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MOLECULAR DYNAMIC SIMULATION – BASED PHYTOCHEMICAL SCREENING OF BUCKWHEAT (*Fagopyrum esculentum*) LEAF EXTRACT AGAINST CANCER BY TARGETING HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR

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Abstract:

Fagopyrum esculentum, a member of the polygonaceae family, is commonly found in India and is known for its anticancer leaves. It is used to treat ulcers, peridontitis, anemia, constipation, and hemostasis. Fagopyrum esculentum is a complete treatment that can be used for lung cancer. Unknown is the exact chemical process that underlies buckwheat's anticancer properties. The Protein Data Bank was used to collected the crystal structure of the human epidermal growth factor receptor. Lung cancer cell growth was markedly inhibited and changed when the active components of Fagopyrum esculentum (rutin, vitexin, and quercetin) were molecularly docked with lung cancer protein. This experiment indicates that Fagopyrum esculentum can prevent lung cancer. The study's conclusions offer significant new data.

KEYWORDS: Fagopyrum esculentum, Rutin,Vitexin, Quercetin and Human Epidermal Growth Factor Receptor

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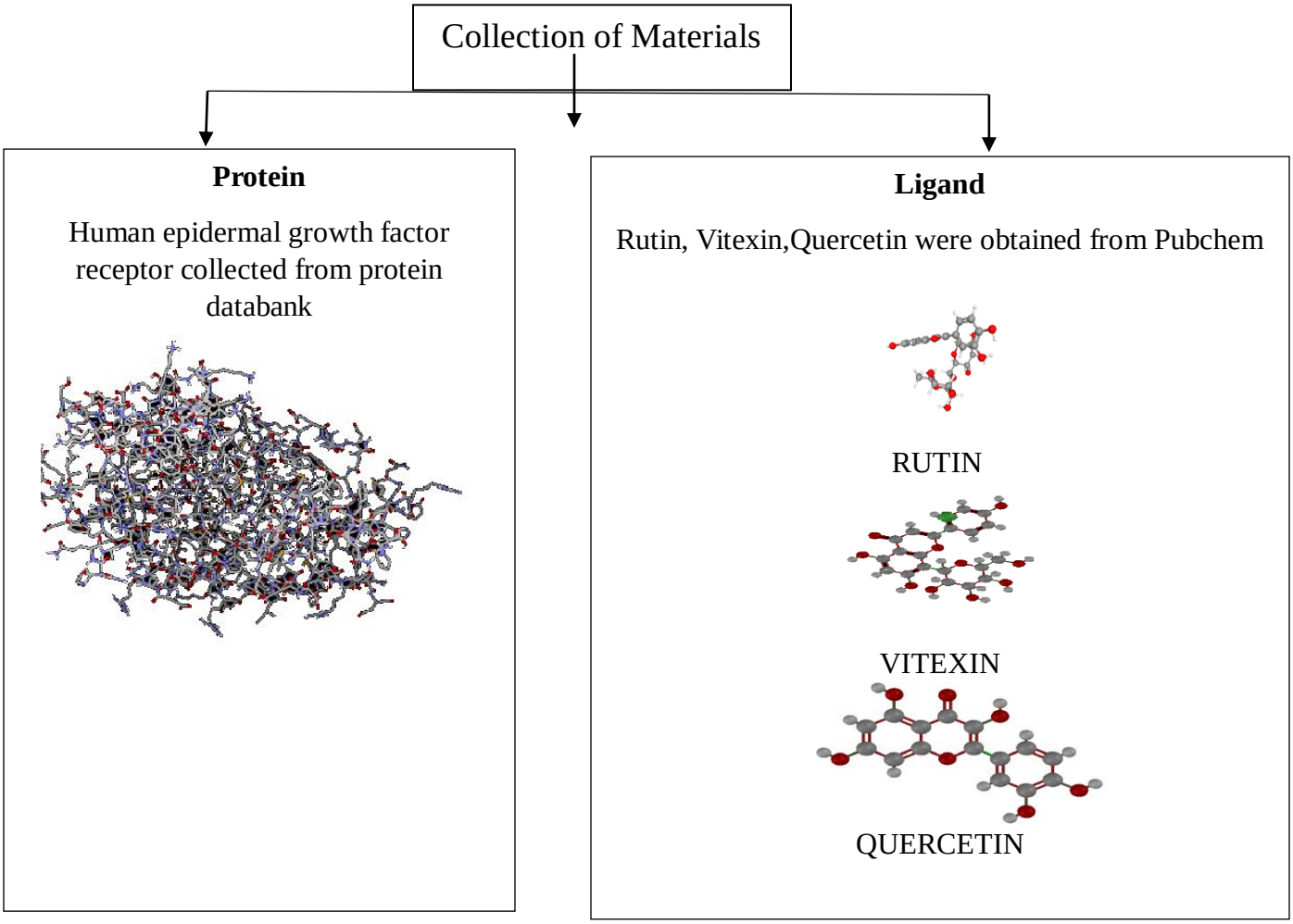
INTRODUCTION:

