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RESEARCH ARTICLE

DOCKING STUDIES OF BCL-2 WITH COSMOSTIGMACORDATUMCOMPUNDS FOR ANTI-CANCER STUDIES

Sravya Jasthi[1], Tejasri Abburu[1], Sai Sree Thanay Allam[1], Geya Govind[1], Nandini Ravula[1], Manas Tripurana[1] and Reethika Singh Ranwas[2]

1. Department of Biotechnology, Koneru Lakshmaiah Education Foundation, Guntur, Andhra Pradesh, India.
2. Department of Molecular Biology, Cresent Biosciences, ICRAB Campus, Kanpur, Uttar Pradesh, India.

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Abstract

Medicinal plants have wide spread properties due to the presence of phytocompounds and are the alternative medicines available for thosewho cannot be helped by conventional medicine. In this work we have selected bioactive compounds from Cosmostigmacordatummedicinal plant extracts. Docked compounds were used for anti-cancer activity by insilico method with BCL-2 which plays prominent role in causing cancer. Out of twentyselected compounds, docking results showedMethyl-1-Cyclo Hexane carboxylate and1,2-diacetoxy-5-idohexane as best docked to the BCL-2.

Introduction:-

Cosmostigmacordatum is a plant species belonging to the family Rubiaceae. It is native to Southeast Asia, particularly found in countries like Thailand, Myanmar, and Laos [1]. Cosmostigmacordatum is commonly known by various names, including Thai violet or violet tree. Cancer is a global health problem with high morbidity and mortality and poses both economic and psychological challenges [2]. Cancer cure and prevention therefore remain a high priority for the scientific community across the world. Insight gained into the etiology of cancer through various epidemiological studies encompassing various parameters such as geographical location, ethnicity, sex, age, and trans-migratory populations have collectively revealed that lifestyle is one of the major influencing factors [3].Docking studies involve the computational prediction of the binding affinity between a protein and a small molecule compound [4]. Studying the interaction between BCL-2, a protein involved in cancer cell survival, and compounds derived from Cosmostigmacordatum for potential anti-cancer applications [5].Cosmostigmacordatum is a plant species found in Asia that has been traditionally used in herbal medicine [6]. It contains various compounds, such as alkaloids, flavonoids, and terpenoids, which may possess bioactive properties [7].Docking studies provide predictions and insights into potential interactions between proteins and ligands [8]. Experimental validation is necessary to confirm the predicted results and evaluate the compounds' efficacy and safety as anti-cancer agents [9].

Methods:-

BCL-2active site identification

The structure of BCL-2 (PDB: 1GJH) was retrieved from PDB database and unnecessary chains, hetero atoms were removed using SPDBV software, hydrogens were added to the protein and used for active site identification.Active site of BCL-2 of Homo sapiens was identified using CASTp server. A new program, CASTp, for automatically

Corresponding Author:- Reethika Singh Ranwas
Address:- Department of Molecular Biology, Cresent Biosciences, ICRAB Campus, Kanpur, Uttar Pradesh, India.

locating and measuring protein pockets and cavities, is based on precise computational geometry methods, including alpha shape and discrete flow theory. CASTp identifies and measures pockets and pocket mouth openings, as well as cavities. The program specifies the atoms lining pockets, pocket openings, and buried cavities; the volume and area of pockets and cavities; and the area and circumference of mouth openings [11].

Docking method

The compounds identified in GC-MS are docked to the active site of the BCL-2 of Homo sapiens using GOLD. The parameters used for GA were population size (100), selection pressure (1.1), number of operations (10,000), number of island (1) and niche size (2). Operator parameters for crossover, mutation and migration were set to 100, 100 and 10 respectively. Default cutoff values of 3.0 A° (dH-X) for hydrogen bonds and 6.0 A° for vanderwaals were employed. During docking, the default algorithm speed was selected and the ligand binding site in the targets were defined within a 10 A° radius with the centroid as CE atom of active residues. The number of poses for each inhibitor was set 100, and early termination was allowed if the top three bound conformations of a ligand were within 1.5A° RMSD. After docking, the individual binding poses of compounds were observed and their interactions with the protein were studied. The best and most energetically favorable conformation of ligands was selected [11].

Results And Discussion:-

From the PDB databank, the PDB files were collected and the final stable structure of the BCL-2 of Homo sapiens obtained is shown in Figure 1. The ligands present in the crystal structure were removed along with hetero atoms for docking studies.

