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IN SILICO STUDY OF TERMINALIA CHEBULA AS AN ANTI-CANCER THERAPY TARGETING DHF REDUCTASE

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ABSTRACT

The study involves the molecular docking of the chemical constituents of Terminalia chebula, with a specific focus on their potential anti-cancer activity. The information provides a comprehensive overview of the drug discovery and development process, the molecular docking technique, cancer types and causes, and the botanical aspects of Terminalia chebula, the aim, objective, plan of work, and experimental methods for the in-silico study are detailed, along with the findings and conclusions of the molecular dockingstudy. It aims to contribute to the understanding of the potential anti-cancer properties of Terminalia chebula and the design of effective Molecules of cancer treatment.

KEYWORDS: In Silico Study, Terminalia Chebula, Anti-Cancer Therapy, DHF Reductase, Phytoconstituents, Ligands, Receptors, Virtual Screening.

1. INRODUCTION

1.1 Drug Discovery and Development

Drug discovery has a long history and dates back to the early days of human civilization. In those ancient times, treatments were often discovered by chance or resulted from observation of nature, typically but not exclusively, using ingredients extracted from plants/animals, and not just used for physical remedy but also for spiritual healing.

Modern drug discovery research started to being performed around the early 1900s. Nowadays, the development of a new medicine usually starts when basic research, often performed in academia, identifies a macromolecule (i.e., a molecule with a large molecular weight like

genes/proteins), or a dysfunctional signaling pathway or a molecular mechanism apparently linked to a disease condition (Pre-discovery stage). In general, at this stage, research teams attempt to identify the so-called therapeutic targets (Often a protein) that are linked to the disease state. To be nominated therapeutic target, scientists will also have to find therapeutic agents that modify the function of the particular target and restore health or alleviate symptoms. Finding the right target is however extremely challenging. Further, drugs are efficient in humans because of specific actions on the intended therapeutic target but also due to interactions with other, unintended (Often unknown) targets. The process continues with the search of therapeutic agents followed by a preclinical phase, during which potential drugs are tested in a battery of animal models, to demonstrate safety and select drug candidates (Novel strategies to avoid animal testing are being developed, see below). Clinical studies in humans can then get started to establish safety and efficacy of the drugs in patients with the highest benefit-to-risk ratio. The studies are then submitted to regulatory agencies, which review the documents and decide about market approval. If the review is positive, the drug can then be released to the market and be administrated to patients.

Once a drug has been approved, investigations continue to monitor putative side effects that could be caused, over time, by the new treatment. This last step is often referred to as pharmacovigilance studies (or real-world evidence), generally dubbed “phase 4” clinical trial. The entire drug discovery and development process involves many disciplines, years of efforts and is very expensive. It also implies the generation and use of vast amount of data usually obtained via different types of high-throughput technologies. Many of these experiments and the analysis of the results can be automated via computer-assisted methods to speed-up some steps of the process, gain knowledge and reduce mistakes.[1]

There are several stages in the drug discovery process that require numerous skills and the use of various advanced technological platforms (Often a combination of computational and experimental approaches) to validate targets and search for therapeutic agents.

When initial experimental compounds have been sufficiently optimized to be selective, potent and safe in preliminary in vitro experiments and animal models, they can be nominated as drug candidates. At this stage, the project focus shifts from drug discovery to drug development to enable human clinical trials. If the therapeutic agent is successful in all three phases of the clinical trials, it goes through regulatory registration and the drug can be marketed.

