IDENTIFYING THE HIT MOLECULES AS MULTI-TARGETED INHIBITORS OF COMMON CANCER RECEPTORS FROM A LIBRARY OF PHYTOCHEMICALS

A thesis submitted toward partial fulfilment of the requirements for the degree of

Master of Engineering in Biomedical Engineering

Jadavpur University

Submitted by

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CERTIFICATE OF RECOMMENDATION

We hereby recommend that the thesis entitled ***IDENTIFYING THE HIT MOLECULES AS MULTI-TARGETED INHIBITORS OF COMMON CANCER RECEPTORS FROM A LIBRARY OF PHYTOCHEMICALS*** carried out under my supervision by **Avik Majumdar** may be accepted in partial fulfilment of the requirement for awarding the Degree of Master in Biomedical Engineering of Jadavpur University. The project, in our opinion, is worthy for its acceptance.

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Certificate of Approval

The forgoing thesis is hereby approved as a creditable study of an engineering subject carriedout and presented in a manner satisfactory to warrant its acceptance as a prerequisite to the degree for which it has been submitted. It is understood that by this approval the undersigned do not necessarily endorse or approve any statement made, opinion expressed or conclusion drawn therein but approve the thesis only for the purpose for which it is submitted.

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I, ***Avik Majumdar*** *, Class* Roll Number – ***002130201003*** , Examination Roll Number - ***M4BMD23003*** , hereby declare that this M.E thesis entitled ***'IDENTIFYING THE HIT MOLECULES AS MULTI-TARGETED INHIBITORS OF COMMON CANCER RECEPTORS FROM A LIBRARY OF PHYTOCHEMICALS'*** presents my original work in Jadavpur university, Kolkata as a postgraduate student of Jadavpur University, Kolkata, and to the best of my knowledge contains no material previously published or writtenby another person, nor any material presented by me for the award of any degree or diploma of Jadavpur University, Kolkata, or any other institution. Any contribution made to this research by others, with whom I have worked at Jadavpur University, or elsewhere, is explicitly acknowledged in the thesis. Works of other authors cited in this dissertation have been duly acknowledged under the section "References".I am fully aware that in case of any non-compliance detected in future, the Senate of JadavpurUniversity, Kolkata may withdraw the degree awarded to me on the basis of the present thesis.

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AVIK MAJUMDAR

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ABSTRACT

Understanding how ligands will attach to receptors is crucial for both molecular biology and medication development. Due to its ability to anticipate ligand-receptor interactions precisely, this approach necessitates the use of the computational method known as molecular docking. In order to evaluate several phytochemicals as prospective anti-cancer medications and take into account their potential applications, this thesis will look at them. A new comparative investigation reveals that just 3.4% of cancer treatments are effective, compared to a success rate of 20.9% for all oncology medications. Although there were numerous anti-cancer medications available at the time, the basic issue is that they are less effective than other oncology drugs, which have a success rate of 20.9%. In addition, not all cancer drugs that pass Phase III trials necessarily offer a therapeutic benefit to a wider population. The immune system is also stimulated by such treatments, which has a number of negative consequences including anemia, diarrhea, appetite loss etc. To find more potent anti-cancer drugs, further investigation is being done. These phytochemicals are produced by a wide variety of plants and have beneficial medicinal properties. These plants are mentioned in Ayurveda as well. The names of several medicinal plants may also be found in Indian Medicinal Plants, Phytochemistry and Therapeutics. There are 4010 Indian medicinal plants, 17967 phytochemicals, and 1095 therapeutic uses present in the IMPPAT database. Our objective was to find phytochemicals that may combat cancer more successfully and with fewer side effects. To achieve this, molecular docking is a great method for examining the bonds between protein and phytochemicals. The most well-liked and useful tool for molecular docking is AutoDock Vina. SwissADME is a tool that allows us to assess the ligand's ADMET qualities, such as its solubility, BB penetration, and GI absorption level, as well as whether the ligand (in this example, a phytochemical) violates Lipinski's rule of five for the possibility that a molecule is a medication.

Keywords: cancer, phytochemical, ADMET, multi-target, molecular docking, VEGFR1, VEGFR2, EGFR

CHAPTER 1:

INTRODUCTION

1.1 BACKGROUND:

Finding the disease's causes would help researchers create plans for early detection, precise diagnosis, efficient treatment, and ultimately eradication. The government provides the majority of funding for cancer research that is conducted in academic, research, and commercial contexts.

History: The father of contemporary chemotherapy is considered as Sidney Farber. For millennia, scientists have been studying cancer. Early studies centred on cancer's causes (Wong C.H. et al., 2019). In 1775, Percivall Pott discovered the first environmental cause of cancer, chimney soot, and in 1950, lung cancer was linked to smoking cigarettes. Early cancer therapies concentrated on honing surgical methods for tumor removal. In the 1900s, radiation therapy gained popularity. The 20th century saw the development and improvement of chemotherapy. According to Hay, M., et al. (2014), the United States proclaimed a "War on Cancer" in the 1970s and expanded funding and support for cancer research. The Hallmarks of Cancer by Douglas Hanahan and Robert Weinberg, published in 2000, and Hallmarks of Cancer: The Next Generation, released in 2011, are two of the most cited and significant research studies. Over 30,000 academic papers have cited these articles collectively.

1.2 RESEARCH OBJECTIVES:

Human body is made of organs and tissues. Organs and Tissues are made of Cells. Old cell dies and new cell take place of that new cell as a natural process. When there is any disturbance in this natural order like virus, cell mutation, carcinogenic chemical etc, the old cell may develop cancerous property i.e, it does not die and starts to divide uncontrollably and diverts the nutrients of the body to itself for its own growth like a parasite or a separate organism. Our cells have several mechanisms for cell death like Apoptosis and Pyroptosis. Due to previous mentioned reasons this process may be hampered and Cancer starts to develop. This thesis intends to identify and assess phytochemicals with Anti-Cancer characteristics using computational methods, particularly molecular docking. Anti-Cancer characteristic may be defined as inhibition of cancer growth, death of existing cancer cell. The main goal is to find the potential ligands which can alter target proteins involved in cancer growth, in the process of uncontrolled cell division. The study also aims to evaluate the therapeutic potential of the identified phytochemicals and clarify the molecular mechanisms underlying their Anti-Cancer effects.

The following research questions are addressed in the thesis:

- Which phytochemicals have the maximum binding affinity and have the greatest potential in Cancer Treatments?
- What are the main molecular interactions and processes through which these phytochemicals influence the pathways leading to Cancer?

1.3 RESEARCH ISSUES:

Manual work of finding random phytochemicals, finding its 3-D structure in SDF format, Converting it to (.pdb), Modifying it to (.pdbqt) format and then individually docking with each protein is very much time consuming and succession is also dependent on the processor of PC. Added to it, simulation cannot be done in normal PC, because it may take week to month. That's why high power Super Computer is needed simulation, which is not accessible to everyone.

CHAPTER 2:

LITERATURE REVIEW

As part of the drug discovery process, a particular chemical molecule with the required biological activity on the target can be picked. This platform employs many techniques to investigate compounds and targets from various perspectives. As medication development and discovery are both labor- and resource-intensive procedures, so they provide a number of challenges for researchers working on varied illnesses including different forms of cancer. As a result, the use of new technologies may help finding new-age drugs which have excellent therapeutic potential. This would be a huge development in the treatment of disease. Compound screening assays, that can help with grand discovery, verification, creating prospects, procedure improvements are covered. One of the approaches for that are Evaluation of the effects of the compounds on the therapeutic objective. As a result of technology improvements and the fusion of computational methods with biological and pharmacological investigations, methods like virtual screening are routinely utilized in drug developing and discovery.

