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'In-silico Screening of Bioactive Compounds Derived from Artemisia annua Against Cancer"

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Abstract

According to WHO Global Cancer Observatory (GLOBOCAN) in 2018; 18.08 millions new cases of cancer have been diagnosed worldwide, from which 2.09 million cases of trachea and bronchus(of lungs), 2.09 million cases of breast and 1,28 million cases of prostate are found frequently.so basically cancer is genetic diseases and mainly arise due to number of reasons including activation of onco-gene, malfunction of tumour suppressor genes or mutagenesis. There are several medicines in market but those are not fully effective and safe. To treat the cancer Artemisia annua is used; which belongs to family Asteraceae and commonly known as sweet wormwood. The 3D crystallographic structure of human progesterone receptor (1E3K) was downloaded from Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) and a protein target for in-silico experiments. Software like PubChem is used to obtain ligand as well as PyRx, Bio Discovery Studio and Ramachandran Plot used for Molecular Docking. This study revels that A. annua may show anticancer activity responsible for cancer as predicted by in-silico. Molecular docking suggest that Quercetin (-8.2kcal/mol) and Kaempferol (-8.1kcal/mol) have higher binding

affinity than Chrysosplenol D(-7.8kcal/mol), Artemisinin (-6.7kcal/mol) and Coumarin (-6.0kcal/mol) which have less binding affinity.

Keyword: Cancer, artemisia annua, human progesterone receptor.

1. **Introduction:**

Cancer comes under genetic disease in which abnormal cells divide uncontrollably and destroy body tissues . This is multistep and multifactorial molecular process which involves interactions between internal factor that is genes and external factor that is environment in which that organisms live called as carcinogenesis or tumorigenesis or oncogenesis [2]. So basically activation of oncogenes happens by two mechanism; either by cell infected by tumour viruses or cellular proto-oncogenes mutation. Oncogenic transformation generate single cell tumour, but some of the tumour have ability to enter other parts of body and spread the cancer which is know as metastasis[1]. Classification of Cancer is as follows-

1) Cancer of Blood and Lymphatic System
a) Hodgkin's diseases b) Leukaemia c) Lymphomas d) Multiple myeloma
e) Waldenstrom's diseases
2) Skin Cancer
a) Malignant Melanoma
3) Cancer of Urinary System
a) Kidney cancer b) Bladder cancer c) Testis cancer d) Prostate cancer
4) Cancer in women
a) Breast cancer b) Ovarian cancer c) Gynaecological cancer d) Choriocarcinoma
5) Cancers of digestive system
a) Oesophageal cancer b) Stomach cancer c) Cancer of pancreas d) Liver cancer
e) Colon and rectal cancer f) Anal cancer
6) Miscellaneous cancers
a) Brain cancer b) Bone cancer c) Characinoid cancer e) Nasopharyngeal cancer
f) Retroperitoneal sarcomas g) Soft tissue cancer h) Thyroid cancer[3]

In 2018 according to WHO Global Cancer Observatory (GLOBOCAN), 18.08 million new cases of cancer have been diagnosed worldwide, from which 2.09 million cases of trachea and bronchus(of lungs), 2.09 million cases of breast and 1,28 million cases of prostate are found frequently [10].

Breast cancer is worldwide common type of cancer. It is likely to develop 1 out of 31 women in south Africa. In India it is the second most common cancer after uterine cervix cancer[3].

Plants have been used in treatment of various diseases including cancer[3]. Artemisia annua is used over here which belongs to family Asteraceae and commonly known as sweet wormwood[4]. This plant is found in Asia, India, Central and Eastern Europe, America (temperate zone), Africa, Australia. Artemisia annua is a short day annual plant having brownish rigid stem. It consist of phytoconstituent like artemisinin, quercetin, flavonoids like artemetin, chrysosplenol D, casticin, essential oils, kaempferol, coumarins, etc[3,4]. These phytoconstituents are the Ligands which are used by body as a signalling compound[5].