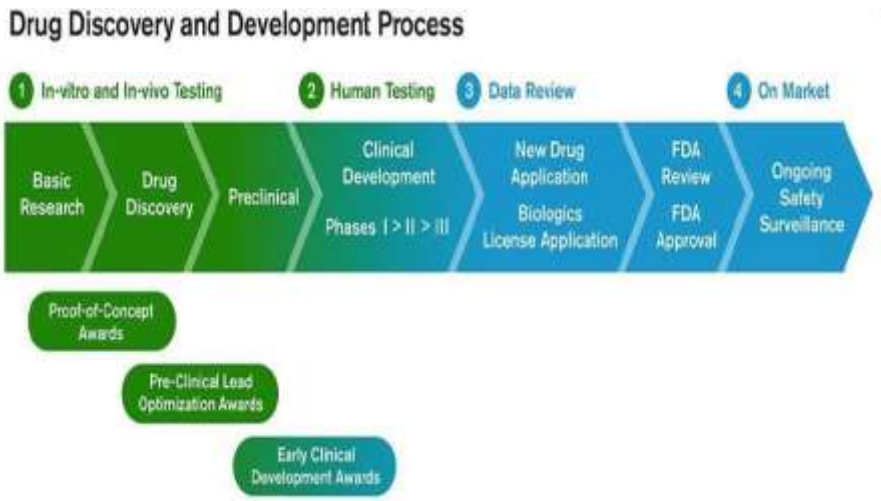


Figure No. 1

1.2 Molecular docking

In the meadow of molecular modelling, docking is a technique which predict the prefer direction of one molecule to a second when jump to each other to form a steady compound.[2] Information of the chosen direction in rotate may be worn to expect the strength of involvement or binding affinity linking two molecules with each, for example, score function. The relations between physically appropriate molecules such as proteins, peptides, nucleic acids, carbohydrates, and lipids play a central role in signal transduction. Furthermore, the relative orientation of the two interact associates may involve the type of signal formed (e.g., agonist vs antagonism). Therefore, docking is helpful for predict both the potency and type of signal produced. Molecular docking is one of the majorities generally used technique in structure-based drug design, due to its capability to forecast the binding-conformation of small molecule ligands to the suitable target binding site. Characterization of the binding performance plays a significant role in rational plan of drugs as well as to explain fundamental biochemical process,[3] The aim of molecular docking is to accomplish an optimized conformation for both the protein and ligand and fundamental direction between protein and ligand so that the free energyof the generally method is minimized.[4] Molecular recognition plays a key role in promote elementary bimolecular proceedings such as enzyme substrate, drug-protein and drug-nucleic acid interactions.[5] Detailed appreciative of the universal principles that administrate the nature of the connections (Van der Waals, hydrogen bonding, electrostatic) involving the ligands and their protein or nucleic acid targets may afford a framework for designing the most wanted potency and specificity of potential drug leads for a given therapeutic target.[6] Practical application of this information requires structural data for the goal of significance and a progression for evaluating candidate ligand.[7] A variety of

computational docking methodsare accessible.[8]

Types of docking

There are 2 types of docking

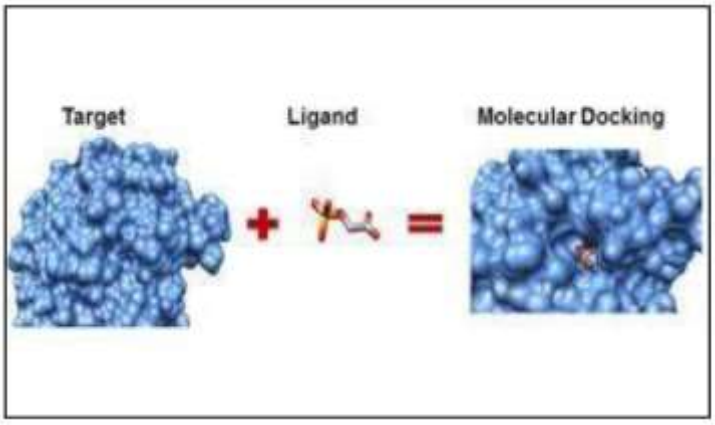
1. Rigid docking
2. Flexible docking

2.1 Rigid docking

If we think that the molecules are rigid, then we are looking for a conversion in 3D space of one of the molecules which bring it to a most favourable fit with the other molecules in provisions of a scoring function. Conformation of the ligand may be generating in the absenceof receptor or in the occurrence of receptor binding activity.

2.2 Flexible docking

We think molecule flexibility then in adding to transformation, our aspire to locate the confirmations of the receptor and the ligand molecules, as they emerge in complex.[9]



1.3 Disease: Cancer

Cancers are a group of diseases characterized by uncontrolled growth and spread of abnormal cells. If the spread of cancer cells this stage is known as metastasis is not controlled, it can result in death. Cancer is caused by many external factors (Tobacco, chemicals, radiation and infectious organisms) as well as some internal factors (Inherited mutations, hormones, immune conditions and random mutations). The causes of cancer are diverse, complex and only partially understood. Many things are known to increase the risk of cancer, including dietary factors, certain infections, lack of physical activity, obesity and environmental pollutants.[10] These factors may act together to initiate or promote carcinogenesis in human

body and thus cancer is leading cause of death.

Cancer has become one of the causes of death in India. It is estimated that there are nearly2 to 2.5 million cancer cases at any given point of time. Over 7 lakhs new cases and 3 lakhsDeaths occur annually due to cancer. Nearly 15 lakh patients require facilities for diagnosis, treatment and follow up at a given time.[11]

Figure No. 3.

Types of cancer

On the basis of tissue effected

Carcinoma

Carcinomas are the most common type of cancer. They are formed by epithelial cells, which are the cells that cover the inside and outside surfaces of the body. There are many types of epithelial cells, which often have a column-like shape when viewed under a microscope.