Approximately 85% of the world's population uses herbal or traditional medicine to treat health problems. As a result, there has been substantial progress in recent years in the field of study that focuses on the scientific evaluation of herbal medicines derived from plants. Cancer, or unchecked cell multiplication, is one of the main causes of death globally. In 2007, around 7,900,000 people died from it worldwide (almost 13% of all deaths)(1*). Fagopyrum esculentum* (Buckwheat) is known as a secondary crop in several nations and is also utilised for a variety of applications, as a result of which it is also known as also known as a multifunctional crop. Leaves from Rutin, Vitexin, Quercetin is extracted from *Fagopyrum esculentum*.While its leaves are consumed as a vegetable. Buckwheat is high in carbohydrates, fats, lipids, proteins, and vital amino acids. It also Contain a Rutin, which has a high therapeutic value. Starch is abundant in buckwheat seeds, accounting for 59% to 79% of the total Globulin is the most abundant protein in buckwheat, accounting for over half of the total protein. Buckwheat contains a lot of fatty acids such palmitic, oleic, linoleic, stearic, and linolenic acid.The therapeutic benefits of *Fagopyrum esculentum* is well established.The presence of flavonoids, anthraquinones, carbohydrates, amino acids, alkaloids, phlobatannins, and tannins was detected in qualitative testing (2). Pharmacological research revealed that Fagopyrum esculentum has antioxidant, anti-inflammatory, cardiovascular, hypolipidemic, antigenotoxic, antidiabetic, reno-protective, anticancer, antimicrobial, wound healing, antistress, memory impairment protection, and photoprotective properties (3) .With an estimated 1.2 million new cases in 2000, lung cancer is the most frequent type of cancer in the world (12.3% of all malignancies). Tobacco smoking is the leading cause of lung cancer, accounting for 80%-90% of cases. There are significant geographic, ethnic, and gender disparities in incidence, and some studies suggest that exposure to carcinogens in tobacco smoke may raise the risk of lung cancer in women. When compared to a lifetime nonsmoker, a lifetime smoker has a 20- to 30-fold greater risk of acquiring lung cancer (4). Lung cancer is the main cause of cancer death globally. However, the incidence and mortality rates of lung cancer vary significantly around the world, reflecting different patterns of tobacco use, exposure to environmental risk factors, and genetics. Tobacco use is the leading cause of lung cancer. Lung cancer incidence is strongly influenced by smoking practices, which vary by gender and economic development. As a result, tobacco control initiatives are an essential component of global strategies to minimise lung cancer mortality. Unprocessed biomass fuels, asbestos, arsenic, and radon are all environmental and occupational lung cancer risk factors (5).In structural molecular biology and computer-assisted drug design, molecular docking is a critical technique. The purpose of ligand—protein docking is to anticipate the most likely binding mode(s) of a ligand with a known three-dimensional structure of a protein. Successful docking systems effectively explore high-dimensional spaces and employ a scoring formula that appropriately ranks candidate dockings. Docking may be used to perform virtual screening on vast libraries of compounds, rate the results, and provide structural theories about how the ligand inhibit the target, which is extremely useful in lead optimisation (6).

IN – SILICO DOCKING STUDY:



