrophobic Interactions between Butanoic Acid, 2-Hydroxy-2-Methyl- Methyl Ester and Brain Cancer Protein (PDB ID: 1QH4).*

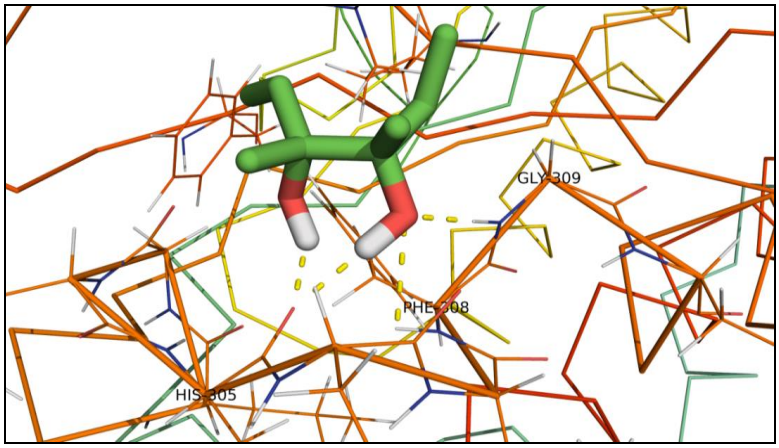


Fig. 6: *Docked Orientation of DL-3, 4-Dimethyl-3, 4-Hexanediol with Hydrogen Bond Interaction of Corresponding Amino Acid Residues of Brain Cancer Protein (PDB ID: 1QH4).*

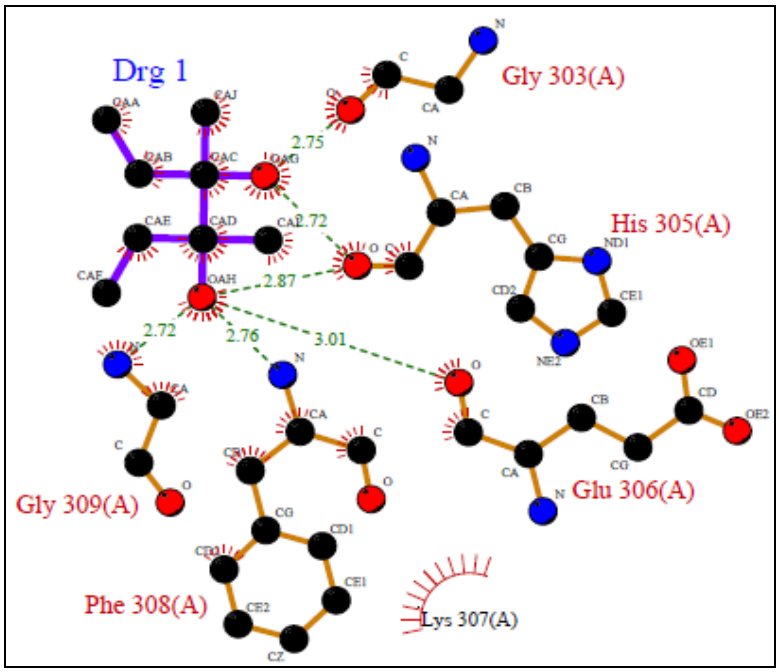


Fig. 7: *Hydrophobic Interactions DL-3, 4-Dimethyl-3, 4-Hexanediol and Brain Cancer Protein (PDB ID: 1QH4).*

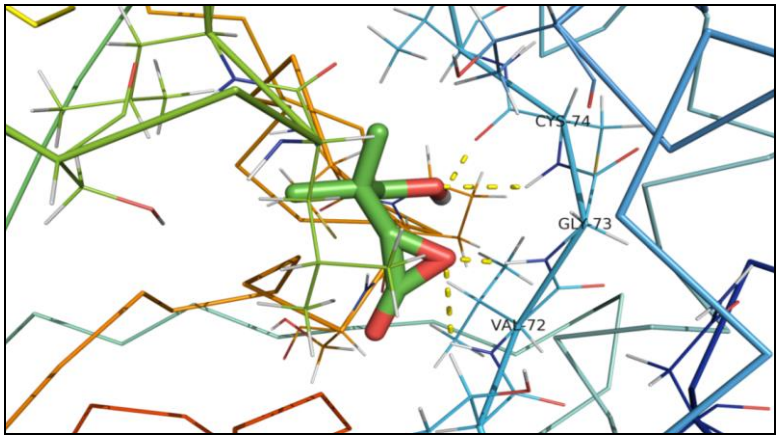


Fig. 8: *Docked Orientation of Pantolactone with Hydrogen Bond Interaction of Corresponding Amino Acid Residues of Brain Cancer Protein (PDB ID: 1QH4).*