Carcinomas that begin in different epithelial cell types have specific name Adenocarcinoma, Adenocarcinoma is a cancer that forms in epithelial cells that produce fluids or mucus. Tissues with this type of epithelial cell are sometimes called glandular tissues. Most cancers of the breast, colon, and prostate are adenocarcinomas.

Basal cell carcinoma is a cancer that begins in the lower or basal (base) layer of the epidermis, which is a person's outer layer of skin.

Squamous cell carcinoma is a cancer that forms in squamous cells, which are epithelial cells that lie just beneath the outer surface of the skin. Squamous cells also line many other organs, including the stomach, intestines, lungs, bladder, and kidneys. Squamous cells look flat, like fish scales, when viewed under a microscope. Squamous cell carcinomas are sometimes called

epidermoid carcinomas.

Transitional cell carcinoma is a cancer that forms in a type of epithelial tissue called transitional epithelium, or urothelium. This tissue, which is made up of many layers of epithelial cells that can get bigger and smaller, is found in the linings of the bladder, ureters, and part of the kidneys (Renal pelvis), and a few other organs. Some cancers of the bladder, ureters, and kidneys are transitional cell carcinomas.

Sarcoma

Sarcomas are cancers that form in bone and soft tissues, including muscle, fat, bloodvessels, lymph vessels, and fibrous tissue (Such as tendons and ligaments).

Leukaemia

Cancers that begin in the blood-forming tissue of the bone marrow are called leukaemia's. These cancers do not form solid tumours. Instead, large numbers of abnormal white blood cells (Leukaemia cells and leukemic blast cells) build up in the blood and bone marrow, crowding out normal blood cells. The low level of normal blood cells can make it harder for the body to get oxygen to its tissues, control bleeding, or fight infections.

There are four common types of leukaemia, which are grouped based on how quickly the disease gets worse (Acute or chronic) and on the type of blood cell the cancer starts in (lymphoblastic or myeloid). Acute forms of leukaemia grow quickly and chronic forms grow more slowly.

Lymphoma

Lymphoma is cancer that begins in lymphocytes (T cells or B cells). These are disease-fighting white blood cells that are part of the immune system. In lymphoma, abnormal lymphocytes build up in lymph nodes and lymph vessels, as well as in other organs of the body.

Multiple myeloma

Multiple myeloma is cancer that begins in plasma cells, another type of immune cell. The abnormal plasma cells, called myeloma cells, build up in the bone marrow and form tumours in bones all through the body. Multiple myeloma is also called plasma cell myeloma and Kahler disease.

Melanoma

Melanoma is cancer that begins in cells that become melanocytes, which are specialized cells that make melanin (The pigment that gives skin its colour). Most melanomas form on the skin, but melanomas can also form in other pigmented tissues, such as the eye.

Brain and Spinal cord tumours

There are different types of brain and spinal cord tumours. These tumours are named based on the type of cell in which they formed and where the tumour first formed in the central nervous system. For example, an astrocytic tumour begins in star-shaped brain cells called astrocytes, which help keep nerve cells healthy. Brain tumours can be benign (not cancer) or malignant (cancer).

On the basis of organ effected

- Colorectal cancer
- Lung Cancer
- Liver Cancer
- Stomach Cancer
- Cervical Cancer
- Bladder Cancer
- Oesophageal Cancer
- Non-Hodgkin Lymphoma
- Cancers of the Lip and Oral Cavity
- Nasopharyngeal Cancer
- Kaposi Sarcoma

Symptoms: Symptoms of cancer depend on the type and location of the cancer. For example, lung cancer can cause coughing, shortness of breath, or chest pain. Colon cancer often causes diarrhoea, constipation and blood.

The following symptoms can occur with most cancers

- Chills
- Fatigue
- Weight loss
- Thickening or lump in the body
- Cough or hoarseness that does not go away

- Obvious change in a wart or mole
- Changes in bowel or bladder habits
- Unexplained bleeding or discharge
- Any sore that does not heal
- Unusual upset stomach or difficulty
- Swallowing.[13,14]

Causes

Cancer grows out of normal cells in the body. Normal cells multiply when the body needs them and die when the body doesn't need them. Cancer appears to occur when the growth of cells in the body is out of control and cells divide too quickly. It can also occur when cells forget how to die.