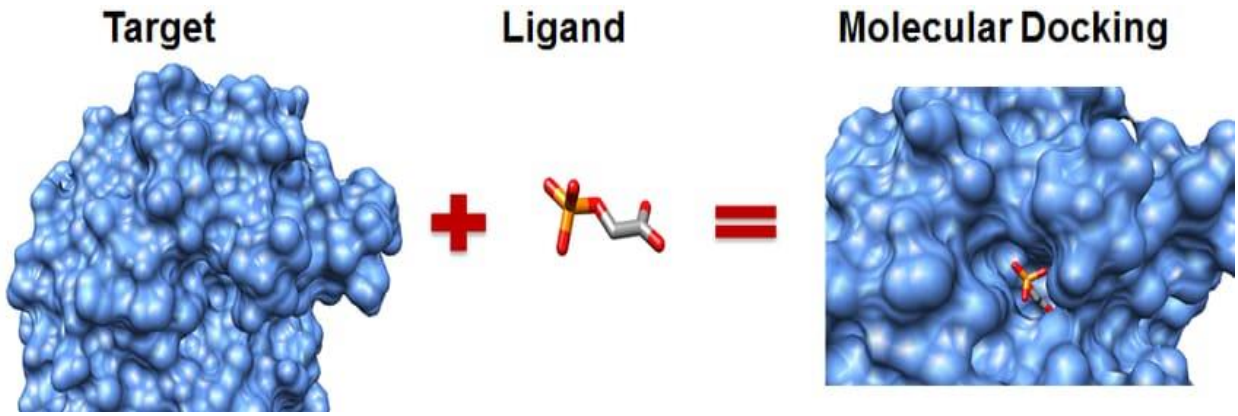


Figure 1: Representation of protein – ligand docking

A review of the literature and the compounds' activities helped choose which one to use for the docking studies. This chemical structure's ligands were selected and used to bind with targets in order to determine the binding affinity for the docking experiments. The discovered compounds were examined using the online docking service seamdock. Three molecules – Rutin, Vitexin, Quercetin

DISEASE PROFILE: Since 1985, lung cancer has been the most frequent cancer in the world, both in

terms of incidence and fatality. Lung cancer is the leading cause of new cancer diagnoses (1,350,000 new cases, accounting for 12.4% of all new cancer cases) and cancer fatalities (1,180,000 deaths, accounting for 17.6% of all cancer deaths).In 2001, an estimated 157,400 Americans died from lung cancer. Lung cancer is the most common malignancy in both men and women. Smoking is the leading cause of lung cancer, accounting for 75-80% of all lung cancer fatalities. Lung malignancies are divided into two types: small-cell carcinomas and non-small-cell carcinomas. Non-small-cell lung cancer is the most frequent kind, accounting for up to 75% of all lung cancers. Chest radiography, sputum cytology, bronchoscopy, needle biopsy, and other procedures are used to diagnose lung cancer. Surgery is utilised extensively in the treatment of stage I and stage II non-small-cell lung cancer, and it may also be employed in the treatment of stage III disease. Patients with stage IIIa illness may be surgical candidates, although the presence of mediastinal lymph nodes diminishes the likelihood of survival (7).As seen by support for prior screening trials utilising chest radiography and cytologic examination of sputum, there has long been interest in screening to detect lung malignancies while they are smaller and presumably at earlier and more curable stages (8). Tobacco use is responsible for around 75% of lung cancer cases worldwide, with a higher estimate of 85% to 90% in the United States. Because tobacco use is a known carcinogen, secondary causes of lung cancer exist (9). Reducing tobacco use is unquestionably the most economical strategy to prevent lung cancer death.Various therapies are available, such as immunotherapy, targeted medication therapy, radiation therapy, chemotherapy, and surgery.

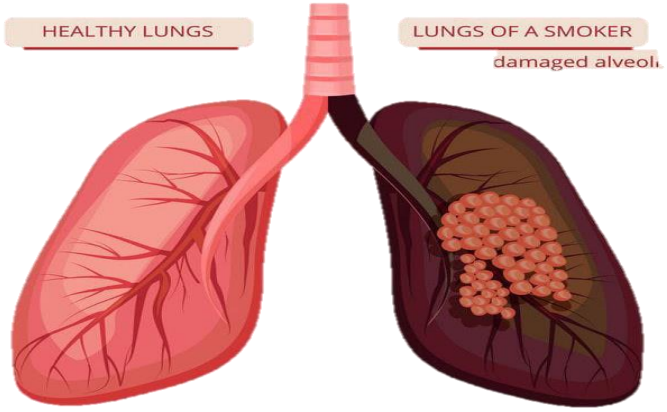
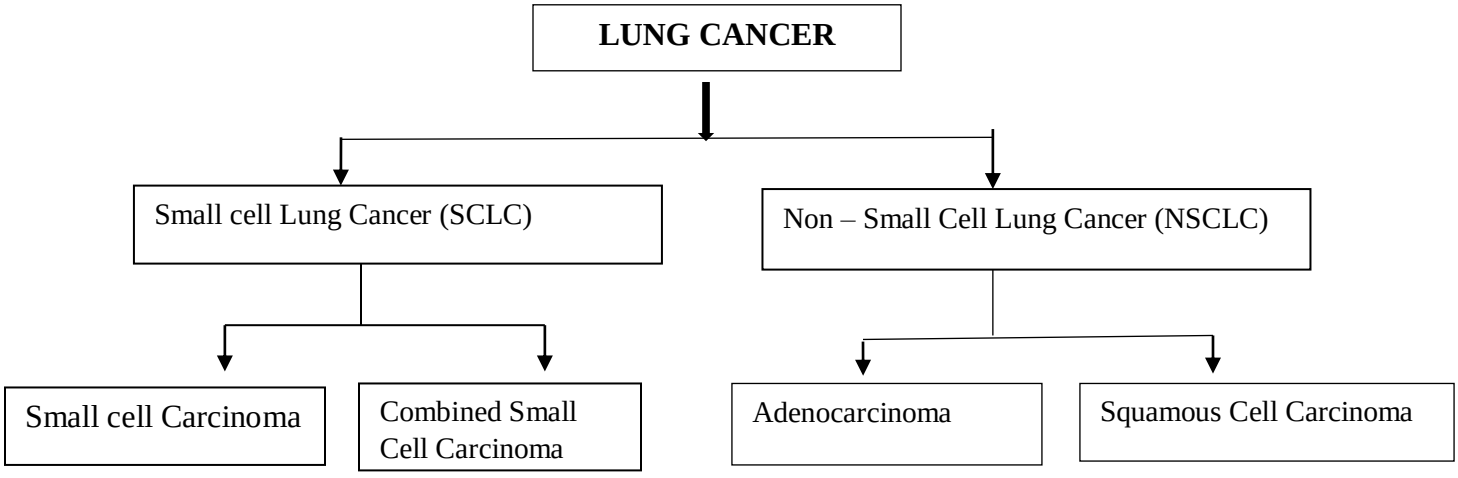


