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Molecular Docking Study Of Some Phytoconstituents Of Alangium Salviifolium Against Colorectal Cancer

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Abstract
The prevalence of unpleasant effects linked to commercially accessible cancer drugs is on the rise, prompting the utilization of natural items to mitigate these symptoms. This experiment utilized the constituents of Alangium salviifolium. Plants contain alkaloids such as beta-carboline harmaline and deoxytubulosine, which has anticancer properties. The alkaloids' anticancer characteristics were analyzed using CADD, a computational design technique. The NPACT database was used to analyze the anticancer properties of the compounds, and the Auto Dock program was employed to do a binding affinity analysis with six different receptors. The outcomes were exhibited in Discovery Studio. The commonly employed pharmaceutical Paclitaxel was utilized to evaluate these results. The addition of zinc oxide to the compounds was made in order to enhance the advantages. The PyRx software was utilized to manipulate the findings of the molecular docking investigation, which were subsequently displayed in Discovery Studio. In order to conduct a pharmacokinetics study using the pkCSM database, it is necessary to validate the beta-carboline harmaline in vitro.

Keywords: Molecular docking, cancer, colon cancer, *Alangium salviifolium*, bioinformatics.

Introduction

Computer-aided drug design, or CADD, is a crucial technology for developing cost-effective medicines and reducing the reliance on animal testing for each potential treatment [1]. It assists in the development of new and safe drug candidates, as well as in the repositioning of existing drugs in the market [2]. Cancer, a very lethal disease, presents a significant threat to public health in both developed and developing countries. It is one of the primary global causes of death [3]. Cancer is a group of illnesses characterized by the uncontrolled proliferation of abnormal cells that infiltrate and harm neighboring organs [4]. Based on the 2008 statistics provided by the International Agency for Cancer Research, there are around 12 million new cases of cancer reported every year, with 7 million deaths occurring within 5 years of diagnosis [5]. Additionally, there are nearly 25 million individuals currently living with cancer. By 2030, it is projected that there will be a total of 26 million newly diagnosed cases of cancer and 17 million deaths caused by the disease [6]. Remedies present in various traditional medical systems, such as Ayurveda, Siddha, and Unani [7]. The tea is originally sourced from China, the Philippines, Ceylon, and South India. The alternate leaves of A. salvifolium are usually asymmetrical, with dimensions ranging from 12.5 to 17 cm in length and 2.5 to 7.0 cm in width [8]. Their shape is oblong-lanceolate or oblongoval, with bases that are rounded or acute, and end that are more or less acuminate and obtuse at the tip [9]. The leaves display three to six pairs of prominently located, extremely slanted veins on their undersides, and produce fragrant white or yellowish-white flowers [10].

A. salvifolium preparations contain a variety of compounds including phenolic chemicals, alkaloids, flavonoids, amino acids, carbohydrates, volatile oil, glycosides, and phenolic glycosides [11]. The popularity of herbal medicine is increasing, and research has demonstrated its efficacy in treating several diseases, including cancer [12]. As stated by

Prathima Shashi Kumara et al., cancer refers to a collection of diseases where cells develop uncontrollably and harm nearby cells. Colorectal cancer (CRC) is also referred to as colon or bowel cancer [13]. According to K. Van Der Jeught et al., colon cancer is the third most common disease that impacts both males and females [14]. At present, 60% of cancer treatments are obtained from over-the-counter medications, with plants being a significant reservoir of these substances [15].