Receptors are protein usually cell surface receptor, which bind to ligand and cause response in the immune system. Different types of receptor such are

1) Internal Receptor
2) Cell Surface Receptors
3) Ion Channel Receptors

4) G-Protein Couple Receptors
5) Enzyme Linked Receptors [5].

Human progesterone is used as receptor which is female hormone that affect female development, maintenance and reproduction which belongs to nuclear receptor (NR) family[6].

2. Material and Method:

2.1. Retrieval and Preparation of Receptor:

For downloading the 3D structure of human progesterone receptor, Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB) is used through which in-silico studies is carried out. RCSB PDB creates 3D macromolecules structure along with crystallography, NMR. In which direct download of receptor is done in PDB Format[7].

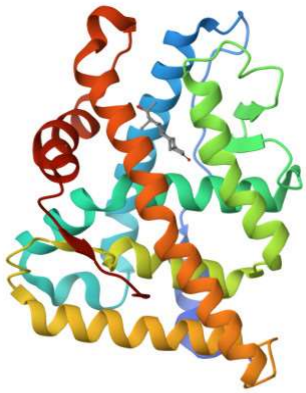
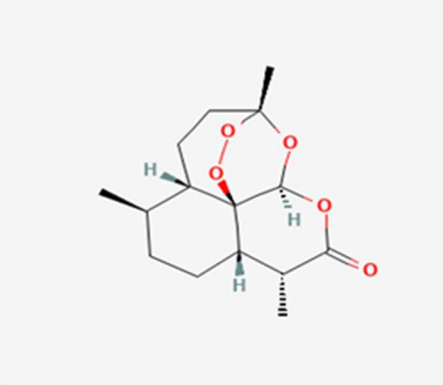


Fig.1. Human Progesterone Receptor (pdb id:1E3K)

2.2. Retrieval and Preparation of Ligand:

Phytochemicals in artemisia annua like Artemisinin, Quercetin, Kaempferol, Coumarin, Chrysosplenol D are analysed and downloaded in structure data file (SDF) format using National Library of Medicine, PubChem. It also has open access for the information about the chemical compounds and it activity. It consist of three interlinked database as Substance, Compound and Bioassay which is launched in 2004 as a part of Molecular Libraries Roadmap Initiatives of the US National Institute of Health (NIH)[8].