Figure 2: Difference between healthy lung and lung cancer

Types of lung cancer:



PLANT PROFILE:

Figure 3*: Fagopyrum esculentum*

KINGTOM	Plantae
CLASS	Magnoliopsida
ORDER	Caryophyllales
FAMILY	Polygonaceae
SPECIES	*Fagopyrum esculentum*
DIVISION	Tracheophyta
GENEUS	Fagopyrum

CHEMMICAL CONSTITUENTS: -

SOURCE	ACTIVE CHEMICAL CONSTITUENTS	NAME OF EXTRACT
Leaves, flowers	Quercein-3-rhamnoglucode (rutin), hyperosid, gallic acid-3-O-glucoside chlorogenic acid, neochlorogenic acid, isoorentin, vitexin.	Ethanolic, methanolic extract.

MATERIALS AND METHODS:

Materials: For our current investigation, we employed biological resources such as PDB (Protein Data Bank), PubChem, seamdock, and tools such as autodock vina.

PDB (Protein Data Bank): The Protein Data Bank (PDB), which was founded in 1971 at Brookhaven National Laboratories (BNL), is the only global database for structural data on biological macromolecules.

PubChem: The public database PubChem (https://pubchem.ncbi.nlm.nih.gov) contains information about substances and their biological roles.

Pub Chem debuted in 2004 as part of the US National Institutes of Health (NIH) Molecular Libraries Roadmap Initiatives. It has now expanded to become a major source of chemical data, assisting scientific communities in cheminformatics, chemical biology, medicinal chemistry, and drug development, among other fields.Over the preceding eleven years, PubChem has grown into a substantial infrastructure that provides access to chemical information to the scientific research community. PubChem is made up of three databases that are linked together: substance, compound, and bioassay.Individual PubChem data contributors provided chemical data to the Substance database, and specific chemical structures were retrieved from the Substance database for the Compound database. The Bio Assay database contains information on the biological activity of

chemical compounds that have been studied in assay experiments. This paper offers an overview of the PubChem Substance and Compound databases, including information on data sources, content, organisation, and chemical structure standards. Web-based interfaces for text and non-text searches, as well as programmatic access, are also included. It also provides an overview of PubChem RDF, a structured version of PubChem data that may be used for data sharing, analysis, and integration with data from other databases, as well as PubChem3D.

AUTODOCK VINA: A virtual screening tool for computational drug development, can test libraries of chemicals against potential therapeutic targets. Virtual screening can be performed by medicinal chemists utilising Autodock Vina, which aids users at every stage of the procedure, from data preparation to examining grid boxes. Although there are no magic buttons for discovering new medications, the Autodock wizard's chemical spreads, heat-like capabilities, and user-friendly interface make it a powerful tool for rational drug design.
The Autodock Vina app will be installed by the application.