E. Solowey et al. assert that the compounds employed in the therapy of cancer encompass vinca alkaloids, Taxus diterpenes, Camptotheca alkaloids, and Podophyllum ligands. P. Aiello et al. establish that the plant-derived medication's action, which entails triggering apoptosis, is very universally applicable [16]. Alangium salviifolium, as stated by S. Shravya et al., is a highly utilized medicinal plant in India and has a broad distribution across Southeast Asia [17]. Furthermore, the plant can be found in tropical regions of Madagascar, Australia, Southern and Eastern Asia, the islands of the Africa, New Pacific Sea, and New Caledonia. M. Ratra et al. provide an extensive list of the plant's medicinal benefits, including anticancer activity demonstrated by P. Bama, the presence of alkaloids Deoxytubulosine and Beta-carboline harmaline, antiarthritic, antihelmintic, antioxidant, antimicrobial, antifertility, analgesic, mitigating, diuretic, antiepileptic, antifungal, and hepatoprotective actions [18]. The research conducted by A. Mondal et al. reveals that the alkaloids belong to the β-carboline-benzo quinolizidine alkaloid family [19]. These alkaloids work by inhibiting the activity of DNA topoisomerases and disrupting DNA synthesis [20].

Material and Methods:

The conventional medication and its bioactive constituents were acquired from DrugBank and the PubChem database. The NPACT database has been used to predict the anticancer properties of active compounds derived from plants. The target molecule for numerous target molecules was obtained using the RCSB Protein Data Bank (PDB), based on the parameters of the test and standard medications [21-23].

Prediction of binding sites of a target molecule

The region where ligands interact to the target molecule in a biological reaction is referred to as the binding site [24]. The CASTp (Computed Atlas of Surface Topography of Proteins) database was utilized to predict the location of the binding site in a target molecule [25, 26].

Binding activity study of the target molecule and active constituents

A molecular docking study was conducted using AutoDock 4 software (MGL tools) to construct binding models for the target molecule and the active components of the plant, as well as the control medicine Paclitaxel [27]. The study aimed to determine the binding affinity and RMSD value [28-35].

Results and Discussion:

Retrieval of the active constituents and the standard drug

According to S. Kim et al., PubChem serves as a searchable database for chemical compounds and the biological activities that go along with them. As such, it was utilized for the bioactive compound and reference medicine extraction. The active components in the study were beta-carboline harmaline and deoxytubulosine. The drug considered as the gold standard for this study was paclitaxel. Using the canonical technique, the Smiles and structure were retrieved from PubChem. S. Bundela et al. found potential compounds for the treatment of oral cancer by utilizing PubChem. According to D. Wishart et al., DrugBank is an online database that provides experimentally generated information about drugs that are sold. The usual medicine used in this trial was paclitaxel. For the treatment of colorectal cancer (CRC), paclitaxel is used. The Pacific Yew tree's bark is a source of the mitotic inhibitor paclitaxel. There are fungi on this tree that yield paclitaxel.

Anticancer properties prediction of the compounds

In this study, the researchers employed the NPACT tool, as outlined by M. Manga et al., to produce predictions. The EC50 value of deoxytubulosine, as determined by NPACT, is 0.05µg/mL. When administered under these circumstances, a concentration of 0.05µg/mL of deoxytubulosine will result in a 50% response. The beta-carboline harmaline has a half-life of 34±12µM, as measured by its IC50 value. In comparison, the standard medicine Paclitaxel has a half-life greater than 10µg/ml. The IC50, or inhibitory concentration 50, refers to the concentration of a substance required to halt a specific biological or metabolic activity. Paclitaxel, a drug with an IC50 value of 34±12µM, exhibits the ability to inhibit cancer progression by fifty percent. Similarly, the administration of beta-carboline harmaline with an IC50 value greater than 10µg/ml will inhibit the biological activity of the cancer-progression-causing cell.

Retrieval of the target molecule

The target molecules are the receptors in the cells that the ligand binds to and triggers the signaling cascade. The target molecule in this experiment was the protein implicated in the disease progression and susceptible to being targeted by medicine for therapeutic purposes. The desired molecule was obtained by utilizing the PDB database. The utilized target

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molecules include the estrogen receptor (1YYE), IGFR (PDB ID: 5FXR), TGF (PDB ID: 1TGJ), and EGFR (PDB ID: 3VJO). Figure 1 illustrates the three-dimensional configuration of the molecules that were obtained.

