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MOLECULAR DYNAMICS SIMULATION-BASED PHYTOCHEMICAL SCREENING OF BITTER LIFE *(VERNONIA AMYGDALINA)* LEAF EXTRACT AGAINST NASOPHARYNGEAL CANCER BY TARGETING EPSTEIN-BARR VIRUS

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Abstract:

The anti-cancer bitter life, vernonia amygdallina, is a member of the Asteraceae family and is commonly found in India. It is used to treat paralysis, rheumatism, leprosy, ulcers, and epilepsy. When treating Nasopharyngeal cancer, vernonia amygdalina can be utilised as a comprehensive treatment. The precise chemical mechanism underlying bitter leaf' anticancer action is still unknown. The Epstein-barr virus (EBV) line's crystal structure was obtained from the Protein Data Bank. When the active ingredients of vernonia amygdallina (rhoifolin, luteolin,diosmetin, and baicalin) were molecularly docked with cervical cancer protein, the proliferation of cervical cancer cells was significantly reduced and altered. Exoecaria agallocha has the ability to prevent cervical cancer, as demonstrated by this experiment. The study's conclusions provide important new information.

Keywords: *Vernonia amygdallina, Epstein-barr virus., rhoifolin, luteolin, diosmetin, and baicalin*

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INTRODUCTION:

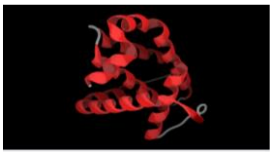
Around the world, 85% of people treat health-related problems with herbal or traditional medicine. As a result, research concerning the scientific assessment of herbal medications made from plants has advanced significantly in the last several years. Cancer, or unchecked cell proliferation, is one of the main causes of death in the world. It caused about 7,900,000 deaths worldwide in 2007 (roughly 13% of all deaths). [1] Nasopharyngeal carcinoma exhibits a unique geographic distribution pattern, with a high incidence rate in east and southeast Asia. Over the last ten years, epidemiological trends have demonstrated a gradual but steady decline in incidence and a significant decline in mortality. These results most likely reflect changes in lifestyle and surroundings, improved knowledge of the etiology and risk factors, population screening, improvements in imaging technology, and personalised, all-encompassing chemoradiotherapy regimens. Specifically, population screening, prognostication, treatment response prediction for therapeutic adaptation, and disease surveillance have all made use of plasma Epstein-Barr virus (EBV) DNA. Furthermore, increased survival with lower toxicities have been facilitated by the widespread use of intensity-modulated radiation and the optimization of chemotherapy techniques (concurrent, adjuvant, and induction). Immune checkpoint treatments are one of the more advanced novel therapeutics currently being developed. (2) Vernonia Amygdalina Del is one of the medicinal plants that are used globally to treat a wide range of illnesses. There have been rumors that V. amygdalina. In Africa and Asia, amygdalina Del plant is used to treat stomach aches, diabetes, dysentery, yellow fever, constipation, and malaria. Furthermore, the plant is widely used as a vegetable and culinary herb in soup throughout Africa.V. amygdalina Del is a member of the Asteraceae family. It is widely grown as a food supplement in West Africa, including Nigeria, and is found throughout Tropical Africa.2.5 Bitter leaf is the common name for V. amygdalina Del; it is also referred to locally as "Shuwaka" in Hausa and "Ewuro" in Yoruba.(3) One such structure-based drug design technique is called "molecular docking," which models molecular interactions and forecasts the binding mode and affinity between ligands and receptors. The field of drug design research has made extensive use of this technology in recent times. It is convenient for researchers to buy, synthesize, and finish follow-up pharmacological tests when they use the compounds database to screen for potential pharmacophores. This approach also significantly increases efficiency and lowers research costs. Furthermore, the development of reverse molecular docking technology may greatly enhance the ability to predict drug targets and comprehend the underlying molecular mechanism for drug design.Lastly, a brief overview of the most recent developments and uses of molecular docking technology is provided in this review. [4]

In-silico docking studies:

Collection of materials

Protein

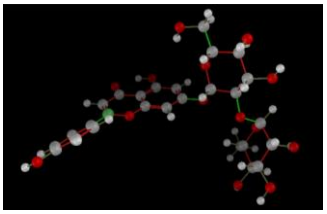
Epstein-barr virus protein was collected from protein data bank.