SEAMDOCK: In silico examination of protein receptor interactions with tiny ligands is now routine in drug discovery pipelines, and a variety of tools and techniques have been developed to that purpose. The online SeamDock service integrates multiple docking methods into a unified framework, allowing for both local and/or global docking of ligands, as well as a hierarchical method that combines the two for straightforward interaction site identification. This service runs on a standard web browser and does not require the installation of any additional software.The seamless library, which connects the RPBS computation server to the user's homepage, allows the user to navigate the SeamDock website quickly and interactively. Much effort has gone into visualising ligand, receptor, and docking poses in three dimensions, as well as how they interact with the receptor. Because of the extensive visualisation features and the seamless library, a user can share a docking session and all of its visualisation states with an infinite number of colleagues. SeamDock is thus a free, simple, educational, dynamic web docking solution that is best suited for teaching and training.

METHODOLOGY:

Docking procedure:

Step1: Preparation of receptor protein: Protein Data Bank (PDB) provided the 3D crystallographic structure of the protein Human Epidermal Growth Factor Receptor (PDB ID:1M17). The protein's three-dimensional structure was found. Open the file and read the molecule.

- Molegro Molecular Viewer → Import file → Export molecule.
- Protein is only applied → Export → Save as pdb file.
- Save as prepared protein (PDB form).

Step2: Preparation of ligand: Quercetin, Rutin, Vitexin, is taken as ligand molecule. They are downloaded from pubchem and then converted into PDB format.

- Molegro Molecular Viewer → Import → File → Export molecule.
- Save as (PDB form)

Step3: Docking:
AUTODOCK:

- File → Read molecule → Select the protein structure.
- Click on edit → Hydrogens → Add polar only.
- click on edit→ Charges → Add compute charges.
- Click on ligand → Choose ligand → Select the ligand structure.
- Click on edit →Charges → Add kollamen charges.
- Click on grid → Select the grid box → Select the dimensions of your grid box. Note your grid dimensions.

Step 4: Docking:

- By using https;//bioserv.rpbs.univ-paris-diderot.fr/services/seamdock
- Click on run seamdock →Choose ligand (in the .PDB, .SDF form) → click on open.
- Click on choose protein →Choose protein (in the form) → click on open.
- Set the dimensions →Adjustingx,y,z → Launch Docking.
- Finally, 2D interactions are predicted from MOLEGRO molecular viewer.

RESULT AND DISCUSSION:

Docking result:

- The 3D structure of Human Epidermal Growth Factor Receptor (PDB ID:5CNN), with a resolution of 1.9Å respectively is obtained from the **protein data bank (RCSB-PDB).**
- The structure of the Vitexin (CID-5280441), rutin (CID_5280805), Quercetin (CID_5280343) was obtained from **Pubchem** .
- The energy minimization of the ligands was performed using **Autodock vina**.
- **Seamdock** is used to estimate the affinities and interactions of protein and ligand.

Chemical Contituents	Protein target	Binding Affinity
Vitexin	HumanEpidermal Growth Receptor (PDB ID:5cnn)	-13.7 kcal/mol
Rutin		-9.5 kcal/mol
Quercetin		-9.7 kcal/mol