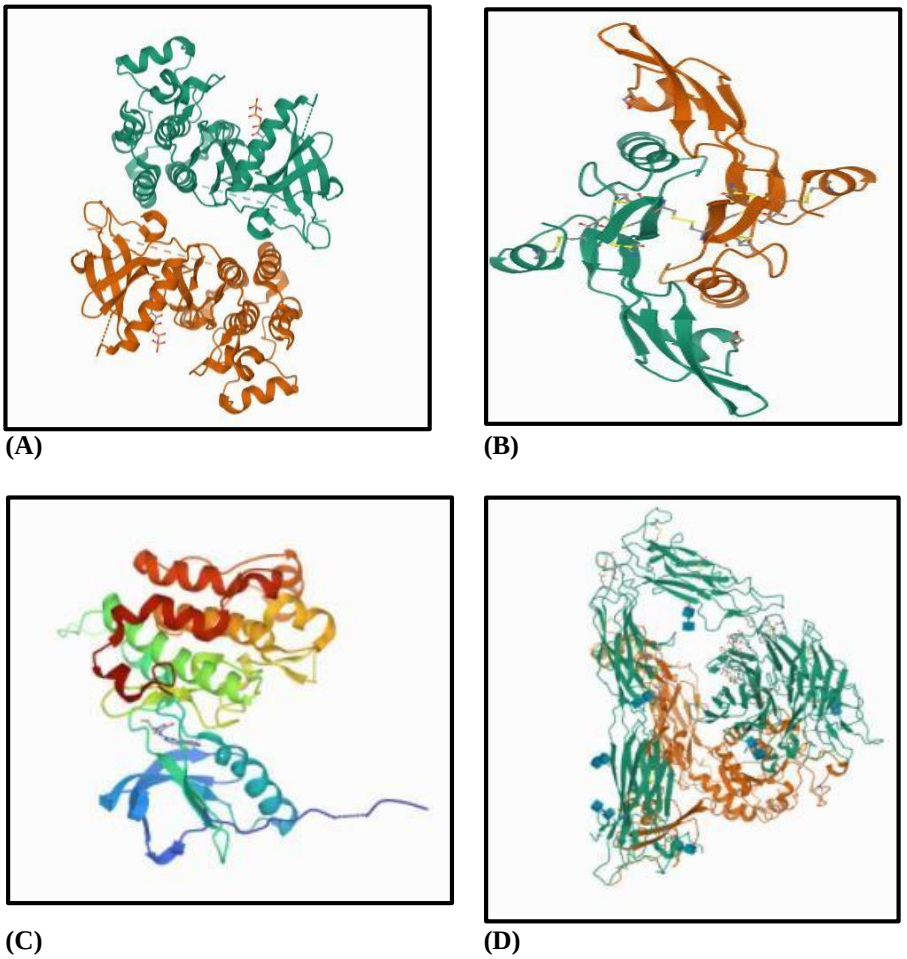
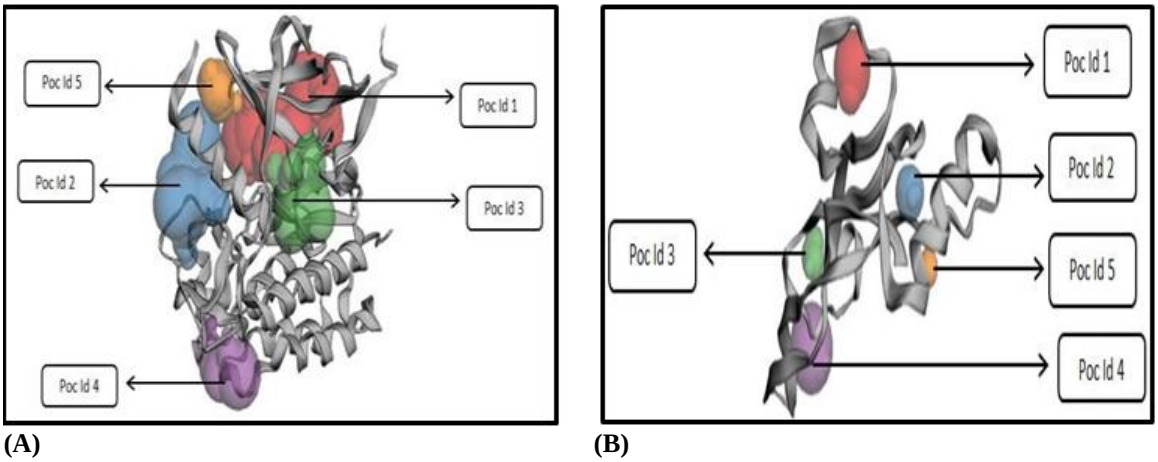