There are many different kinds of cancer. Cancer can develop in almost any organ or tissue, such as the lung, colon, breast, skin, bones, or nerve tissue. There are many causes of cancer, including

- Benzene and other chemicals
- Drinking excess alcohol
- Environmental toxins, such as certain poisonous mushrooms and a type of poison thatcan grow on peanut plants (Aflatoxins) Excessive sunlight exposure
- Genetic problems
- Obesity
- Viruses[13,14]

1.4 Plant

Terminalia chebula

Terminalia chebula Is found throughout southern and southeast Asia including in India, Sri Lanka, Bhutan, Nepal, Bangladesh, Myanmar, Cambodia, Laos, Vietnam, Indonesia, Malaysia, Pakistan and Thailand. In China, it is native in western Yunnan and cultivated in Fujian, Guangdong, Guangxi (Nanning), and Taiwan (Nantou).[15]

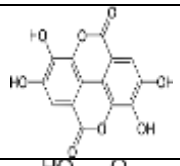
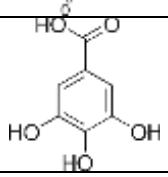
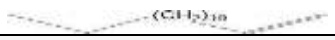
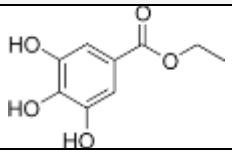
Figure no. 4

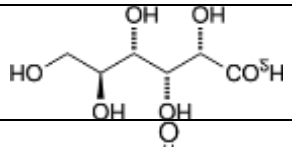
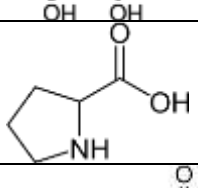
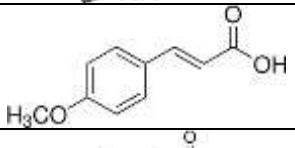
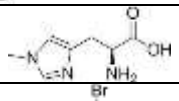
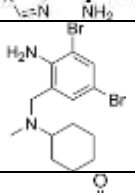
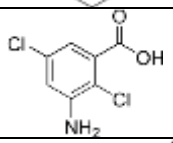
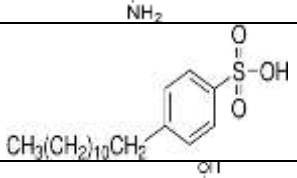
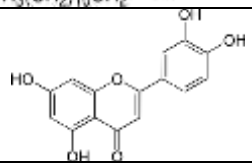
Biological source: It consists of dried ripe fruits of the plant Terminalia beleric Linn, belonging to family Combretaceae.

Chemical constituents: Tannins, flavonoids, sterols, amino acids, fructose, and resins.USES:

- It is good to increase appetite digestive aid
- Liver stimulant
- Stomachic
- Gastrointestinal prokinetic agent
- Mild laxative.

Table No. 1: Chemical constituents of terminalia chebula.

Sr. No.	Chemical constituents	Structures
1.	Ellagic acid	
2.	Galic acid	
3.	1-tricosene	
4.	Octadec-9-ene	
5.	Ethyl gallate	

6.	Gluconic acid	
7.	Proline	
8.	4-methoxycinnamic acid	
9.	1-methyl histidine	
10.	Bromhexine	
11.	Chloramben	
12.	4-dodecylbenzenesulfonicacid	
13.	Luteolin	

2. AIM AND OBJECTIVE

Aim

To perform virtual screening of biologically active ligands which is anticancer drugs on DHFRase (Dihydro folate reductase)

Objective

- To design the Chemical Constituents of Terminalia Chebula
- To study the molecular docking of the Chemical Constituents of Terminalia Chebula
- To Study the Physicochemical properties
- To Evaluate the ADME study

3. Plan of work

1. Downloading and installing all the required software Program
2. Preparation of the Ligands
3. Preparation of Receptor

4. Virtual Screening
5. SwissADME (Evaluate Physicochemical Properties)

4. Experimental work

4.1 Downloading and Installing all the required software Program

a) Chemsketch
b) Avogadro
c) PyRx
d) Discovery Studio

a) Chemsketch

This open-source software is a chemical molecule or molecular modelling program used to create, draw and modify images of chemical structures or compounds and there is software that allows molecule and molecular models displayed in two and three dimensions, to understand the structure of chemical bonds and nature of the functional groups. This tool enables us to draw chemical molecules and save them directly in several formats like. mol,. jpg, png and many more formats. We can also generate the international union of pure and applied chemistry (IUPAC) of the chemical structures. ChemSketch is a molecular modelling 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, to understand the structure of chemical bonds and the nature of the functional groups. This software also helps us for generation of simplified molecular input line entry system (SMILES) of the desired chemical structure.[16]

b) Avogadro software

Avogadro software was used to convert the. mol file to. pdb format. This is again opensource software that helps optimize the chemical structure. This also helps in minimizing the energy which is very important protocol for in silico studies. The software also allows generation of structure through SMILES or by drawing tool. These chemical structures were saved in the format of. pdb format which is required for docking purpose.[16]

c) PyRx software

PyRx software was used for virtual screening of library of derivatives. The pyrx software is a open software for virtual screening. The approach includes blasting of several ligand molecules to a target and segregate the best fit molecules from the library. The tool includes a 4step

protocol and can screen a big library of molecules simultaneously on a defined site of target/receptor. The results can easily be exported in Microsoft excel format as. csv file.[16]

d) Biovia discovery studio

BIOVIA Discovery Studio brings together over 30 years of peer-reviewed research and world-class in silico techniques such as molecular mechanics, free energy calculations, biotherapeutics developability and more into a common environment. It provides researchers with a complete toolset to explore the nuances of protein chemistry and catalyse discovery of small and large molecule therapeutics from Target ID to Lead Optimization.[16]