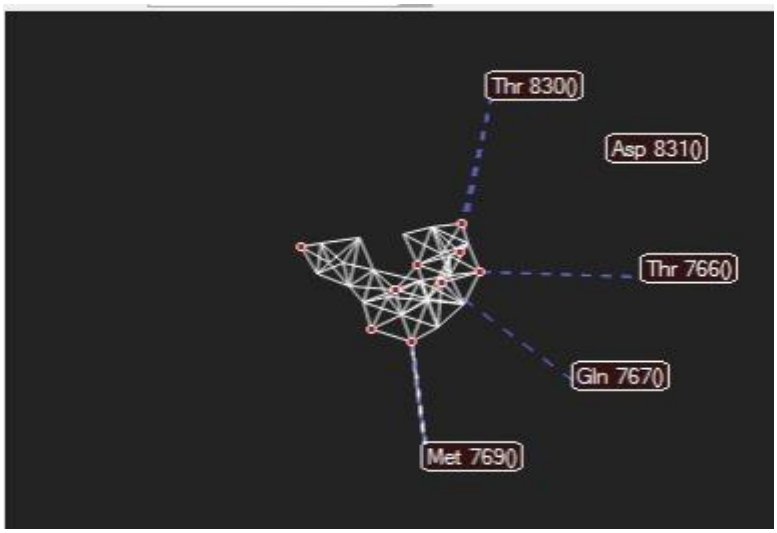


Figure 4: 2D interaction of Vitexin with EGFR

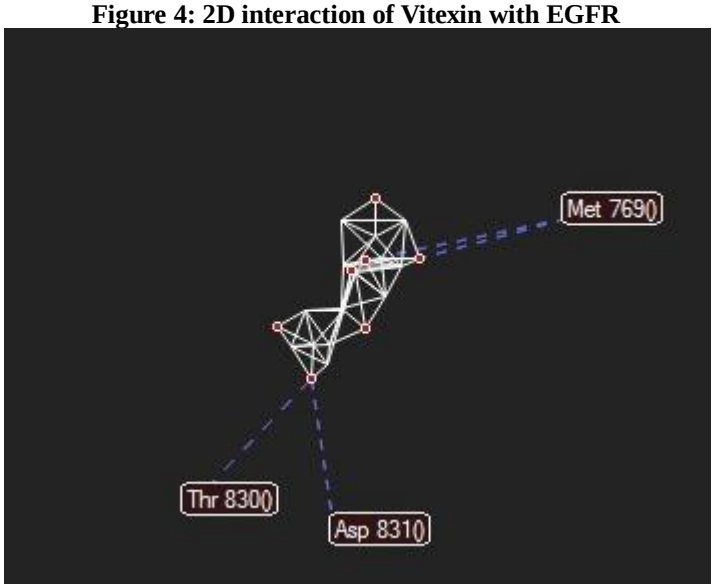


Figure 5: 2D interaction of Quercetin with EGFR

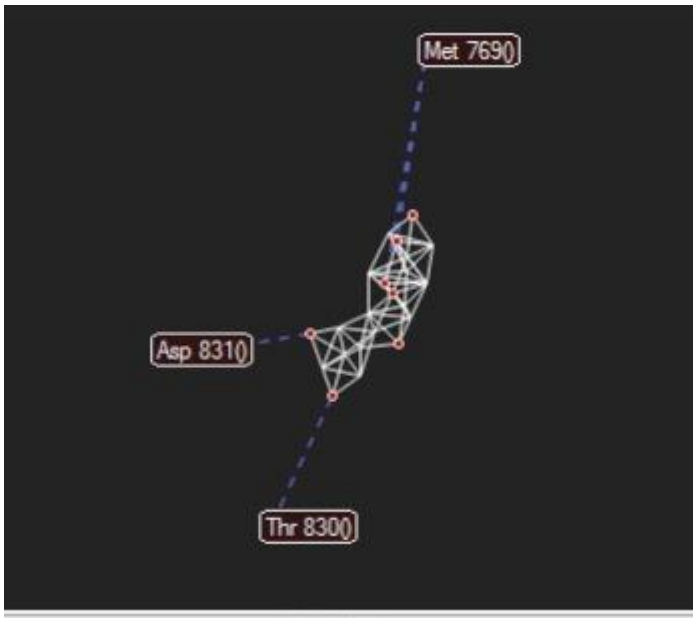


Figure 6: 2D interaction of Rutin with EGFR