2.1 MECHANISMS OF CANCER:

Years of research have shown that improving patient outcomes requires a thorough understanding of the fundamental mechanics of cancer, including how it develops, why it persists, and how it spreads throughout the body. Patients will benefit from new fields of fundamental cancer research that examine the differences between individual cells with tumors, the effects of the environment on tumor growth, and the effectiveness of an individual's immune system in mounting a defense. Currently, cancer researchers are using novel methods, technologies, and instruments to increase their understanding of the mechanisms behind cancer. Researchers are looking into minute differences that affect the behavior of cancer cells, not just between individuals or cancer kinds but also within the various cell types that make up a single tumor. At the same time, scientists are shifting their attention from tumors to other parts of the body to understand how those elements affect a patient's sickness. Studies of cancer biology have until now mostly concentrated on how tumor cells vary from healthy cells. But it is now obvious that different tumor cells can exist even within a single tumor. The ability to divide and support the tumor's growth may only be present in a tiny subset of a tumor's cells. Given that this diversity has significant clinical repercussions, it will be crucial to comprehend human cancer on a cell-by-cell basis, we now know. Researchers can now analyze the DNA, RNA, and proteins of thousands of individual cells using recently developed high-throughput technologies to describe this heterogeneity and learn how it impacts tumor growth, metastasis, and patients' responses to treatment. It is

now clear that a tumor's ability to grow is influenced by factors other than the characteristics of its own cells. Equally important are the milieu in which a tumor develops and the ferocity with which the body's immune system detects and combats malignancies. Understanding the connections between tumors and their microenvironments is a difficult task. At some point, we will need to understand the signals that tumors transmit to adjacent immune cells and identify the environmental factors that influence whether a tumor remains small and benign or spreads rapidly. **Figure-1** illustrates that under a microscope how a malignant tissue uses the circulatory system of its host to grow. Three enzymes or proteins are the key growth factors in the human body's cancer-causing mechanism. These are listed below:

1. **VEGFR1 (PDB CID: 3HNG)**
2. **VEGFR2 (PDB CID: 3VHE)**
3. **EGFR (PDB CID: 1M17)**

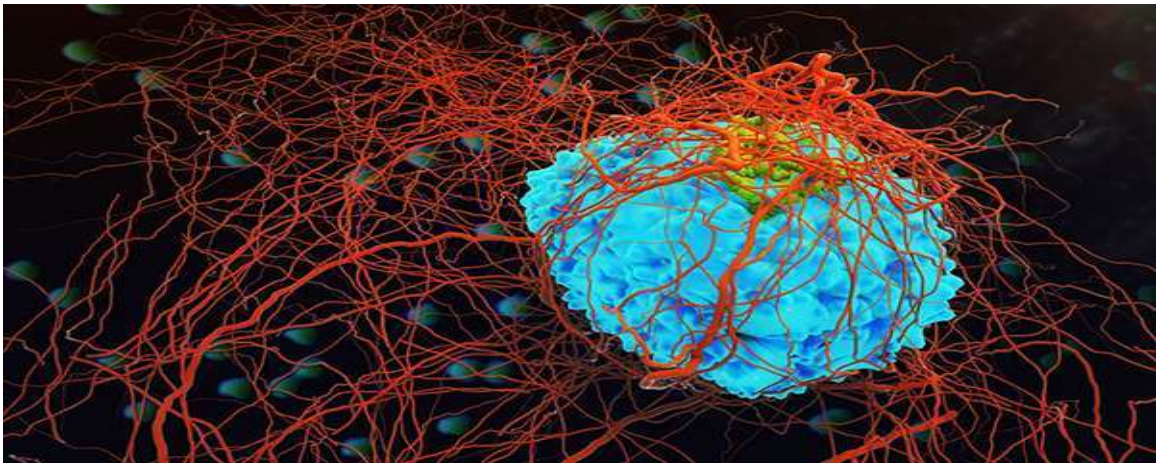


Figure-1: Cancerous Tissue

It makes sense that targeted medicines would be developed to hinder certain molecular functions that are essential for the survival, development, or growth of malignancies. A variety of targeted drugs with anti-tumor action provide objective responses like delay the progression of illness, prolong patient survival with advanced malignancies in human cancer cell lines and xenograft models. VEGF, HER2, and EGFR are validated targets for cancer therapy based on preclinical and clinical evidence and they continue to be the focus of intense research. EGFR and HER2 are known to be targets on cancer cells, but VEGF is a target that works in the tumor microenvironment. While other research examines if various strategies for blocking certain targets will be more advantageous, clinical research focuses on the best ways to incorporate targeted therapy into current treatment programs.The outcomes of targeted medicines to date are encouraging, but they also highlight the need for more preclinical and clinical research.

The primary source of new blood vessel creation brought on by malignancies is microvascular endothelial cells (EC) of the host organ, and the microvasculature of the liver and lung are quite different. VEGF is thought to stimulate tumor angiogenesis, and it is thought that the VEGFR-2 plays a significant part in this process. In this study, although the VEGFR-1 had no effect, the VEGFR-2 dramatically decreased the development of lung metastases of RenCa renal cell carcinoma by 26%. VEGFR-2 neutralization had little effect on RenCa liver metastases, despite VEGFR- reduced liver metastases by 31%. Both VEGFR-1 and VEGFR-2 inhibition was required to prevent the formation of CT26 colon cancer liver metastases. Instead of preventing the growth of micrometastases, inhibition of VEGFR-1 or VEGFR-2 decreased tumor burden by lowering vascularization and proliferation of micrometastases by 55% and 43%, respectively. VEGF enhanced the phosphorylation of VEGFR-1 and VEGFR-2 in ECs from the liver and lungs, respectively. For lung EC and liver EC, inhibiting VEGFR-2 and VEGFR-1 more successfully decreased EC migration, proliferation, and capillary tube formation in vitro. Overall, our results demonstrate that, due to the distinct VEGFR activity patterns of liver EC and lung EC, liver metastases are more dependent on VEGFR-1 than lung metastases to promote angiogenesis. As a result, the targeted metastatic disease regions should be considered while developing medications that block certain VEGFRs.