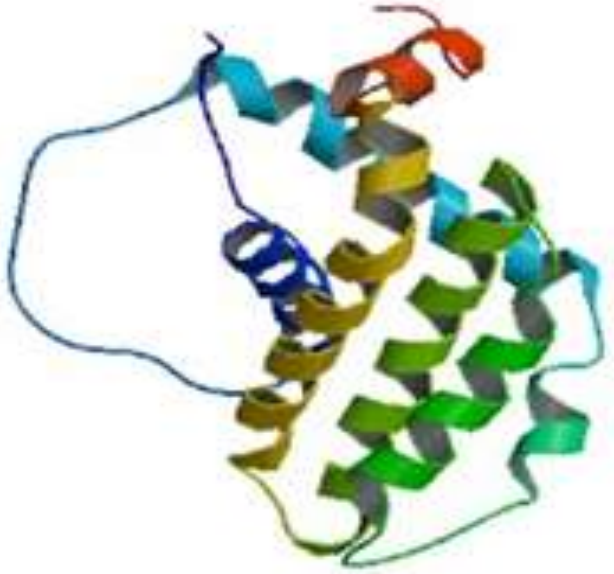

Figure 1:- Structure of BCL-2 retrieved from Protein data bank with seven helices.

Active site Identification

After the final model was built, the possible binding sites of BCL-2 was searched based on the structural comparison of template and the model build and with CASTP server and was shown in Figure 2. Infact from the final refined model of BCL-2 domain using SPDBV program, it was found that secondary structures are highly conserved and the residues shown below

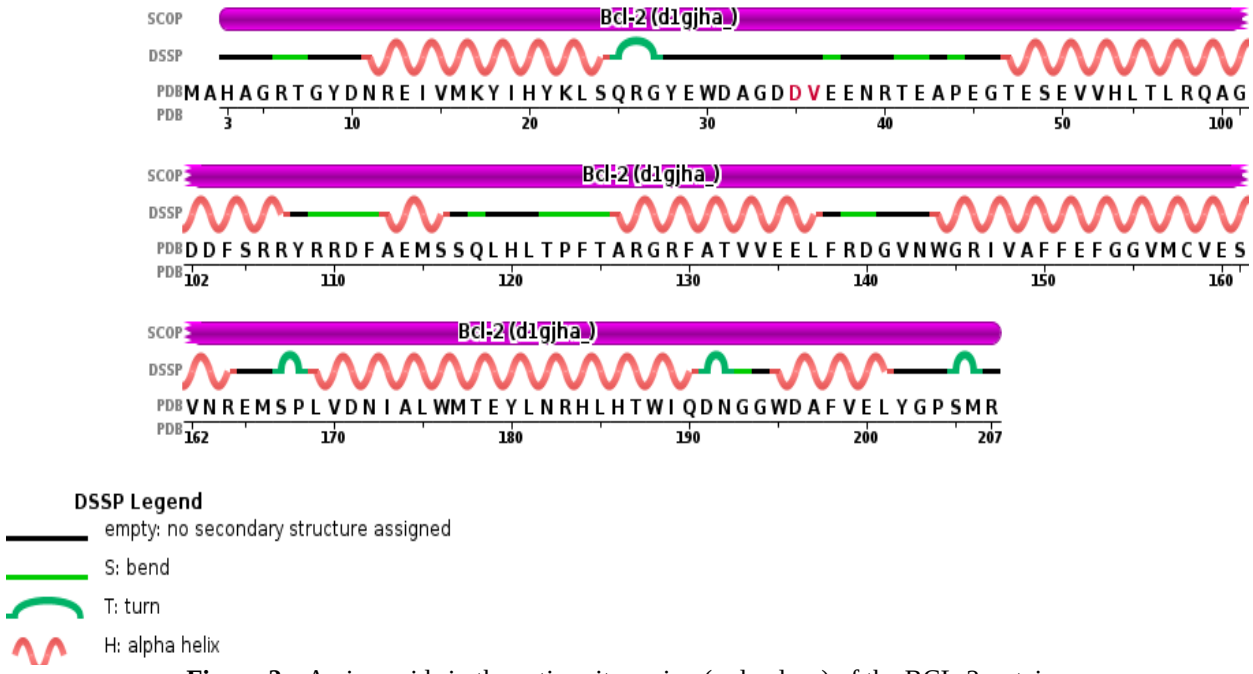

Figure 2:- Amino acids in the active site region (red colour) of the BCL-2protein.

Docking of inhibitors with the active site

Docking of the compounds with BCL-2 was performed using GOLD 3.0.1, which is based on genetic algorithm. This program generates an ensemble of different rigid body orientations (poses) for each compound conformer within the binding pocket and then passes each molecule against a negative image of the binding site. Poses clashing with this 'bump map' are eliminated. Poses surviving the bump test are then scored and ranked with a Gaussian shape function. We defined the binding pocket using the ligand-free protein structure and a box enclosing the binding site. This box was defined by extending the size of a cocrystalized ligand by 4A. This dimension was considered here appropriate to allow, for instance, compounds larger than the cocrystallized ones to fit into the binding site. One unique pose for each of the best-scored compounds was saved for the subsequent steps. The compounds used for docking was converted in 3D with SILVER. To this set, the substrate corresponding to the protein was added. Docking of best inhibitor with the active site of protein showed the activity of the molecule on protein function.