Figure 1: Structure of the target molecule. [(A) EFGR, (B) TGF, (C) IFGR, (D) Estrogen receptor]

Prediction of binding sites of the target molecule

The specific region on the protein where the ligand attaches during the biological reaction is referred to as the binding site. A protein that possesses several binding sites is involved in the biological reaction. The CASTp service was utilized to predict the binding site within a protein. Five binding sites were chosen from a vast pool of options. In 85% of situations, the larger binding site, which has a greater size and volume, is responsible for interacting with the ligand. Figure 2 displays the specific locations where the target molecules bind.



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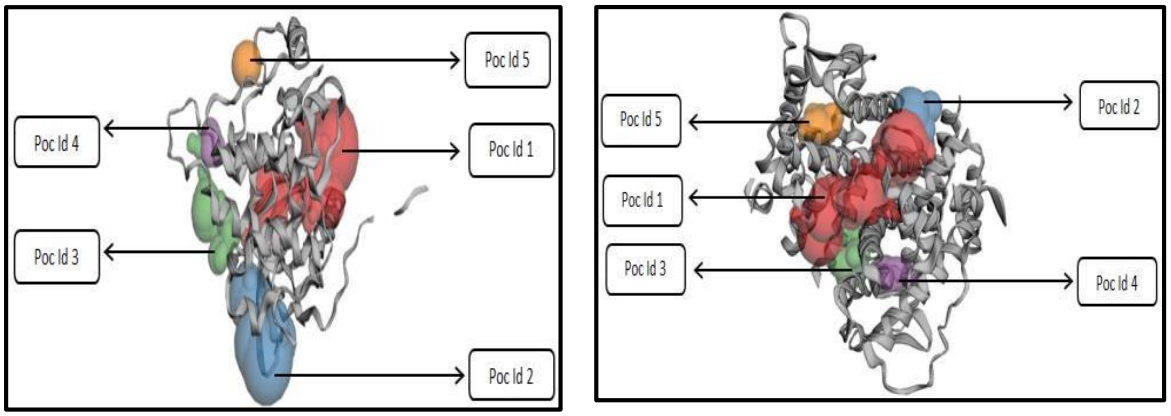


(C) **(D)**

Figure 2: Binding site of target molecule [(A) EGFR, (B) TGF, (C) IGFR, (D) Estrogen receptor]

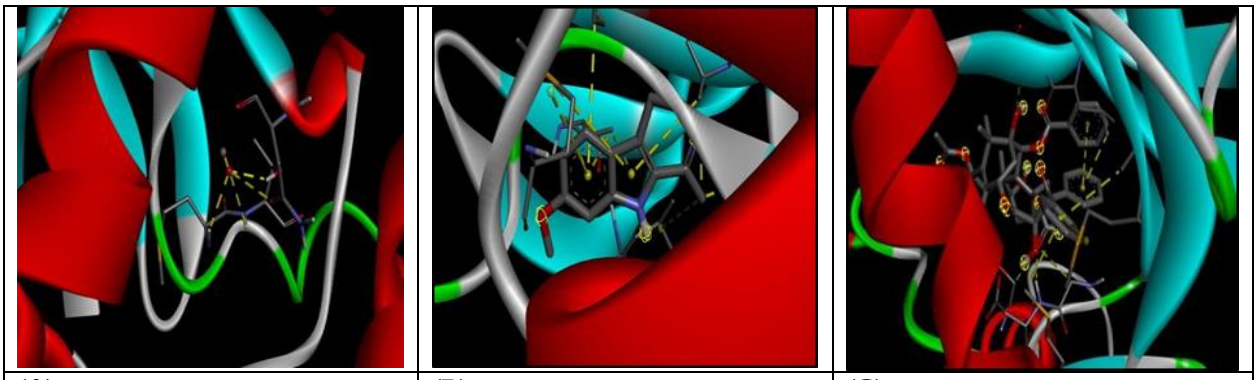
Binding affinity study of target molecule and ligand