2.2 ANTI-CANCER CHEMICALS:

While cultures in Asia and Africa have used medicinal plants for thousands of years in traditional medicines. Developed nations uses the therapeutic benefits of compounds obtained from natural sources, some nations remain primarily rely on therapies that are plant-based.

a. Polyphenols: The polyphenolic compounds are all known to have anticancer effects. Red wine, grapes, and peanuts are a few examples of foods that contain resveratrol. Gallacatechins are found in green tea. Because polyphenols are natural antioxidants, it is thought that include them in one's diet can improve one's health and reduce the chance of developing cancer.

b. Flavonoids: Flavonoids are a diverse family of plant secondary metabolites and a subclass of polyphenolic compounds, with 10,000 known structural variants. They are plant chemicals with physiological activity that are receiving a lot of scientific attention for their possible health benefits.

c. Brassinosteroids: Brassinosteroids (BRs) are naturally occurring compounds found in plants that serve a number of purposes, such as controlling hormone communication to

control cell development and differentiation, lengthening stem and root cells. BRs are also used to manage the senescence of plants. They are essential for the growth and development of plants. Another chemical with therapeutic potential in the battle against cancer is BRs.

d. Plant-based cancer treatment options Plant-based medications are utilized to treat cancer because they are secure and convenient. They are simple to give the patient orally as part of their diet. Due to the fact that they are naturally occurring compounds derived from plants, they are frequently more tolerable and non-toxic to healthy human cells. A few taxanes, lectins, saponins, lignans, and cyanogenetic glycosides are exceptions to this rule, though. Methytransferase inhibitors, antioxidants that prevent DNA damage, histone deacetylases (HDAC) inhibitors, and mitotic disruptors are the four classes into which plant-derived drugs may be divided depending on their activity. As a control medicine for our thesis, we employed already-approved anti-cancer medications Trastuzumab Deruxtecan, Ribociclib, Sunitinib, and Ibrutinib.

2.3 TECHNIQUES FOR MOLECULAR DOCKING:

A popular computer method for analyzing and predicting the interactions between ligands (phytochemicals) and target proteins is molecular docking. Docking techniques make use of scoring functions to determine the binding affinity and find optimal binding conformations. The docking program attempts to compute binding energy at various locations while doing many docking runs, just like for the same protein and ligand. The position and binding energy of that maximal pass are taken as the major data among all the findings.The popular molecular docking programs AutoDock and Vina offer a selection of search strategies and scoring choices. These techniques provide valuable data on ligand-receptor interactions and have been beneficial in lead optimization and virtual screening.

The goal of virtual screening in this case is to use mathematical calculations to examine and choose a few chemicals from vast list micro-molecules. One virtual screening technique utilized in structure-based (SBVS), which tries to simulate and assess the functional bond configuration between a micro-molecule and a macro-molecule is the molecular docking method. The most efficient and stable state of the ligand-receptor complex may be predicted using the most advanced computational drug design technique, molecular docking. The major objective of the entire process is to comprehend the three-dimensional structures of the target and ligand molecules. As a consequence, several methods may be used to determine the molecular structure of substances as well as to develop supporting tools for the development of medications. Molecular docking has two crucial elements of docking programs, searching algorithms and scoring functions. A method that might lead to the examination of the well-liked and effective is searching algorithms.

2.4 BENEFITS OF MOLECULAR DOCKING IN RESEARCH ON CANCER:

For investigations on anti-cancer agents, molecular docking provides a number of advantages, including the ability to search through enormous chemical databases in search of potential anti-cancer compounds. The computational approach is useful for both the investigation of structure-activity correlations and the rational creation of anti-cancer medicines.

The Organization (2020) and Vineis and Wild (2014) both rank cancer among the most dangerous and prevalent causes of death worldwide. On December 14, 2020, there were 19.3 million new instances of the illness and 10.3 million fatalities attributable to cancer, according to the most recent. Given the fast improvement of oncology research and the development of innovative biotechnology techniques, knowing many elements of cancer progression can lead to better cancer prognoses and treatment alternatives (Goyal et al., 2006; Charmsaz et al., 2018; Pucci et al., 2019). As a result, a full understanding of tumor heterogeneity can aid in the development of new cancer treatments and provide a complete picture of the progression of cancer (Cajal et al., 2020). Tumor heterogeneity, as defined by Prager et al. (2019), is a condition in which tumor cells differ in a range of biological traits, such as function, differentiation, carcinogenesis, and sensitivity to anti-cancer therapy. Furthermore, heterogeneous groupings of tumor cells may contain comparable or dissimilar genetic contents depending on the degree of heterogeneity (Prager et al., 2019). In addition, a variety of factors, including genetics, epigenetics, and several microenvironmental traits, can contribute to it (Wang et al., 2015). In fact, a subpopulation of cancerous tumor cells called CSCs display their stemness traits similarly to normal stem cells. For instance, they may self-renew to produce daughter cells that are exactly like them and can differentiate into several cell lineages that lead to tumors. The quiescence state may potentially contribute to the growth of cancer and the emergence of resistance to therapy. This is one trait (Hung et al., 2019; Lee et al., 2020) that separates malignant stem cells from healthy stem cells. Because they are resistant to chemotherapy and radiation therapy, CSCs can make the healing process even more difficult. The expression of multidrug resistance proteins (MRPs), different signaling pathways, efficient DNA damage resistance mechanisms, and the epithelial-to-mesenchymal transition (EMT) procedure are a few of the components and mechanisms that may be in charge of the aforementioned therapeutic resistance (Phi et al., 2018). According to several cellular and molecular level studies, CSCs exhibit multiple metabolic activities (Chae and Kim, 2018; Yadav et al., 2020). For the purpose of identifying CSC behaviors and creating specialized therapeutic strategies for various cancer types, the science of metabolomics as well as an understanding of changes related to metabolic

processes may be helpful (Gilany et al., 2018; Rahim et al., 2018; Arjmand, 2019a, 2019b; Goodarzi et al., 2019; Larijani et al., 2019; Tayanloo-Beik et al., 2020). The development of tailored therapy modalities for various cancer types may benefit from an understanding of metabolic process alterations in addition to CSC activity (Cuyàs et al., 2017). Scientists have also been compelled to employ customized methods for treating cancer as a result of problems with CSCs resistance to treatment strategies. Docking is essential in the creation of novel medications and pharmaceutical research. This mathematical algorithm-based strategy for computer-assisted drug design enables the assessment of the real biological binding arrangement between the ligand and the target protein. In fact, the molecular structure serves as the basis for the aforementioned medication designing since it allows for the modeling and prediction of molecular interactions as well as the evaluation of biochemical processes (Meng et al., 2011; Phillips et al., 2018).

2.5 MOLECULAR DOCKING:

The bonding energy of a ligand interacting with a macromolecule is predicted through molecular docking. Additionally, it forecasts which side of the macromolecule the ligand will bind to. With the exception of a solid commitment or bond, information can be mounted in any direction of rotation. By affinity, two molecules connect to one another. The human body relies heavily on molecules including proteins, peptides, nucleic acids, carbohydrates, and lipids for signal transmission. In addition, the couples' relative orientations when engaging the kind of signal that forms may be impacted. Since docking may alter a molecule's workflow and serve as a medicine, it aids in the prediction of potency to target certain macromolecules **Figure-2**.

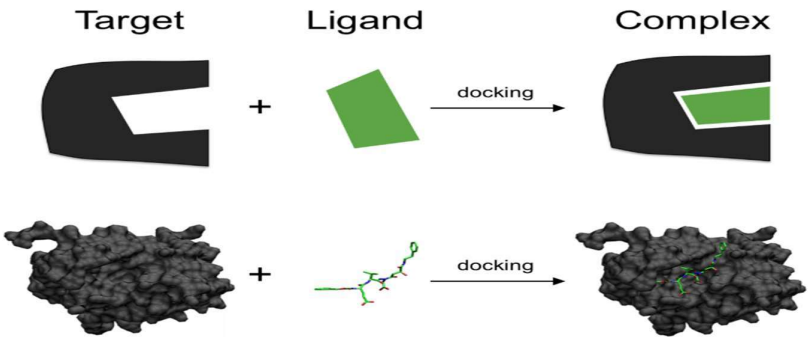


Figure-2: Molecular Docking

2.6 MECHANISM OF DOCKING WITH ITS IMPORTANCE:

Through the use of molecular binding methods, the atomic level interactions between minute substances and proteins may be modeled. This explains how tiny molecules behave at the binding site. The joining process comprises just two basic steps. determining the ligand's shape, placement, and orientation inside these sites (commonly referred to as postpositions), as well as the binding affinity. These two acts have to deal with sampling methods and scoring systems. Knowing the location of the binding point before docking greatly improves the efficiency of docking. When the ligand binds, the binding site is typically already known. Comparing the target protein to a protein that crystallizes with a protein family or another ligand with a related function can also reveal information about the location.