With discovery studio you can

- Investigate and test hypotheses in silico prior to costly experimental implementation, thusreducing the time and expense involved in bringing products to market.
- Drive scientific exploration from target identification to lead optimization with a wealth oftrusted life science modelling and simulation tools.
- Leverage BIOVIA Pipeline Pilot to automate processes, create and deploy custom workflows, and integrate data types, databases, and third-party or in-house tools.

4.2 Preparation of ligands

Library of active phytochemicals of Terminalia Chebula plant species which is responsible for anti-Cancer activity were retrieved from literature. PubChem compound database (https://pubchem.ncbi.nlm.nih.gov) was used for the retrieval of structures in PDB (Protein data bank) format. Preparation of ligand file used the software's and online library from the PubChem for their specification Smiles notation were copied from PubChem database and then structure was generated from this smile notation in ChemSketch afterwards this smile notation was used to retrieve ligands to 3D PDB format with the help of Avogadro software.

4.3 Preparation of receptor

RCSB (Research Collaboratory for Structural Bioinformatics) Protein Data Bank was used to retrieve the three-dimensional structure of receptor PDB ID: 1dlr download the structure in. pdb format from the online database and was rectified using auto dock software which is already present in the PyRx software. Preparation of receptor was done with the help of Discovery studio. The pdb format is opened in the discovery studio and then press Ctrl + H and then remove the pre-associated ligand present in the receptor alsoheteroatoms and water molecules present in structure were cleaned and the active sites were identified and then

saved in the working folder as pdb file.

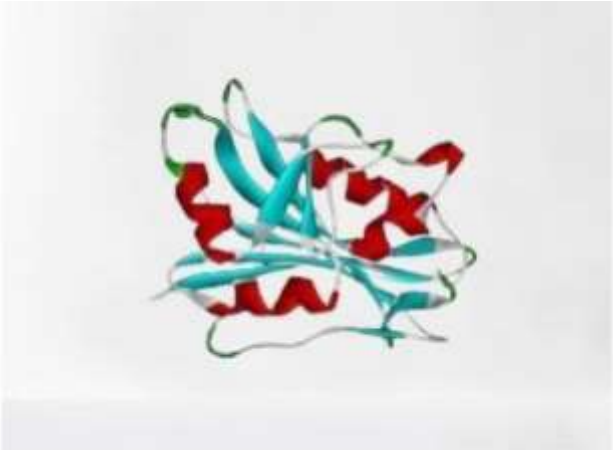


Figure no. 5

5. RESULT AND DISCUSSION

The docking of the receptor 1dlr with chemical constituents of Terminalia chebula has been done by using. The table shows the binding affinity and inhibition constant of 14 compounds including standard. In silico studies revealed that all the chemical constituents show good binding affinity toward the target protein.

Table No. 2: Ligands with their binding affinity.

Sr. No.	Ligands	Binding Affinity (Kcal/mol)
1.	**Methotrexate**	**-9.9**
2.	Ellagic acid (R1)	-8.3
3.	**Galic acid (R2)**	**-10.4**
4.	1-Tricosene (R3)	-7.3
5.	Octadec-9-ENE (R4)	-7.8
6.	Ethyl gallate (R5)	-6.3
7.	Gluconic ACID (R6)	-5.5
8.	Proline (R7)	-4.6
9.	4-Methoxycinnamic ACID (R8)	-6.7
10.	1-Methyl HISTIDINE (R9)	-5.8
11.	Luteolin (R10)	-8.8
12.	Chloramben (R11)	-6.6
13.	4-Dodecylbenzenesulfonic acid (R12)	-9
14.	Bromhexine (R13)	-8

5.1 Interaction of ligands with amino acid residue of Dihydro folate receptor with PDB ID: 1dlr

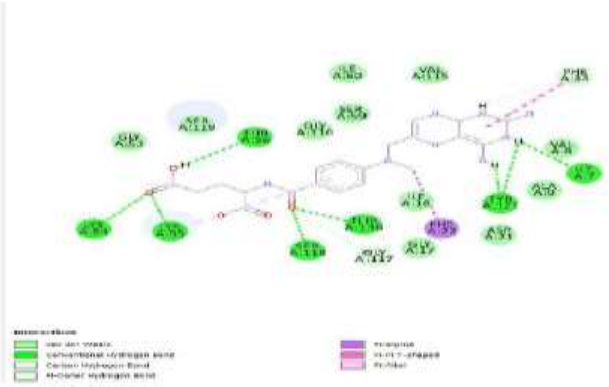


Figure No. 6: Methotrexate with Receptor 1dlr.