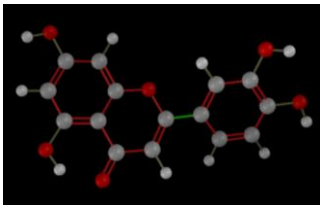
6o0k Protein structure

Ligand

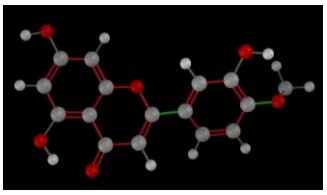
rhoifolin, luteolin, and diosmetin was obtained from pubchem.



Rhoifolin



Luteolin



Diosmetin

REFERENCE:

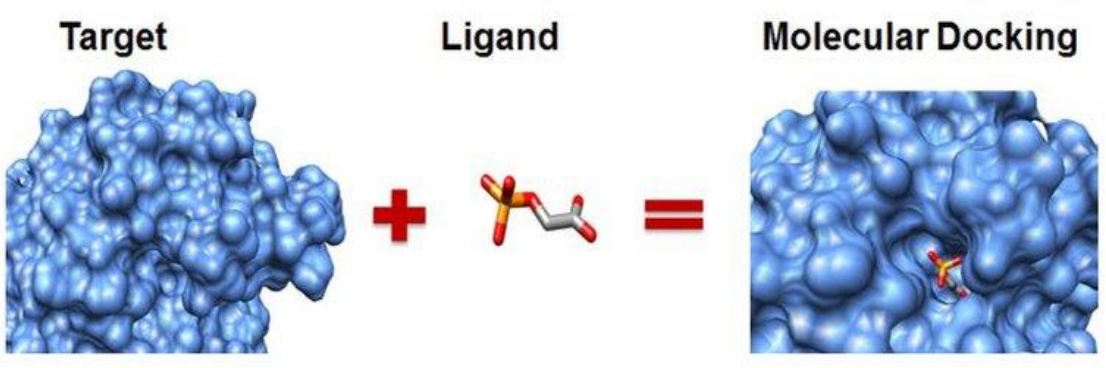


Fig 1: Representation of protein - ligand docking

The compound selected for the docking studies was determined by a review of the literature and the activity of the compounds. To find the binding affinity for the docking studies, ligands with this chemical structure were chosen and used to bind with targets. The online docking website seamdock was used to study the compounds that were identified. Three molecules— rhoifolin, luteolin, diosmetin, and baicalin —make up the protein sequence of the human growth factor(1ivo).

Disease profile:

Nasopharyngeal (nay-zoh-fuh-RIN-jee-ul) carcinoma is cancer that occurs in the nasopharynx, which is located behind your nose and above the back of your throat. Nasopharyngeal carcinoma is rare in the United States. It occurs much more frequently in other parts of the world — specifically Southeast Asia. Nasopharyngeal carcinoma is difficult to detect early. That's probably because the nasopharynx isn't easy to examine and symptoms of nasopharyngeal carcinoma mimic those of other, more-common conditions. Treatment for nasopharyngeal carcinoma usually involves radiation therapy, chemotherapy or a combination of the two. You can work with your doctor to determine the exact approach depending on your particular situation.

Causes :

Cancer begins when one or more genetic mutations cause normal cells to grow out of control, invade surrounding structures and eventually spread (metastasize) to other parts of the body. In nasopharyngeal carcinomas, this process begins in the squamous cells that line the surface of the nasopharynx.

Exactly what causes the gene mutations that lead to nasopharyngeal carcinoma isn't known, though factors, such as the Epstein-Barr virus, that increase the risk of this cancer have been identified. However, it isn't clear why some people with all the risk factors never develop cancer, while others who have no apparent risk factors do.