THEORY OF DOCKING: The goal of molecular docking is to predict the structure of the ligand receptor complex using computational techniques. Two interconnected phases can complete the docking process. Next, rank these conformations according to a scoring system.

IMPORTANCE OF MOLECULAR DOCKING: 1. Predicting the binding affinity (scoring function) 2. Identifying the ligands in binding sites. 3. Designing of drugs rationally

RECEPTOR SELECTION AND PREPRATIONS: First we have to identify macromolecule responsible for some disease or the important macromolecule for the workflow of the disease. In case of cancer, we observe that VEGFR1, VEGFR2 and EGFR are being expressed more than normal.

BULIDING THE RECEPTORS: It is recommended to get the 3-D receptor structures in (.pdb) file format from the RCSB official website. Processing of the uncleaned(Ligand/Water Molecule may be present) structures is required. The receptors ought to be stable and biologically active.

ASSESSMENT OF THE ACTIVE SITE: It is important to locate the receptors' active location. Although the receptors may have several active sites, the active site will be the one with the highest amount of binding energy.

SELECTION OF LIGAND: It may be obtained from a number of databases, including PubChem, etc. Following docking of the ligands onto the receptors, interactions are evaluated. The scoring algorithm then determines the scores based on which ligand is the best match.

THE USE OF AUTODOCK: A quick gradient-optimized conformational tool and a

straightforward scoring function constitute the foundation of the computer-assisted docking application AutoDock Vina. Drug-like ligands can be efficiently and quickly docked to proteins. This docking software for molecules is available for free. Its initial conception and execution took place at the Molecular Graphics Lab. The following are the justifications given by AutoDock Vina for docking:

1. Accuracy: AutoDock Vina significantly improves the typical accuracy of the result predictions.
2. 2. Easy to use: All that's needed is that the structures of the molecules being docked and the specification of the search area including the binding site.

2.7 DIFFERENT TYPES OF DOCKING:

RIGID DOCKING: The internal geometry of both the ligands and receptors are treated as rigid. These are also known as lock and key.

FLEXIBLE DOCKING: Generally, smaller molecules are counted as they rotate, and after each revolution, energy is computed to determine the best position. Protein-ligand, protein-protein, and protein-nucleotide interactions may all be docked. There are several troops operating at the moment.

Both type of docking shown in **Figure-3.**

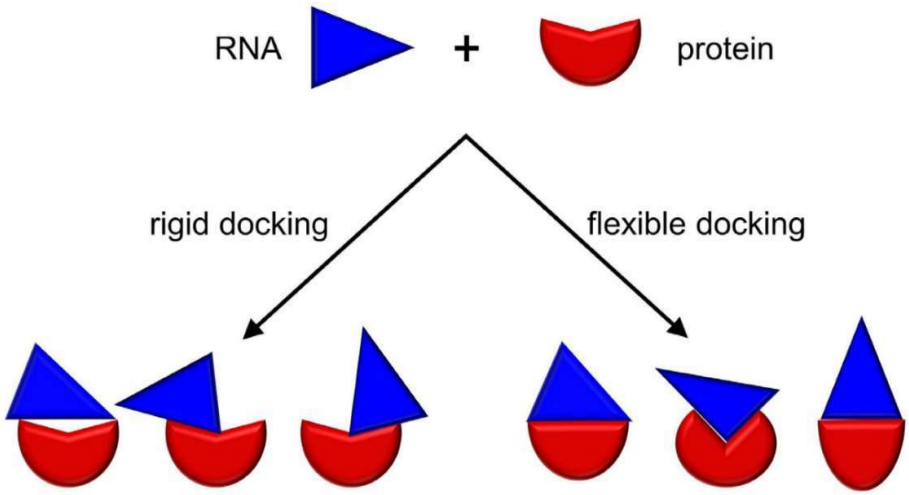


Figure-3: Rigid and flexible docking

CHAPTER 3:

METHODOLOGY

Flowchart of Molecular Docking process shown in **Figure-4** (Ahmad F Eweas, 2014).

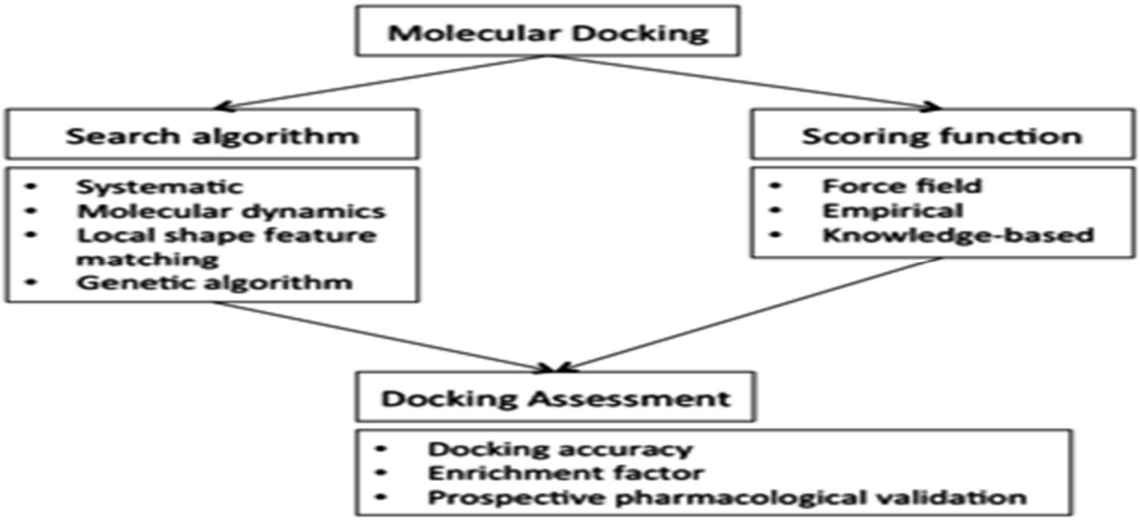


Figure-4: Flowchart of Molecular Docking

3.1 PHYTOCHEMICAL DATABASE SELECTION:

A broad and varied database of phytochemicals is necessary to undertake the screening of Anti-Cancer phytochemicals. Compounds are selected randomly from IMPPAT and the availability of structural data are among the selection criteria for the phytochemical database. For gathering the required molecules, well-known databases like PubChem phytochemical databases might be an invaluable resource. In PubChem we can also find canonical smiles for individual compound.