Above figure shows the amino acid interaction of standard Methotrexate with 1dlr gives Binding affinity score -9.9

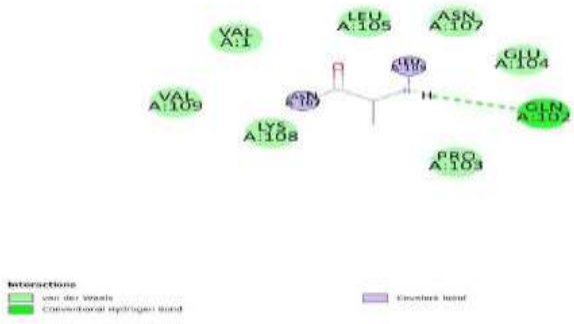


Figure No. 7: Ligand (R1) with Receptor 1dlr.

Above figure shows the amino acid interaction of ellagic acid (R1) with 1dlr gives Binding affinity score -8.3

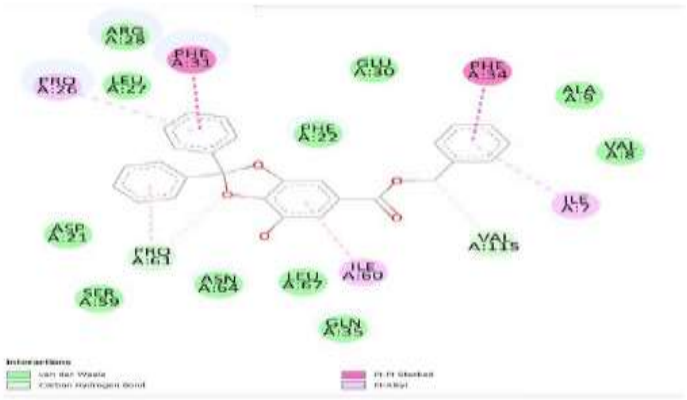


Figure No. 8: Ligand (R2) with Receptor 1dlr.

Above figure shows the amino acid interaction of Galic acid (R2) with 1dlr gives Binding affinity score -10.4

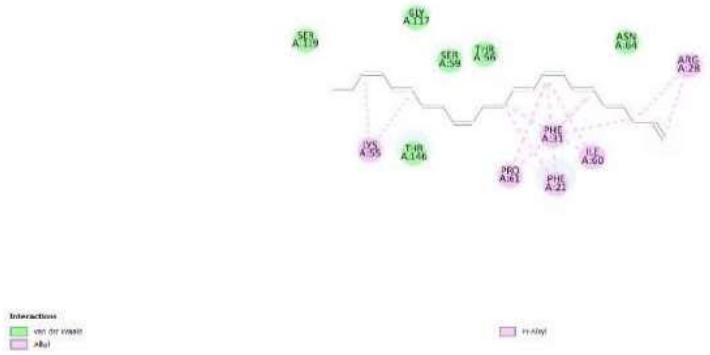


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Figure No. 9: Ligand (R3) with Receptor 1dlr.

Above figure shows the amino acid interaction of 1-Tricosene (R3) with 1dlr gives Binding affinity score -7.3

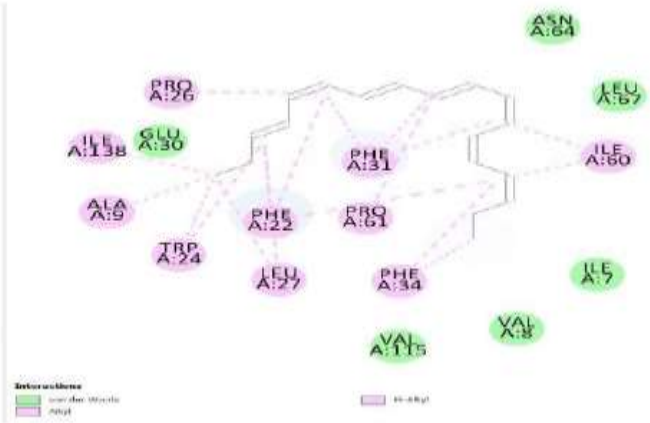

Figure No. 10: Ligand (R4) with Receptor 1dlr.