Tests to screen for nasopharyngeal carcinoma

In the United States and in other areas where the disease is rare, routine screening for nasopharyngeal carcinoma isn't done. But in areas of the world where nasopharyngeal carcinoma is much more common — for instance, in some areas of China — doctors may offer screenings to people thought to be at high risk of the disease. Screening may involve blood tests to detect the Epstein-Barr virus.

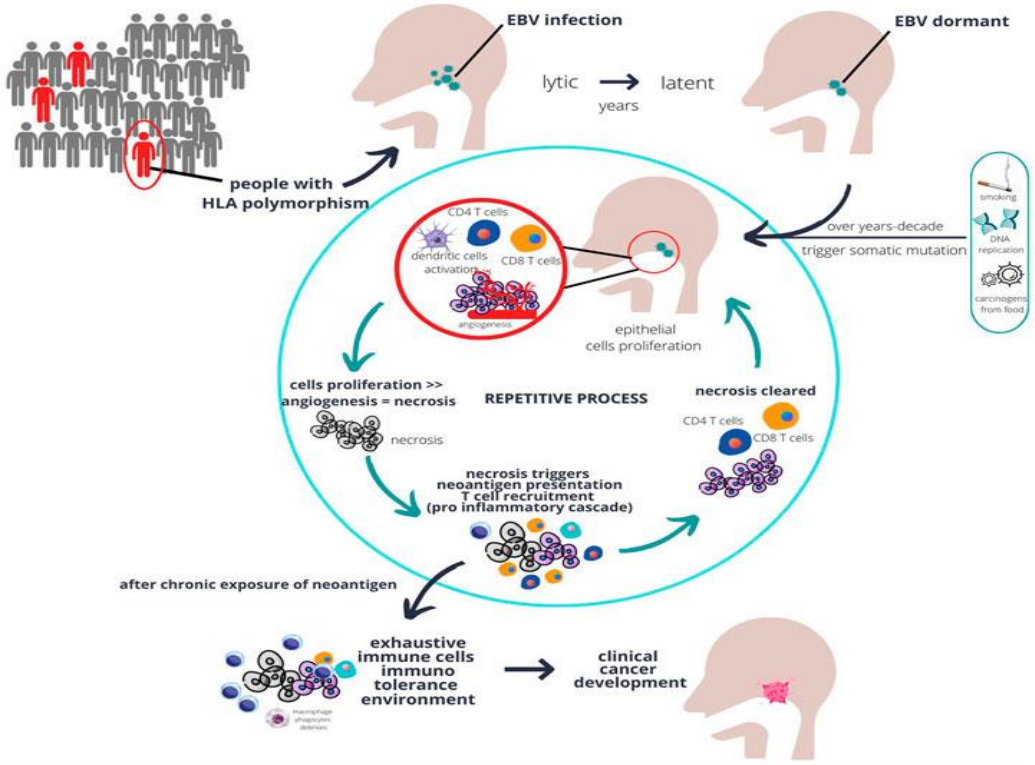


Fig 2: Representation of nasopharyngeal cancer

Epstein-Barr virus :

since its discovery 50 years ago, Epstein-Barr virus

(EBV) has been linked to the development of cancers originating from both lymphoid and epithelial cells. Approximately 95% of the world's population sustains an asymptomatic, life-long infection with EBV. The virus persists in the memory B-cell pool of normal healthy individuals, and any disruption of this interaction results in virus-associated B-cell tumors. The association of EBV with epithelial cell tumors, specifically nasopharyngeal carcinoma (NPC) and EBV-positive gastric carcinoma (EBV-GC), is less clear and is currently thought to be caused by the aberrant establishment of virus latency in epithelial cells that display premalignant genetic changes. Although the precise role of EBV in the carcinogenic process is currently poorly understood, the presence of the virus in all tumor cells provides opportunities for developing novel therapeutic and diagnostic approaches. The study of EBV and its role in carcinomas continues to provide insight into the carcinogenic process that is relevant to a broader understanding of tumor pathogenesis and to the development of targeted cancer therapies.