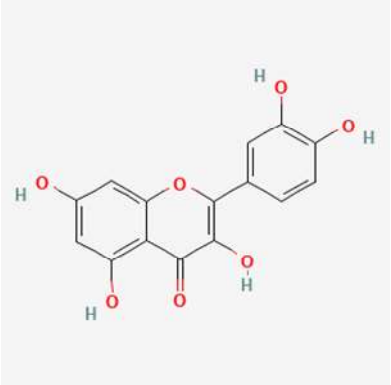


Fig.2. Aretmisinin

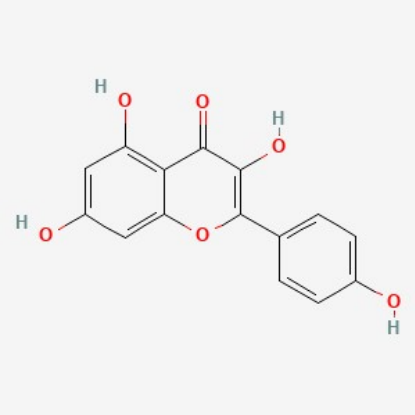


Fig.3. Quercetin

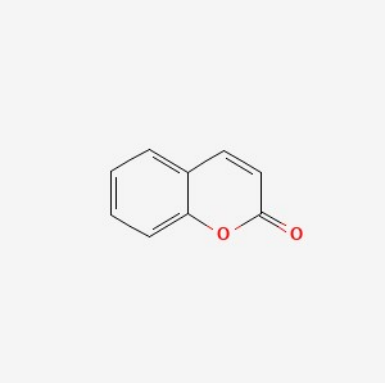


Fig.4. Kaempferol

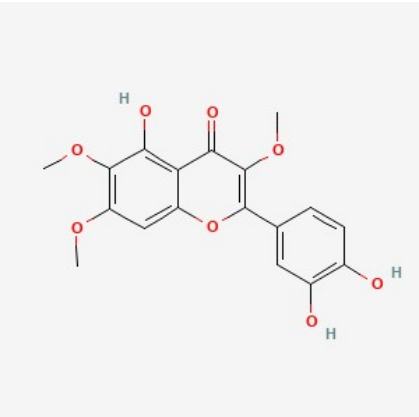


Fig.5. Coumarin

Fig.6. Chrysosplenol D

2.3. Molecular Docking:

Molecular docking is the study of how two or more molecular structure (eg; protein and ligand interactions) fit together. In simple way, docking is a molecular modelling technique that is used to predict how receptor interacts with ligand[9].

The docking consist of two basic steps

Prediction of ligand conformation along with its position

Orientation within protein binding site and assessment of quality of pose using a scoring functions.

PyRx software is used which is virtual screening software for computational drug discovery that is used to screen libraries of compounds against potential drug targets[11].

BIOVIA Discovery Studio is used for viewing, sharing and analyzing protein or receptor and small molecule data.

Ramachandran plot is a space filling model of peptides used to visualize energetically possible (eg; sterically permitted) values for dihedral angles against for a polypeptide chain. The Ramachandran principle says that alpha helices, bets strands and turns are the most likely conformations for a polypeptide chain to adopt. For this we used PDBsum (Pictorial database of 3D structures in the Protein Data Bank.

3. **Results and Discussion:**

3.1. Ramachandran plot:

In Ramachandran plot the Red colour shows residue in the most favoured region. Brown colour are shown additional allowed region. And yellow colour show generously allowed regions.