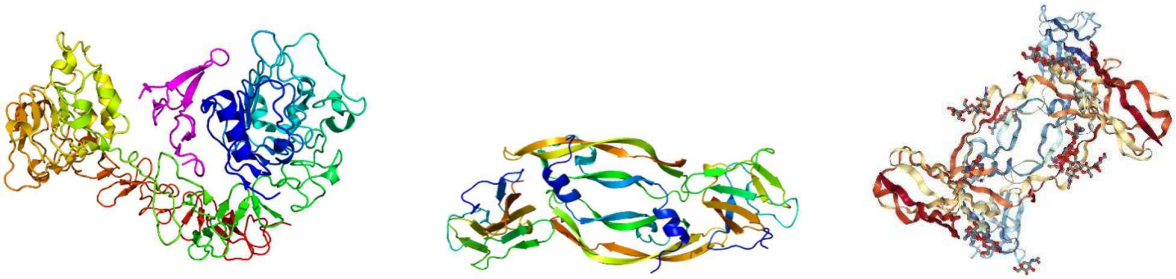
ADMET properties: ADMET Properties of the ligands can be found by searching the canonical smiles of that ligand in SwissADME application.

3.2 SELECTION OF PROTEIN TARGETS:

It is crucial to locate significant protein targets linked to cancerous cells for the screening process. Target proteins should include important enzymes involved in the production and control of cancerous cell or important in structural configuration, such as VEGFR1, EGFR, and VEGFR2. In the thesis paper we have taken those three types of protein such as:

1. VEGFR1 (PDB CID: 3HNG) 2. VEGFR2 (PDB CID: 3VHE) 3. EGFR (PDB CID: 1M17)

These proteins are potential locations for the control of cancer and play crucial functions in the cancer development process especially in skin cancers. **Figure-5** shows the structure of EGFR, VEGFR1 and VEGFR2 (Left to Right).



EGFR **VEGFR1** **VEGFR2**

Figure-5: The structures of the chosen receptor molecules

3.3 PROTOCOL FOR MOLECULAR DOCKING:

STEP-1: Getting the complex PDB.

STEP-2: Cleaning the complex by removing H2O molecule and extra ligands.

STEP-3: Adding the missing hydrogels/side chain atoms (Poler).

STEP-4: Adding Kollman charges.

STEP-5: Distributing the charge.

STEP-6: Grid Preparation For that macromolecule.

STEP-7: Saving the Macromolecule as (.pdbqt) Format.

STEP-8: Preparing Configuration file for docking.

STEP-9: Selecting the Ligand.

STEP-10: Downloading Ligand Structure in (.sdf) 3-D format.

STEP-11: Converting Ligand to (.pdb) format.

STEP-12: Modifying the Ligand and Saving in (.pdbqt) format.

STEP-13: Running the docking code in CMD prompt.

STEP-14: Analyzing the results of docking.

These steps have been shown in **Figure-6**.

The docking code used in command prompt is as follows:

cd {Location Of MM and Ligand as (.pdbqt) format in the file explorer}"

{Location of (vina.exe) in file explorer}\vina.exe" --receptor MM_File_Name.pdbqt --ligand Ligand_File_Name.pdbqt --config Configuration_File_Name.txt --log Log_File_Name.txt --out Output_File_Name.pdbqt

(*MM stands for Macromolecule)

3.4 PREPARATION OF LIGAND:

The phytochemicals from the chosen database need to be prepared as ligands prior to docking simulations. Only those ligands will be taken in action which does not violate Lipinski's rule of five for drug likeliness of a molecule. In order to make a ligand, molecule geometry must be optimized. For ligand preparation chores, software tools like Open Babel and AutoDock tool can be employed.

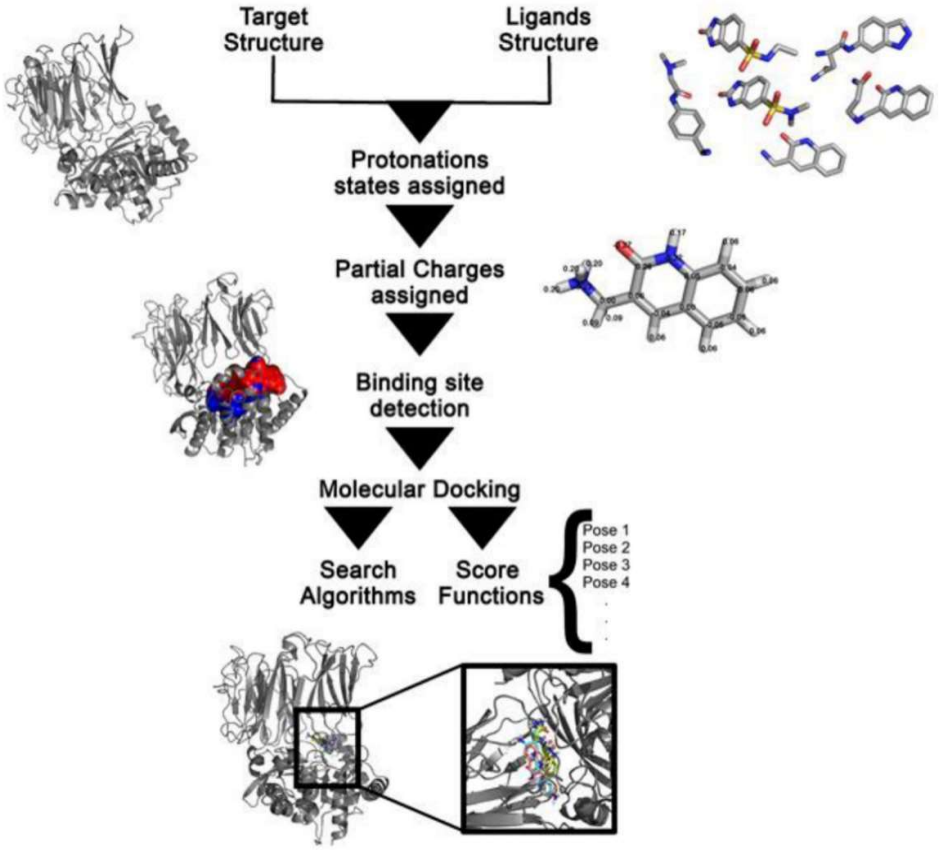


Figure-6: Basic Steps of Docking

3.5 PREPARATION OF PROTEIN:

Prior to running docking simulations, the chosen protein structures must be ready (for example, from the Protein Data Bank). In order to prepare proteins, water molecules and extra ligand must be removed, Poler Hydrogen atoms must be added, Partial Charge (Kollman Charge) must be assigned, distributed and then the protein structure must be optimized. After that protein file is saved in (.pdbqt) format. For the preparation of proteins, we utilized AutoDock Tools.

3.6 GRID GENERATION:

To specify the area where ligand binding should take place, a docking grid is created around the target protein. The active site or pertinent binding pockets, where ligands are anticipated to interact with the protein, are covered by the grid.To guarantee thorough sampling while retaining computational efficiency, the grid size and spacing parameters should be properly specified. **Figure-7** Shows How grid is selected for a specific protein.

3.7 SCORING AND DOCKING SIMULATION:

By putting the ready-made ligands inside the created docking grid, docking simulations are carried out. While looking for the ideal binding pose, the docking program investigates various ligand conformations and orientations. Ranking algorithms assess the ligands' anticipated binding energies and rank them according to their binding affinities. To improve sampling and capture ligand flexibility, we have used several dockings (run number was set to 9).