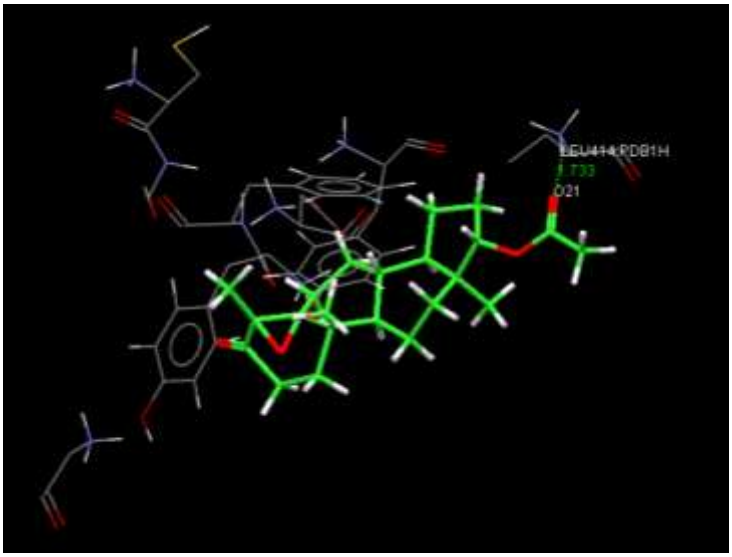

Figure 3:- Methyl-1-Cyclo Hexane carboxylate docked to BCL-2 active site.

In docking studies, Methyl-1-Cyclo Hexane carboxylate showed a docking energy of 22.56K.cal/mol with BCL-2. In docking, Methyl-1-Cyclo Hexane carboxylate (O21) docked to LEU414 with a bond length of 1.733A^{o}.

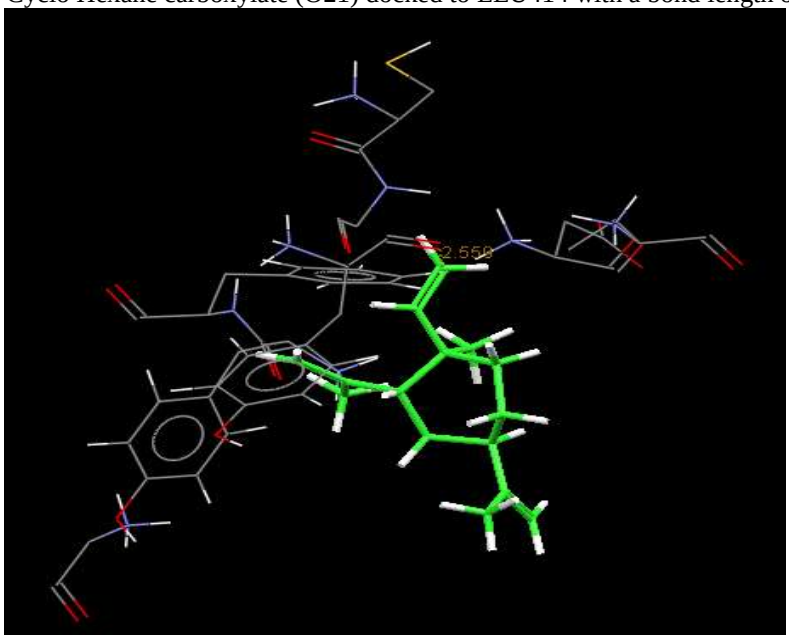

Figure 4:- 1,2-diacetoxy-5-idohexanedocked to BCL-2 active site.

In docking studies, 1,2-diacetoxy-5-idohexane showed a docking energy of 20.24K.cal/mol with BCL-2. In docking, 1,2-diacetoxy-5-idohexane (H33) docked to LEU414 with a bond length of 2.559A^{o}.

Conclusion:-

From the studies, dockedphytocompounds were checked for their anti-cancer activity using insilico method.BCL-2 protein was retrieved from the database and its active site was identified using CASTp server. Among the phytocompounds docked, Methyl-1-Cyclo Hexane carboxylate showed a docking energy of 22.56K.cal/mol and 1,2-diacetoxy-5-idohexaneshowed 20.24K.cal/molwithBCL-2.From these docking studies we can conclude that among the phytocompounds identified, these two compounds have good BCL-2 inhibitory activity.The retrieval of the BCL-2 protein from the database and subsequent identification of its active site using the CASTp server have provided valuable insights into the functional characteristics of this protein. The active site of a protein refers to a specific region where interactions with other molecules, such as ligands or substrates, take place, ultimately influencing its biological activity. By identifying the active site of the BCL-2 protein, researchers can gain a deeper understanding of its structure-function relationship and potentially explore its role in various cellular processes.

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