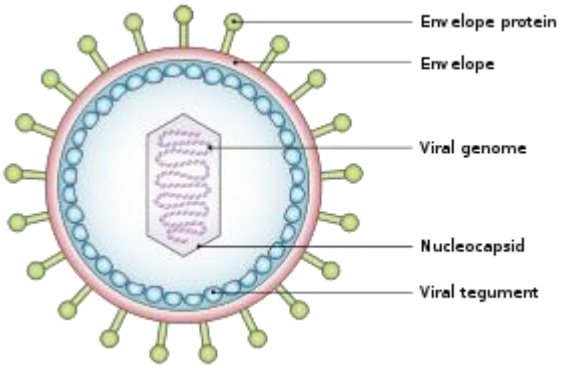


Figure 3 : Representation of Epstein-Barr virus .

Plant profile:

Botanical name	Vernonia amygdallina
Synonym	Vernonia
Family	Asteraceae
English name	Bitter life
Phylum	Tracheophyta
Class	Eudicots
Order	Tracheophyta
Species	*V. amygdalina*

Figure 4 : Vernonia amygdallina

MATERIALS AND METHODS:

Materials:

We used biological databases such as PDB (Protein Data Bank), PubChem, seamdock, and software such as autodock vina for our current study.

PDB (Protein Data Bank):

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

PubChem:

Details about chemicals and their biological roles can be found in the public database PubChem (https://pubchem.ncbi.nlm.nih.gov).

Pub Chem was first launched in 2004 as a component of the US National Institutes of Health (NIH) Molecular Libraries Roadmap Initiatives. Since then, it has grown to become a major repository of chemical data supporting scientific communities in cheminformatics, chemical biology, medicinal chemistry, and drug discovery, among other areas.

PubChem has grown over the previous eleven years into a sizable infrastructure that gives access to chemical information to the scientific research community. PubChem is made up of three interconnected databases: substance, compound, and bioassay.

Chemical data has been added to the Substance database by individual PubChem data contributors, and certain chemical structures have been extracted for the Compound database from the Substance database. Information about the biological activity of chemical compounds that have been investigated in assay tests can be found in the Bio Assay database.

This document provides an overview of the PubChem Substance and Compound databases, including information on their data sources, contents, organisation, and standardisation of chemical structures. It also includes web-based interfaces for text and non-text searches, as well as programmatic access.

It also gives a brief overview of PubChem RDF, a formatted version of PubChem data for use in data sharing, analysis, and integration with data from other databases, and PubChem3D, a resource built from theoretically accurate three-dimensional models of molecules in PubChem.

Autodocking:

Libraries of compounds can be screened against possible drug targets using AUTODOCK VINA, a virtual screening tool for computational drug discovery. Medicinal chemists can conduct virtual screening using Autodock Vina, which assists users with every stage of the process, from preparing data to viewing grid boxes. Although there aren't any magic buttons that can be used to find new drugs, the Autodock wizard's chemical spreads heat-like functionality and user-friendly interface make it a useful tool for rational drug design.

The application will install the Autodock Vina app.

SEAMDOCK:

Drug discovery pipelines now routinely include in silico evaluation of protein receptor interactions with small ligands, and a plethora of tools and protocols

have been created to that end. The online SeamDock service unifies various docking tools into a unified framework, enabling both local and/or global docking of ligands as well as a hierarchical method that combines the two for simple interaction site identification. This service only requires a standard web browser to operate, and it doesn't require the installation of any additional software. The user can navigate the SeamDock website easily and interactively by using the seamless library, which connects the RPBS calculation server to the user's webpage. A significant amount of work has gone into visualizing ligand, receptor, and docking poses in three dimensions as well as how they interact with the receptor. A user can share a docking session and all of its visualization states with an infinite number of collaborators thanks to the advanced visualization features and the seamless library. Seam Dock is therefore a free, straightforward, instructional, dynamic online docking tool that is most appropriate 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:6o0k). 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:

Rhoifolin, luteolin, and diosmetin 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 →Adujusting x,y,z → Launch Docking.

Finally 2D interactions are predicted from MOLEGRO molecular viewer.

RESULT AND DISCUSSION:

Docking result:

- The 3D structure of epstein-barr virus protein (PDB ID:6o0k) ,with a resolution of 1.30Å respectively is obtained from the **protein data bank (RCSB-PDB).**
- The structure of the rhoifolin (CID_5282150), luteolin (CID_5280445),diosmetin (CID_5281612) 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.