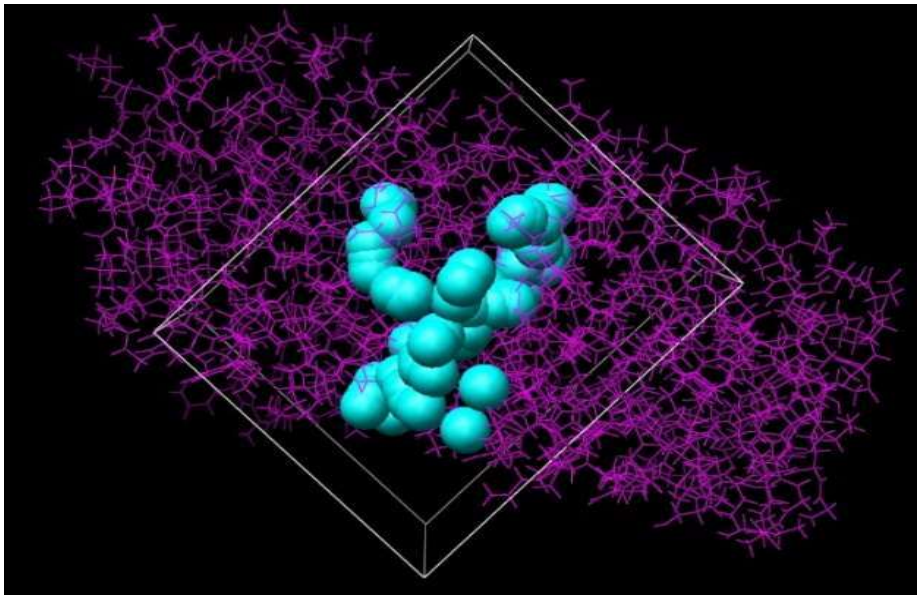


Figure-7: Grid Box

3.8. EVALUATION AND ANALYSIS:

The results of the docking simulations are examined to find top-ranked ligands that may have cancer-killing potential. Focusing on important residues and binding motifs, the molecular interactions between the ligands and target proteins are investigated. Molecular Docking is done for control drugs with VEGFR1, VEGFR2 and EGFR. The binding affinity of the phytochemicals is compared with that of the control drugs to highlight the compound that can multitarget cancer receptors with low inhibition constant.

CHAPTER 4:

RESULTS AND ANALYSIS

4.1 VIRTUAL SCREENING:

We have initially chosen 308 phytochemicals as our compound database after taking into account several medicinal plants that are said to have anti-cancer properties. 270 phytochemicals passed Lipinski's rule of five (for drug likeliness of chemical compounds) when ADMET attributes were predicted using SWISSADME. Compounds 271 to 308 were in violation of Lipinski's criterion and were thus excluded from consideration in our future docking investigation, according to the data provided in the supplemental material (**Table SM 1**).

By employing molecular docking to check the phytochemical database against the selected protein targets, a set of docking findings are generated. The results of the docking provide information on the predicted binding modalities and affinities of the ligands with the target proteins. The extent of the link between the ligand and the protein is demonstrated by the binding affinities, which are frequently provided as docking scores or binding energies. The next step is to identify the ligands from the outcomes of this experiment with the highest binding affinities that may have anti-cancer potential.

The affinity of the selected phytochemicals for the cancer receptors EGFR, VEGFR1 and VEGFR2 is shown in **Table SM 2**. **Table 2** lists the possible multi-targeted inhibitors of EGFR, VEGFR1, and VEGFR2 and highlights the phytochemicals that display significant protein-ligand interaction (similar to the outcomes of conventional anti-cancer medications shown in **Table 1**). These phytochemicals exhibited a binding affinity value of higher or close to that of standard drug compounds with all the chosen three receptors. However, the stability of these protein-ligand complexes under physiological settings will be determined by further molecular dynamics modeling.

Table 1: Existing Drug (Control) Docking Result and Threshold Calculations

Sl. No.	Existing Cancer Drug Name	Interaction with Proteins		
		VEGFR2 Binding Energy (in kcal/mol)	VEGFR1 Binding Energy (in kcal/mol)	EGFR Binding Energy (in kcal/mol)
1	Trastuzumab Deruxtecan	-8.7	-8.4	-8.2
2	Ribociclib	-7.7	-8.8	-8.6
3	Sunitinib	-8.3	-7.9	-8
4	Ibrutinib	-8.7	-9.3	-9.4

Table 2: Phytochemicals that are highlighted as potential candidates for anti-cancer agents

Sl. No.	Phytochemical Name	Interaction with Proteins Binding Energy (in kcal/mol)		
		VEGFR2	VEGFR1	EGFR
1	Syringin	-9.4	-9.1	-9.5
2	Tannic Acid	-9.3	-8.3	-9.5
3	Betulin	-8.3	-8.4	-8.5
4	Alpha-Amyrin	-9.8	-9.2	-9.9
5	Ursolic Acid	-9.5	-8.8	-9.8
6	Limonin	-8.7	-9.5	-9
7	Luteolin	-10.3	-8.3	-8.7
8	Isovitexin	-8.4	-8.2	-9.4
9	Dtxsid10942442	-8.2	-8.9	-8.1
10	Obacunone	-8.1	-9.1	-9
11	Lupeol	-9	-8.6	-9.2
12	Stigmasterol	-8.3	-8.3	-9.9
13	Taraxerol Acetate	-9.9	-9.6	-9.5
14	Hibiscetin	-8.8	-8	-8.8
15	Gossypetin	-7.9	-8.2	-8.9
16	Ergosterol	-9.3	-8.9	-9.3
17	Acetylursolic Acid	-9.5	-8.8	-9.5
18	Chrysoeriol	-8.1	-8.7	-9
19	Isohydnocarpin	-8.3	-8.9	-9.1
20	Hydnocarpin	-9.2	-8	-9.4
21	Beta-Amyrin	-9.5	-8.9	-9.3
22	Isoginkgetin	-9.3	-8.5	-10.1
23	Amentoflavone dimethyl ether	-9.5	-8.5	-8.5
24	Sugiol	-8	-8.3	-8.2
25	Podocarpusflavone A	-9.5	-9.2	-9.7
26	Epibetulinic Acid	-8.5	-8.2	-8.6
27	Cardenolide 2	-7.9	-9.7	-8.6
28	Beta-Yohimbine	-8.9	-7.7	-8.9
29	Ajmaline	-8.7	-7.7	-8.3
30	Vincoside lactam	-8.1	-9.7	-9.4
31	Raunescine	-8.2	-8.5	-9
32	Normacusine B	-8.5	-8.3	-8.6
33	Allo-Yohimbine	-9	-8.7	-8.9

4.2 ANALYSIS OF MOLECULAR INTERACTIONS:

The analysis's primary objective is to examine specific molecular bonding between top-ranked ligands and the target proteins. Among the interactions are stacking interactions, electrostatic interactions, hydrogen bonds, and hydrophobic contacts. 33 phytochemicals are included in **Table 2** that can targets EGFR, VEGFR1 and VEGFR2 respectively (based on the binding affinity values shown in **Table 1). Figures 8** and **9** show, respectively, the 2D binding pocket and 2D interaction diagram of the anti-cancer medication trastuzumab deruxtecan and the phytochemical syringin with EGFR. Comparing the two compounds reveals that they have comparable interaction residues, which suggests a similar mode of action on EGFR.The identification of important residues involved in ligand-protein interactions highlights the binding motifs and potential hotspots. We now have a better comprehension of the molecular mechanisms by which the ligands affect the target proteins and inhibit malignancy. Rankings of potential anti-cancer medicines are determined by molecular interactions, or binding affinities. Highest binding affinities, strong molecular interactions, and favourable structural traits make ligands the most promising candidates. Using further computational methods or experimental testing, potential anti-cancer effects of those the selected candidates can be verified.