Above figure shows the amino acid interaction of Octadec-9-ene (R4) with 1dlr givesBinding affinity score -7.8

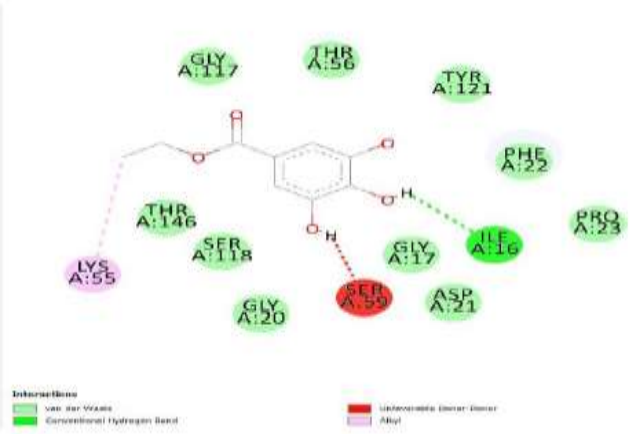

Figure No. 11: Ligand (R5) with Receptor 1dlr.

Above figure shows the amino acid interaction of Ethyl Gallate (R5) with 1dlr gives Binding affinity score -6.3

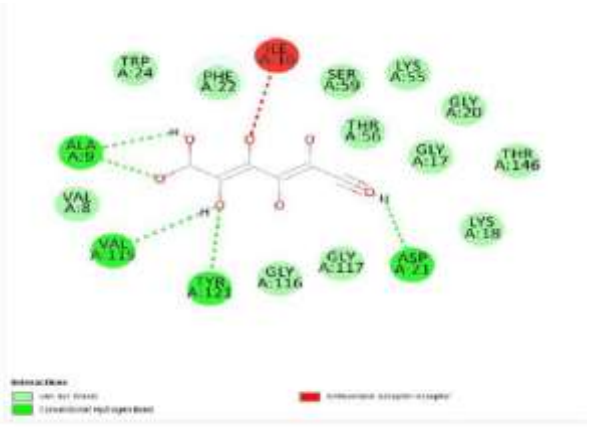

Figure No. 12: Ligand (R6) with Receptor 1dlr.

Above figure shows the amino acid interaction of Gluconic acid (R6) with 1dlr gives Binding affinity score -5.5

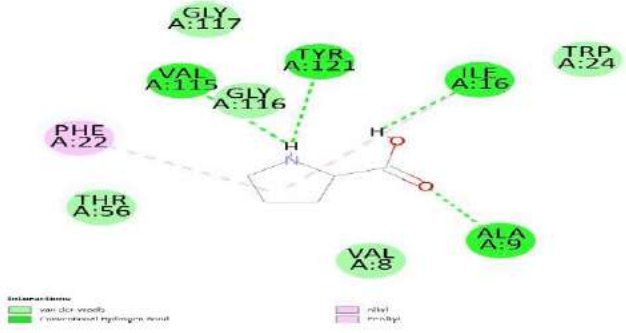

Figure No. 13: Ligand (R7) with Receptor 1dlr.

Above figure shows the amino acid interaction of Proline (R7) with 1dlr gives Binding affinity score -4.6

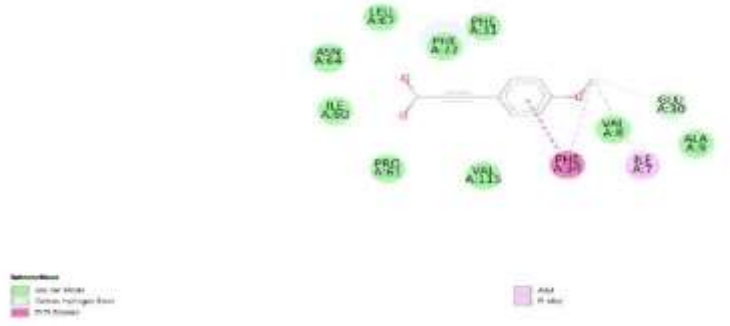

Figure No. 14: Ligand (R8) with Receptor 1dlr.

Above figure shows the amino acid interaction of 4-Methoxycinnamic acid (R8) with 1dlr gives Binding affinity score -6.7

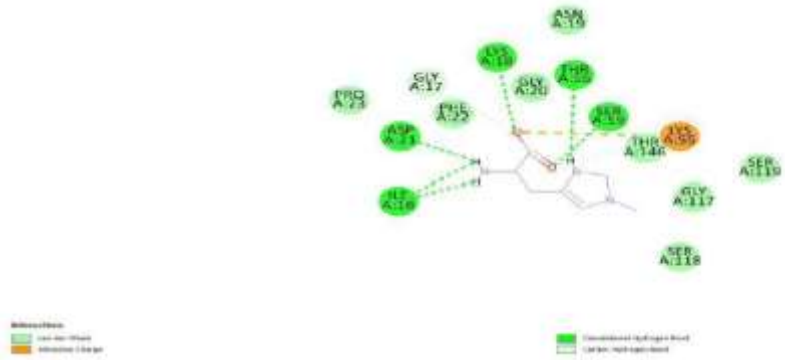

Figure No. 15: Ligand (R9) with Receptor 1dlr.