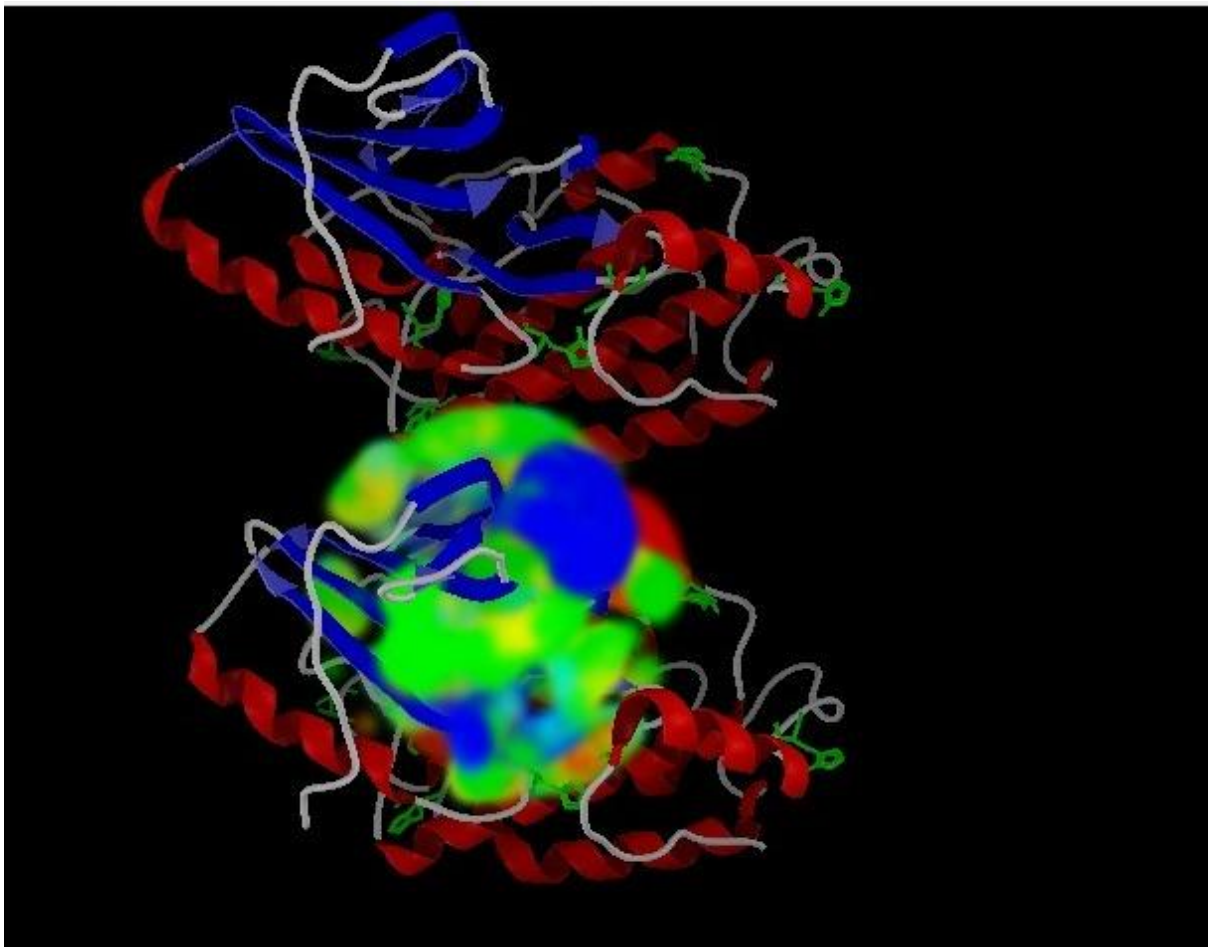


Figure 7: 3D representation with energy mapping of interaction of vitexin with EGFR

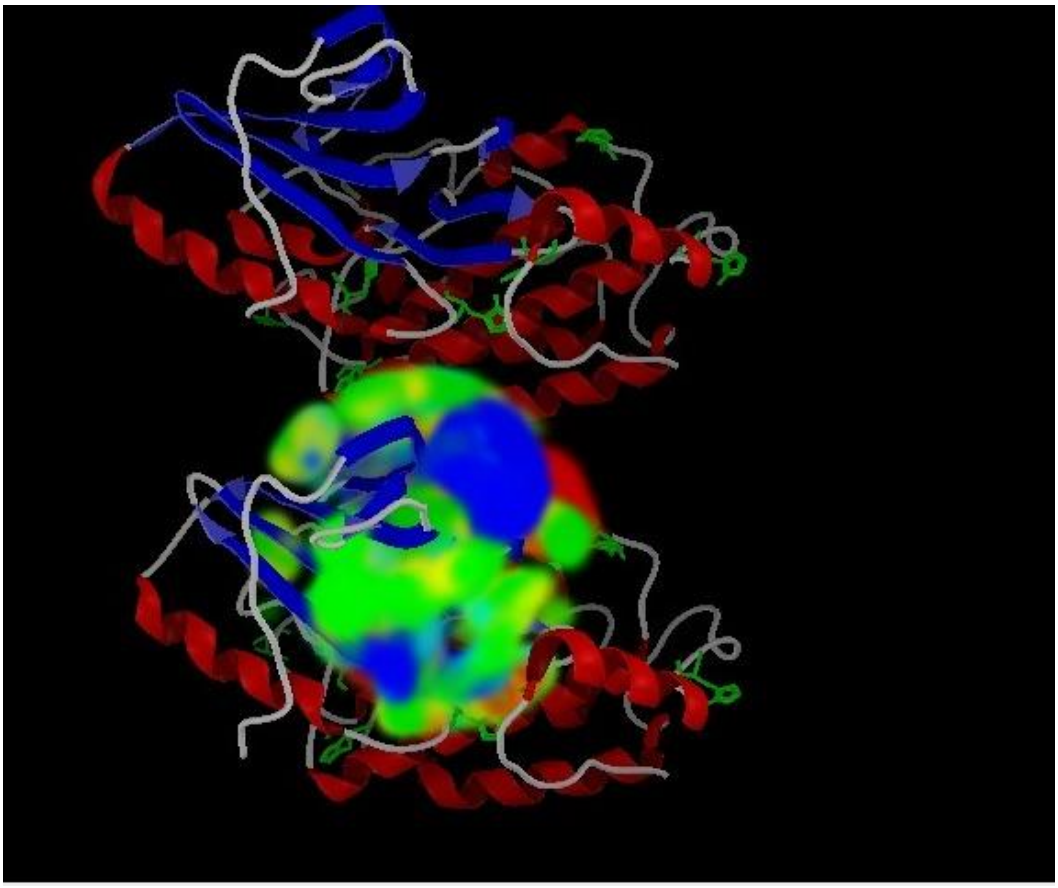


Figure 8: 3D representation with energy mapping of interaction of Quercetin with EGFR