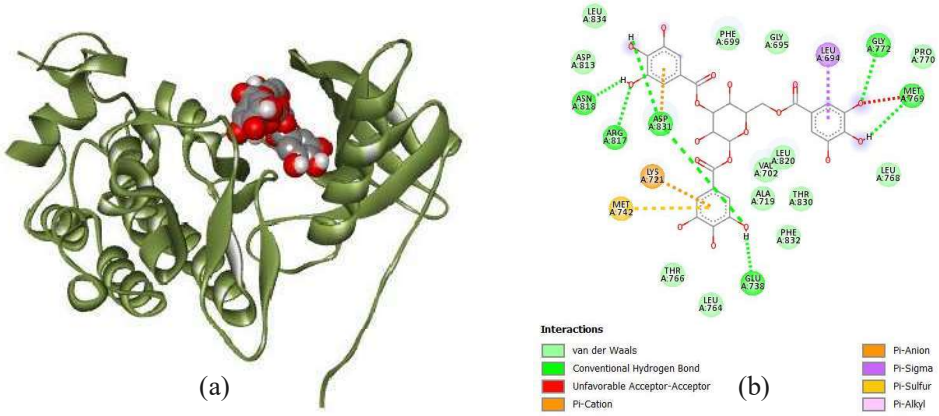


Figure 8: The binding pockect (a) and 2D interaction diagram (b) of the phytochemical syringin with EGFR

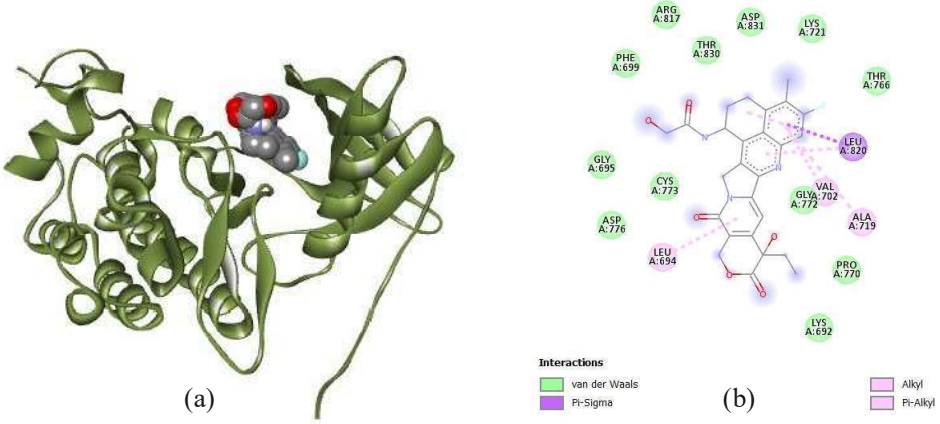


Figure 9: The binding pockect (a) and 2D interaction diagram (b) of the standard anti-cancer drug trastuzumab deruxtecan with EGFR

CHAPTER 5:

SUMMARY AND FUTURE SCOPE

New genomic and computational methods have significantly sped up the hunt for information regarding the molecular abnormalities that underlie cancer, even though there is still much to discover. Researchers can now classify and analyze hundreds of patient tumors, allowing them to find characteristics that affect cancer risk even when they are uncommon or have a minimal overall impact. It is hoped that identifying these characteristics would help us identify crucial cancer pathways and novel areas for intervention.

Our researchers are in a good position to continue understanding the underlying cellular pathways that underlie all forms of cancer by building on the CCR's long-standing excellent portfolio of basic research and the freedom of CCR main scientists to freely pursue fundamental topics in biology. We are also looking at the genetically distinct but uncommon malignancies that may be model systems for understanding more universally relevant cancer processes. As in the past, inquiries into the fundamental processes of cancer promise to accelerate the discovery of new and improved diagnostic and treatment techniques.

We identified thirty-three phytochemicals in our thesis that may be able to treat cancer. This selection is based on the binding affinity values, i.e., phytochemicals exhibiting ΔG values higher or close to that of standard compounds are identified as hit molecules. Syringin, Tannic Acid, Betulin, Alpha-Amyrin, Ursolic Acid, Limonin, Luteolin, Isovitexin, Dtxsid10942442, Obacunone, Lupeol, Stigmasterol, Taraxerol Acetate, Hibiscetin, Gossypetin, Ergosterol, Acetylursolic Acid, Chrysoeriol, Isohydnocarpin, Hydnocarpin, Beta-Amyrin, Isoginkgetin, Amentoflavone dimethyl ether, Sugiol, Podocarpusflavone A, Epibetulinic Acid, Cardenolide 2, Beta-Yohimbine, Ajmaline, Vincoside lactam, Raunescine, Normacusine B, Allo-Yohimbine are those phytochemicals with anti-cancer properties. However, that may be verified in future following modelling, in vivo and in vitro testing, and clinical trials.

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SUPPLEMENTARY MATERIAL

Table SM 1: Selected ligands and the ADMET Properties

SL. NO.	PHYTOCHEMICAL NAME	ADMET AND DRUG-LIKENESS OF THE PHYTOCHEMICAL			
		SOLUBILITY	GI ABSORPTION	BBB PERMEANT	LIPINSKI
1	Myrcene	1.22e-01 mg/ml ; 8.96e-04 mol/l	Low	Yes	Yes
2	Tricyclene	2.56e-01 mg/ml ; 1.88e-03 mol/l	Low	Yes	Yes
3	Citronellyl Acetate	7.37e-02 mg/ml ; 3.72e-04 mol/l	High	Yes	Yes
4	d-Borneol	4.77e-01 mg/ml ; 3.09e-03 mol/l	High	Yes	Yes
5	Geranyl Acetate	1.22e-01 mg/ml ; 6.22e-04 mol/l	High	Yes	Yes
6	Beta-Phellandrene	2.23e-01 mg/ml ; 1.64e-03 mol/l	Low	Yes	Yes
7	Camphor	1.04e+00 mg/ml ; 6.86e-03 mol/l	High	Yes	Yes
8	Alpha-Pinene	4.24e-02 mg/ml ; 3.11e-04 mol/l	Low	Yes	Yes
9	O-Cymene	2.08e-02 mg/ml ; 1.55e-04 mol/l	Low	Yes	Yes
10	Thymol methyl ether	5.71e-02 mg/ml ; 3.48e-04 mol/l	High	Yes	Yes
11	Isogermacrene D	1.92e-02 mg/ml ; 9.39e-05 mol/l	Low	No	Yes
12	Vanillic Acid	1.60e+00 mg/ml ; 9.52e-03 mol/l	High	No	Yes
13	Naphthalene	4.51e-02 mg/ml ; 3.52e-04 mol/l	Low	Yes	Yes
14	Syringin	3.46e+01 mg/ml ; 9.29e-02 mol/l	Low	No	Yes
15	Tannic Acid	Na	Na	Na	Na
16	Mannitol	3.75e+03 mg/ml ; 2.06e+01 mol/l	Low	No	Yes
17	2-C-Methyl-D-Erythritol	1.07e+03 mg/ml ; 7.83e+00 mol/l	High	No	Yes
18	Hyoscine	1.87e+00 mg/ml ; 6.17e-03 mol/l	High	No	Yes
19	Hyoscyamine	6.21e-01 mg/ml ; 2.15e-03 mol/l	High	Yes	Yes
20	Betulin	9.48e-06 mg/ml ; 2.14e-08 mol/l	Low	No	Yes