Above figure shows the amino acid interaction of 1-Methyl Histidine (R9) with 1dlr gives Binding affinity score -5.8

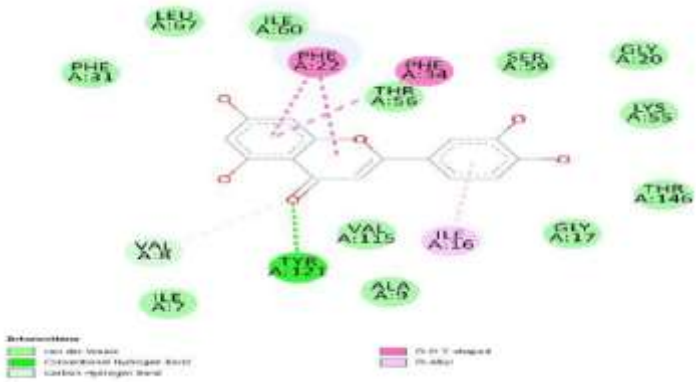

Figure No. 16: Ligand (R10) with Receptor 1dlr.

Above figure shows the amino acid interaction of Luteolin (R10) with 1dlr gives Binding affinity score -8.8

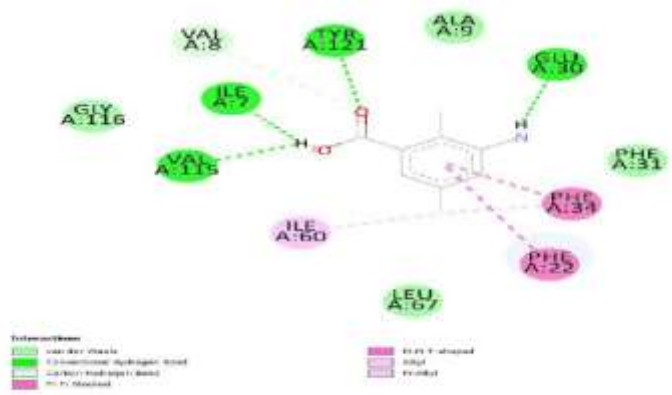

Figure No. 17: Ligand (R11) with Receptor 1dlr.

Above figure shows the amino acid interaction of Chloramben (R11) with 1dlr gives Binding affinity score -6.6

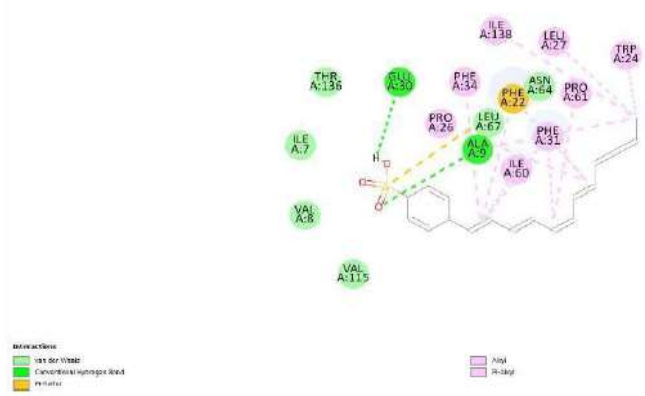

Figure No. 18: Ligand (R12) with Receptor 1dlr.

Above figure shows the amino acid interaction of 4-Dodecylbenzenesulfonic (R12) acid with 1dlr gives Binding affinity score -9

6. CONCLUSION

The In-silico study showed Phytoconstituents of the Terminalia Chebula having potent Anti-cancer activity. These studies can be helpful to design molecule with better specificity at receptor level and be safe. The compound Galic acid shows best affinity towards 1dlr anti-cancer receptor. From this Docking results identified the best molecule interact with receptor these selected one molecule used for the anti-cancer activity Methotrexate standard

interactionsof amino acid with 1dlr receptor gets the Docking score -9.9. LYS A 54, LYS A 55, THR A 56,SER A 118, THR A 146, PHE A 22, TYR A 121, ILE A 7 this amino acid found and anti-cancer activity done with with the PDB ID 1dlr. Figure No. shows the amino acid interaction of Galic acid - 1dlr gives the Binding score -10.4. PRO A 26, PHE A 31, PRO A 61, ILE A 60, VAL A115, ILE A 7, PHE A 34.

7. REFERANCE

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