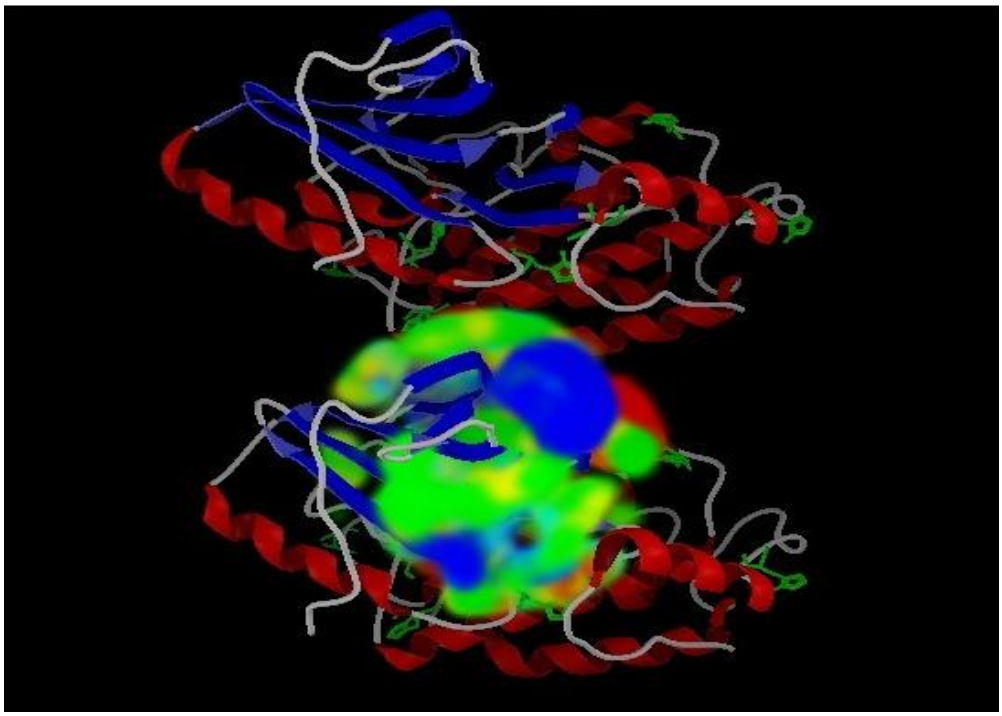


Figure 9: 3D representation with energy mapping of interaction of Rutin with EGFR

DISCUSSION:

- ❖ According to Ahammad et al. Briefings in Bioinformatics, 22(5) Pharmacoinformatics and molecular dynamics simulation-based phytochemical screening of herbal plants *against human cancer* by targeting protein was taken……
- ❖ According to Jin-Shuang Zhao anti-cancer activity of *Fagopyrum esculentum* leaf extract against cell line was taken for present docking studies.
- ❖ According to. Nida Iqbal1 and Naveed Iqbal2 , Human Epidermal Growth Factor Receptor are the causatives for lung cancer was taken for the present docking studies.
- ❖ In the current study, the protein human epidermal growth factor receptors was docked with vitexin, quercetin, and rutin using Seamdock
- ❖ The binding scores of the anti-cancer protein ligands were -13.7 kcal/mol, 9.5 kcal/mol, and -9.7 kcal/mol.
- ❖ Thus, when the docking score is least negative, the protein and ligand have a larger binding affinity. It was discovered that vitexin's binding energy to the Human Epidermal Growth Factor Receptor was -13.7 kcal/mol.

CONCLUSION:

- ➢ The results of the insilico investigate given a valuable derivation with respect to the compounds' utilization, illustrating expanded authoritative vitality and fondness towards chemicals and being used as lung cancer treatment helps..
- ➢ In the current examination, the target protein Human Epidermal Development Figure Receptors cell line within the was effectively docked with dynamic constituents (Rutin,vitexin,and quercetin). Vitexin's official vitality was recored at -13.7 kcal/mol.
- ➢ Because the protein and ligand have a more grounded official liking when there's less negative binding score, this seem possibly be a medicine with anti-cancer action.

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