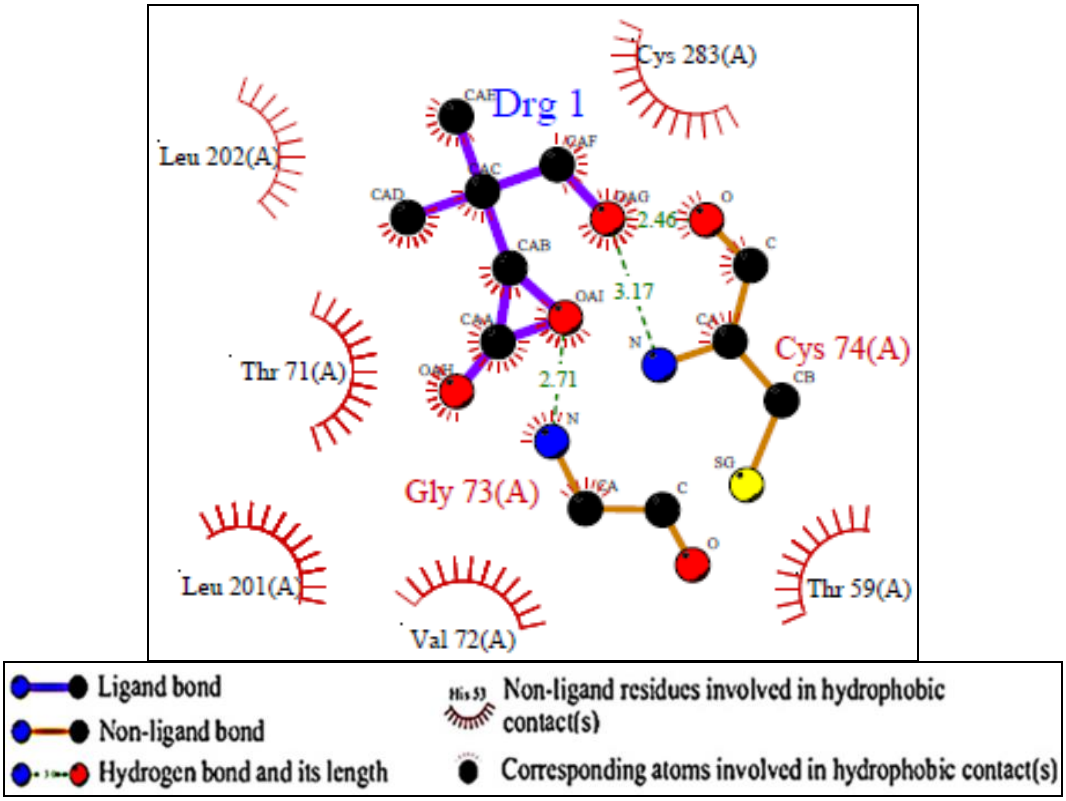


Fig. 9: *Hydrophobic Interactions Pantolactone and Brain Cancer Protein (PDB ID: 1QH4) by LIGPLOT Program.*

DISCUSSION

In recent research, computational techniques have enabled researchers to estimate the binding affinity of different molecules before their synthesis and evaluation in lab. Molecular docking is used to find out the binding orientation of the small molecules against their targets. Thus, molecular docking is considered as important technique in drug designing and screening of novel compounds against this dreadful and challenging diseases [20]. The current study focused on the docking of the plant phytochemicals against 1QH4 proteins.

In our study, Pantolactone shows binding with GLY 73/HN 23 ATOMS 2.71 Å, CYS 74/HN 33 ATOMS 3.17 Å, CYS 74/O 23 ATOMS 2.46 Å to inhibit the brain creatine kinase (1QH4) with highest least energy value. followed by compounds 1,3-Dioxolane, 2-(3-bromo-5,5,5-tricloro-2,2-dimethylpentyl)-

shows binding with ASP 195/3.00 Å12 ATOMS DL-3, 4-Dimethyl-3, 4-hexanediol shows binding with HIS 305/O 18 ATOMS 2.72 Å, PHE 308/HN 38 ATOMS 2.76 Å, GLY 309/HN 45 ATOMS 2.72 Å Butanoic acid, 2-hydroxy-2-methyl-, methyl ester shows binding with LEU 193/HN 19 ATOMS 2.91 Å, PHE 192/HN 39 ATOMS 3.02 Å, HIS191/HN 56 ATOMS 3.09 Å, ILE 188/O 75 ATOMS, LEU 187/O 94 ATOMS 2.76 Å. The binding amino acids are in the active pockets and occupied more area in the protein. Some of the previous studies mentioned this target and proved the anticancer properties including the brain cancer [24].

CONCLUSION

Docking studies of the *M. concanensis* Nimmo leaf, four phytocompounds such as: 1, 3-Dioxolane, 2-(3-bromo-5, 5, 5-tricloro-2, 2-dimethylpentyl)-, Butanoic acid, 2-hydroxy-2-methyl-, methyl ester, DL-3,4-Dimethyl-3,4-hexanediol, Pantolactone ligand with brain cancer (PDB ID: 1QH4) proteins showed that this is a good molecule which docks well with various targets related to brain cancer. Thus 1, 3-Dioxolane, 2-(3-bromo-5, 5, 5-tricloro-2, 2-dimethylpentyl)-, Butanoic acid, 2-hydroxy-2-methyl-, methyl ester, DL-3,4-Dimethyl-3,4-hexanediol, Pantolactone can be considered for developing into a potent brain cancer drug.

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