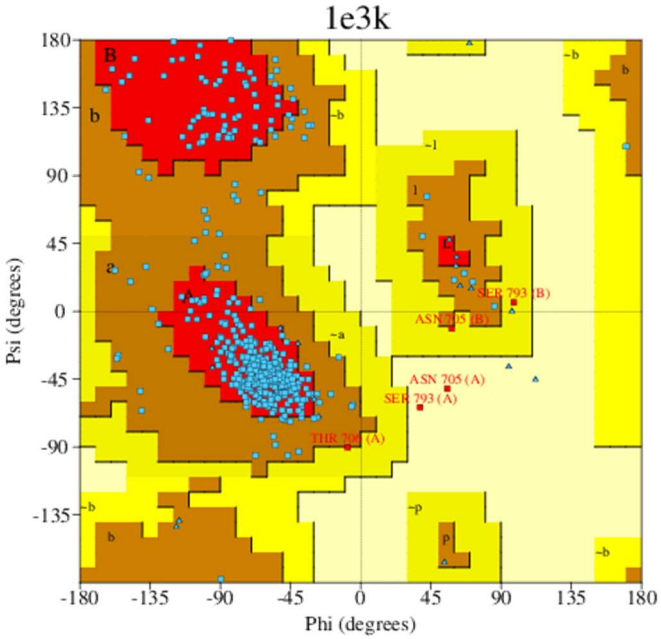


Fig.7. 1E3K

3.2. Ligand binding preparation:

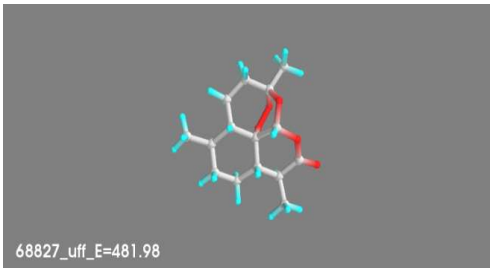


Fig.8. 1E3K and Artemisinin

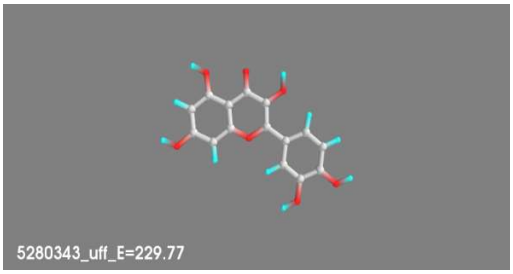


Fig.9. 1E3K and Quercetin

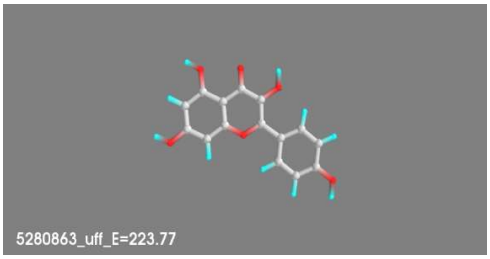


Fig.10. 1E3K and Kaempferol

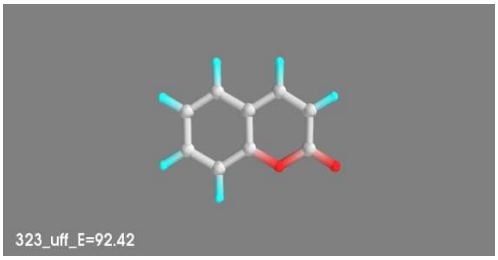


Fig.11. 1E3K and Coumarin

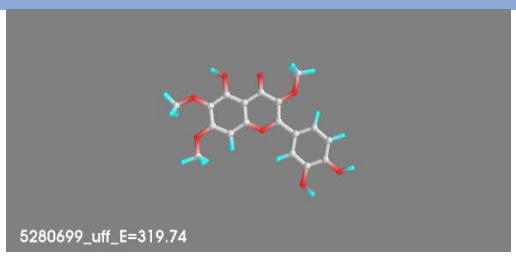


Fig.12. 1E3K and Chrysosplenol D

3.3. Parameter gride and docking simulation:

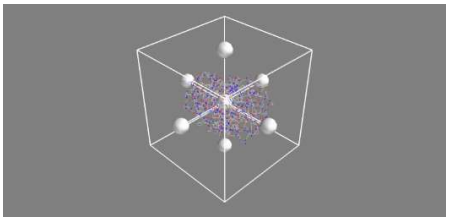


Fig.13. 1E3K and Artemisinin

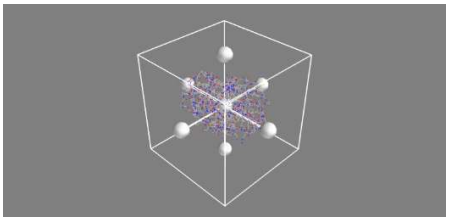


Fig.14. 1E3K and Quercetin

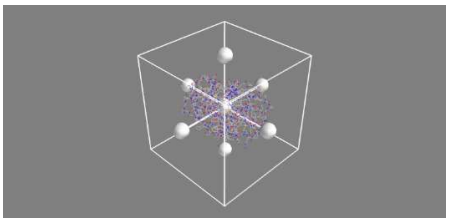


Fig.15. 1E3K and Kaempferol

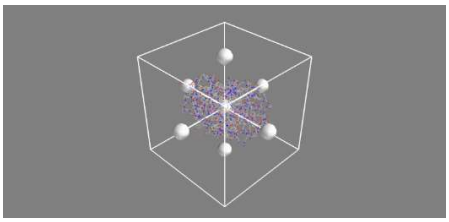


Fig.17. 1E3K and Coumarin

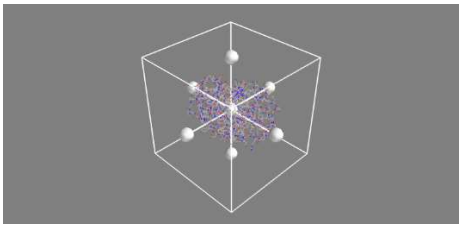


Fig.18. 1E3K and Chrysosplenol D

3.4. Binding results:

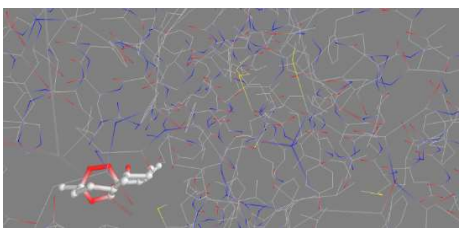