Table 2 : Binding affinities

Chemical Contituents	Protein target	Binding Affinity
Rhoifolin	epstein-barr virus protein (PDB ID:6o0k)	-8.7 kcal/mol
Luteolin		-7.2 kcal/mol
Diosmetin		-7.3 kcal/mol

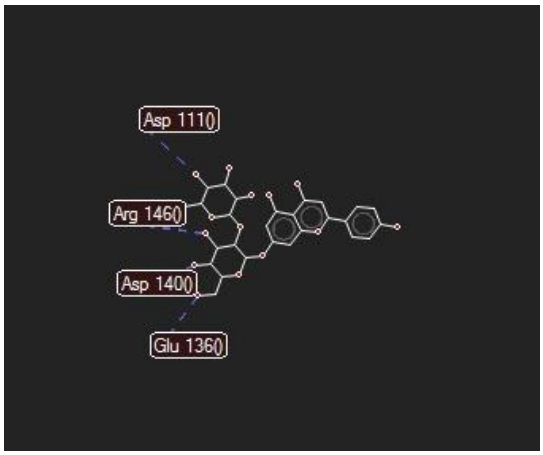


Figure 6 : 2D interaction of rhoifolin with Epstein-barr virus.

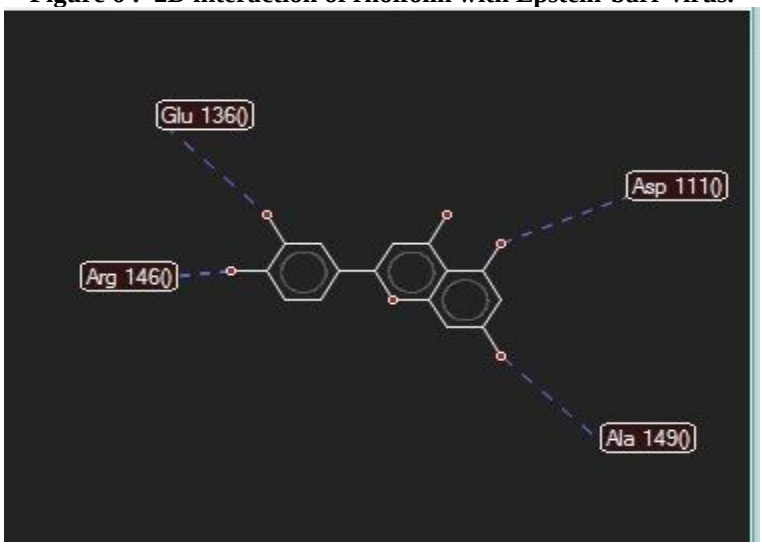


Figure 7 : 2D interaction of luteolin with Epstein-barr virus

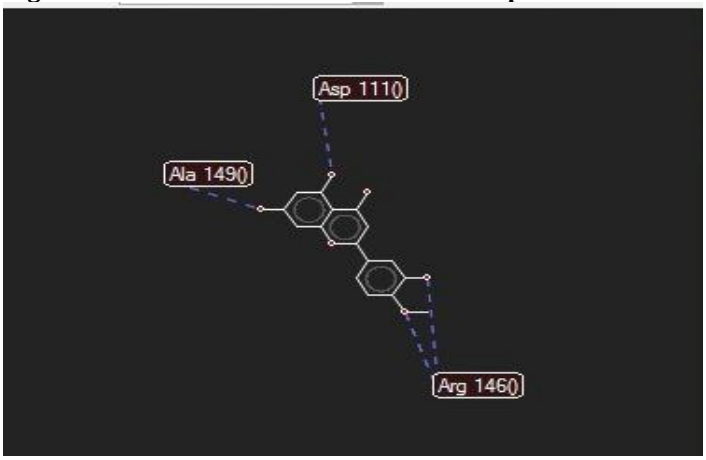


Figure 8: 2D interaction of diosmetin with Epstein-barr virus

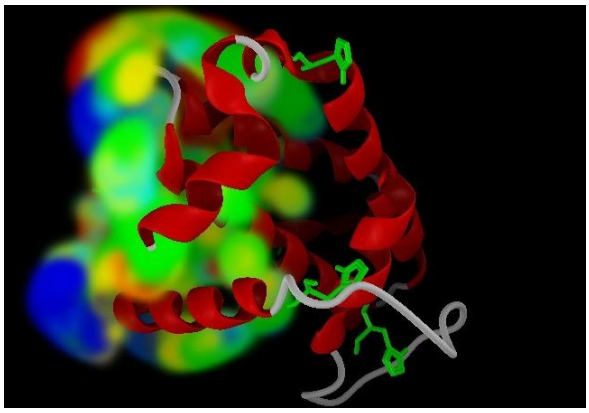


Figure 9: 3D representation with energy mapping of interaction of rhoifolin with Epstein-barr virus.

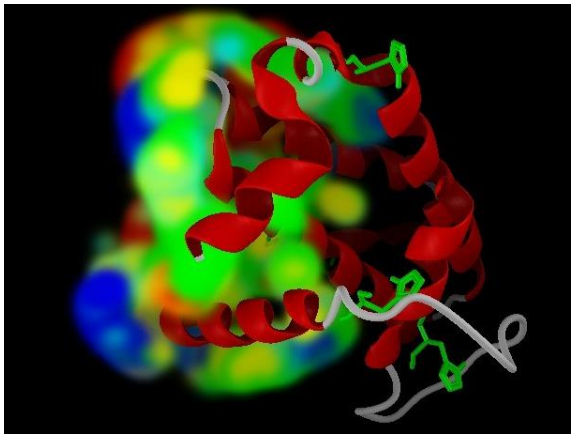


Figure 10: 3D representation with energy mapping of luteolin with Epstein-barr virus

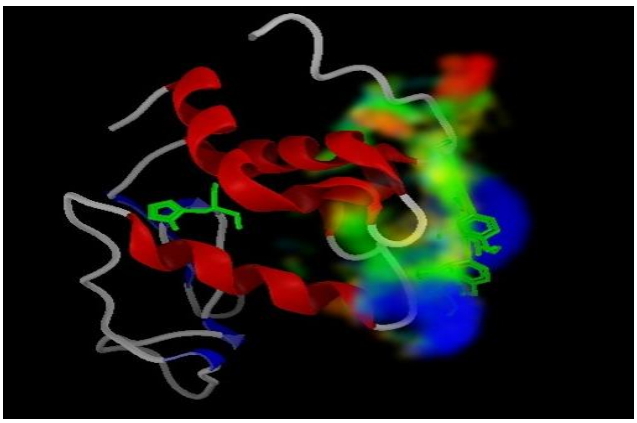


Figure 11: 3D representation with energy mapping of of diosmetin with Epstein-barr virus

DISCUSSION:

- According to Ahammad et al. Briefings in Bioinformatics, 22(5) Pharmacoinformatic and molecular dynamics simulation-based phytochemical screening of herbal plants *against human cancer* by targeting protein was taken……
- The protein Epstein-barr virus was docked with rhoifolin, luteolin, and diosmetin using Seamdock in the current investigation.
- The anti-cancer protein ligands' binding scores were -8.7 kcal/mol, -7.2 kcal/mol, and -7.3 kcal/mol.
- As a result, the protein and ligand have a stronger binding affinity when the docking score is least negative. The binding energy of rhoifolin with the Epstein-barr virus was found to be -8.7 kcal/mol.

CONCLUSION:

- The outcomes of the insilico research provided a useful deduction regarding the compounds' usage, demonstrating increased binding energy and affinity towards enzymes and being utilised as cervical cancer treatment aids..
- In the current investigation, the target protein Human growth factor in the Epstein-barr Virus was successfully docked with active constituents (rhoifolin, luteolin, diosmetin). Rhoifolin's binding energy was recored at -8.7 kcal/mol.
  Because the protein and ligand have a stronger binding affinity when there is less negative binding score, this could potentially be a medication with anti-cancer activity.

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