Binding affinity refers to the strength of the reversible interaction between the ligand and target molecules. The binding affinity of a ligand is used to determine the level of accuracy with which it is linked to its target molecule. Molecular docking is employed to determine the binding affinity between the ligand and target molecule. Molecular docking is a technique used to predict the compatibility between a target molecule and a ligand molecule. Docking is a computational method commonly employed to predict the interactions between a protein and smaller molecules in molecular modeling. Hence, many molecular docking techniques are employed to forecast the binding affinity. The AutoDock tool is utilized to conduct molecular docking in this study. Table 1 provides an account of the receptor's binding affinity with the ligand molecule.

Table 1: Binding affinity of the target molecule with ligand

Sr. No	Name of the target molecule	Deoxytubulosine (kcal/mol)	Beta-carboline harmaline (kcal/mol)	Paclitaxel (kcal/mol)
1	EGFR	-1.7	-9.1	-5.9
2	TGF	-1.6	-6.6	-5.8
3	IGFR	-1.9	-6.9	-7.9
4	Estrogen receptor	-1.6	-5.9	-6.5

The table 1 clearly demonstrates a notable disparity in the binding affinities of the medicines Paclitaxel and Deoxytubulosine. Nevertheless, the affinity between beta-carboline harmaline and the medicine Paclitaxel differed. Going forward, the compound beta-carboline harmaline can serve as a primary molecule for the development of a drug that can be used to treat colorectal cancer (CRC). Table 1 shows that beta-carboline harmaline (-9.1 kcal/mol), paclitaxel (-7.9 kcal/mol), and deoxytubulosine (-1.9 kcal/mol) have the highest binding affinity with the IGFR among the ligand compounds. Therefore, the decision was made to utilize the IGFR receptor further. Figure 3 illustrates the process of ligand binding to the IGFR receptor.



(A) **(B)** **(C)**

Figure 3: Binding between IGFR and the compounds (A. IGFR with deoxytubulosine; B. IGFR with Beta-carboline harmaline; C. IGFR with Paclitaxel)

Conclusion

Specific phytochemicals possess anti-cancer properties, and a subset of these compounds are now being utilized. This experiment utilized alkaloids derived from the plant A. salviifolium, which are believed to possess anticancer properties. The alkaloids deoxytubulosine and beta-carboline harmaline are present. By utilizing the NPACT database, the compounds were assessed for their anticancer potential. In comparison to the common medication Paclitaxel, it is expected that the compound Beta-carboline harmaline will demonstrate more efficacy than Deoxytubulosine. Following that, a study was performed to assess the strength of binding between various substances and the IGFR receptor. The results showed that beta-carboline harmaline (-9.1 kcal/mol) had a higher level of binding activity compared to deoxytubulosine (-1.9 kcal/mol) and paclitaxel (-7.9 kcal/mol). It can be inferred that harmaline, a beta-carboline compound, which has lesser toxicity and fewer potential bad effects, can be utilized for in vitro drug testing in the future.

Declarations:

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

All the authors approved the manuscript for publication.

Availability of data and material:

All required data is available.

Competing interests:

All authors declare no competing interests.

Funding:

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