Fig.19. 1E3K and Artemisinin

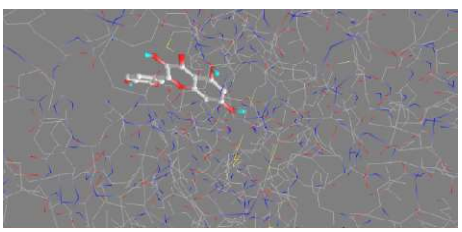


Fig.20. 1E3K and Quercetin

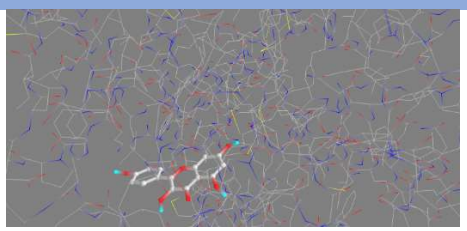


Fig.21. 1E3K and Kaempferol

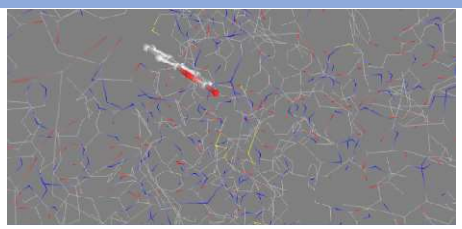


Fig.22. 1E3K and Coumarin

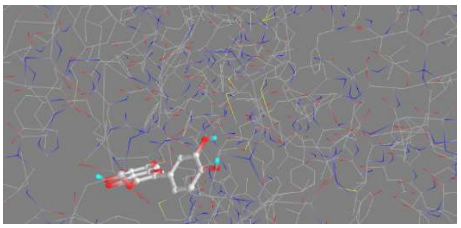


Fig.23. 1E3K and Chrysosplenol D

3.5. Bio discovery docking :

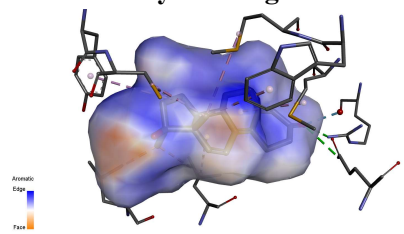


Fig.23. 1E3K and Artemisinin

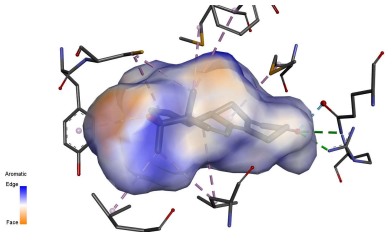


Fig.25. 1E3K and Quercetin

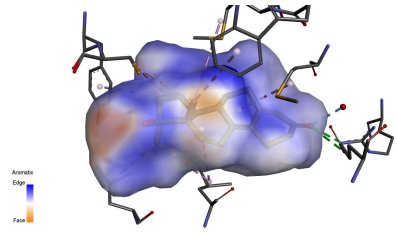


Fig.26. 1E3K and Kaempferol

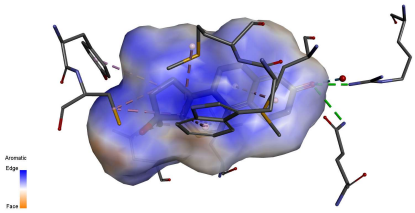


Fig.27. 1E3K and Coumarin

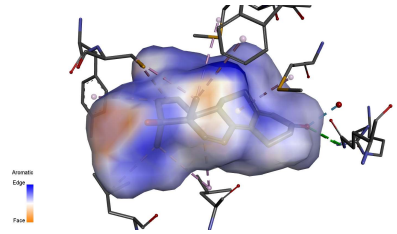


Fig.28. 1E3K and Chrysosplenol D

3.6. Amino acid (2D Structure) illustration of the interaction of the ligand-protein complex is interpreted in discovery studio client, where the residual numbers are the binding cavity residue of SmSrtA forming hydrogen bond with following:

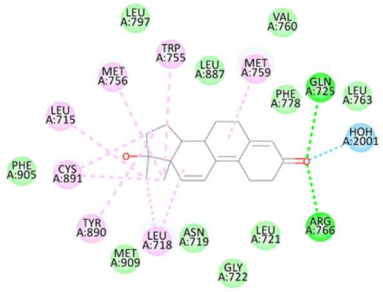


Fig.29. 1E3K and Artemisinin

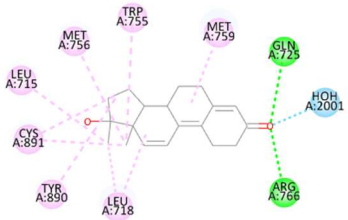


Fig.30. 1E3K and Quercetin

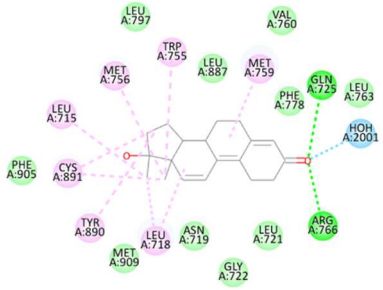


Fig.31. 1E3K and Kaempferol

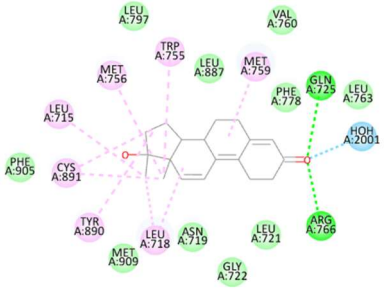


Fig.32. 1E3K and Coumarin

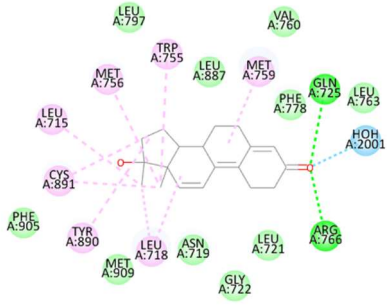


Fig.33. 1E3K and Chrysosplenol D

Water Hydrogen Bond
Conventional Hydrogen Bond
Pi-sigma

3.7. Binding Energy:

Table.1: Binding energy's of Protein and Receptor

Sr. no.	Receptor	Ligand	Binding energy
1.	Human Progesterone Receptor (1E3K)	Artemisinin	-6.7kcal/mol
2.		Quercetin	-8.2kcal/mol
3.		Kaempferol	-8.1kcal/mol
4.		Coumarin	-6.0kcal/mol
5.		Chrysosplenol D	-7.8kcal/mol

Conclusion:

In-silico molecular docking studies of A. annua revealed potential phytochemical targets, including Artemisinin, Quercetin, Kaempferol, Coumarin and Chrysosplenol D phytoconstituents classes and structural manifolds. These phytoconstituents are likely to target the receptor of cancer. This review suggest that A. annua, may have a anticancer activity. Molecular docking indicated that Quercetin (-8.2kcal/mol) and Kaempferol (-8.1kcal/mol) have higher binding affinity than Chrysosplenol (-7.8kcal/mol), Artemisinin (-6.7kcal/mol) and Coumarin (-6.0kcal/mol) which have less binding affinity. The ligand molecule binds accurately to the receptor's active site, which is determine by presence of amino acids.

Reference

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