21	**Alpha-Amyrin**	**2.94e-06 mg/ml ; 6.89e-09 mol/l**	**Low**	**No**	**Yes**
22	**Beta-Sitosterol**	**5.23e-06 mg/ml ; 1.26e-08 mol/l**	**Low**	**No**	**Yes**
23	**N,N-Dimethyl-5-Methoxytryptamine**	**1.72e-01 mg/ml ; 7.88e-04 mol/l**	**High**	**Yes**	**Yes**
24	**Linoleic Acid**	**2.49e-03 mg/ml ; 8.87e-06 mol/l**	**High**	**Yes**	**Yes**
25	**Digitolutein**	**5.65e-02 mg/ml ; 2.11e-04 mol/l**	**High**	**Yes**	**Yes**
26	**Digitoxigenin**	**6.52e-02 mg/ml ; 1.74e-04 mol/l**	**High**	**Yes**	**Yes**
27	**Ursolic Acid**	**2.69e-05 mg/ml ; 5.89e-08 mol/l**	**Low**	**No**	**Yes**
28	**Ellagic Acid**	**3.43e-01 mg/ml ; 1.14e-03 mol/l**	**High**	**No**	**Yes**
29	**Betulinic Acid**	**8.87e-06 mg/ml ; 1.94e-08 mol/l**	**Low**	**No**	**Yes**
30	**Cadalene**	**1.96e-03 mg/ml ; 9.86e-06 mol/l**	**Low**	**No**	**Yes**
31	**Hexadecane**	**5.66e-04 mg/ml ; 2.50e-06 mol/l**	**Low**	**No**	**Yes**
32	**Chrysanthenone**	**2.13e+00 mg/ml ; 1.42e-02 mol/l**	**High**	**Yes**	**Yes**
33	**Carvacrol**	**7.40e-02 mg/ml ; 4.92e-04 mol/l**	**High**	**Yes**	**Yes**
34	**Geranylacetone**	**2.04e-01 mg/ml ; 1.05e-03 mol/l**	**High**	**Yes**	**Yes**
35	**Jasmone**	**1.48e+00 mg/ml ; 8.99e-03 mol/l**	**High**	**Yes**	**Yes**
36	**Ilicic Acid**	**1.38e-01 mg/ml ; 5.45e-04 mol/l**	**High**	**Yes**	**Yes**
37	**Octadecane**	**Na**	**Na**	**Na**	**Na**
38	**3-Octanol**	**1.11e+00 mg/ml ; 8.53e-03 mol/l**	**High**	**Yes**	**Yes**
39	**3-Octanone**	**9.08e-02 mg/ml ; 3.54e-04 mol/l**	**High**	**Yes**	**Yes**
40	**Acetophenone**	**1.18e+00 mg/ml ; 9.83e-03 mol/l**	**High**	**Yes**	**Yes**
41	**Eucalyptol**	**4.63e-01 mg/ml ; 3.00e-03 mol/l**	**High**	**Yes**	**Yes**
42	**Byakangelicin**	**3.56e-01 mg/ml ; 1.06e-03 mol/l**	**High**	**No**	**Yes**
43	**Coumarin**	**7.42e-01 mg/ml ; 5.08e-03 mol/l**	**High**	**Yes**	**Yes**
44	**Limonin**	**5.72e-02 mg/ml ; 1.22e-04 mol/l**	**High**	**No**	**Yes**
45	**Ostruthin**	**2.60e-03 mg/ml ; 8.70e-06 mol/l**	**High**	**Yes**	**Yes**
46	**Ascorbic Acid**	**3.01e+02 mg/ml ; 1.71e+00 mol/l**	**High**	**No**	**Yes**

47	**Luteolin**	**5.63e-02 mg/ml ; 1.97e-04 mol/l**	**High**	**No**	**Yes**
48	**Apigenin**	**3.07e-02 mg/ml ; 1.14e-04 mol/l**	**High**	**No**	**Yes**
49	**Vitexin**	**6.29e-01 mg/ml ; 1.46e-03 mol/l**	**Low**	**No**	**Yes**
50	**Lycorenine**	**7.53e-01 mg/ml ; 2.37e-03 mol/l**	**High**	**Yes**	**Yes**
51	**Isovitexin**	**6.29e-01 mg/ml ; 1.46e-03 mol/l**	**Low**	**No**	**Yes**
52	**4-Hydroxybenzoic Acid**	**1.18e+00 mg/ml ; 8.52e-03 mol/l**	**High**	**Yes**	**Yes**
53	**Hellebrigenin**	**2.66e-01 mg/ml ; 6.39e-04 mol/l**	**High**	**No**	**Yes**
54	**Dtxsid10942442**	**3.35e-01 mg/ml ; 5.95e-04 mol/l**	**Low**	**No**	**Yes**
55	**Corytuberine**	**9.91e-02 mg/ml ; 3.03e-04 mol/l**	**High**	**Yes**	**Yes**
56	**Magnoflorine**	**4.19e-02 mg/ml ; 1.22e-04 mol/l**	**High**	**Yes**	**Yes**
57	**Methoxsalen**	**2.29e-01 mg/ml ; 1.06e-03 mol/l**	**High**	**Yes**	**Yes**
58	**Luvangetin**	**7.64e-02 mg/ml ; 2.96e-04 mol/l**	**High**	**Yes**	**Yes**
59	**Umbelliferone**	**5.66e-01 mg/ml ; 3.49e-03 mol/l**	**High**	**Yes**	**Yes**
60	**Obacunone**	**9.18e-03 mg/ml ; 2.02e-05 mol/l**	**High**	**No**	**Yes**
61	**4-Methoxy-1-Methylquinolin-2-one**	**1.09e+00 mg/ml ; 5.78e-03 mol/l**	**High**	**Yes**	**Yes**
62	**Bergapten**	**2.53e-01 mg/ml ; 1.17e-03 mol/l**	**High**	**Yes**	**Yes**
63	**Psoralen**	**3.44e-01 mg/ml ; 1.85e-03 mol/l**	**High**	**Yes**	**Yes**
64	**Marmesin**	**2.99e-01 mg/ml ; 1.22e-03 mol/l**	**High**	**Yes**	**Yes**
65	**Lupeol**	**9.83e-07 mg/ml ; 2.30e-09 mol/l**	**Low**	**No**	**Yes**
66	**Suberosin**	**2.63e-02 mg/ml ; 1.08e-04 mol/l**	**High**	**Yes**	**Yes**
67	**Lauric Acid**	**1.71e-01 mg/ml ; 8.55e-04 mol/l**	**High**	**Yes**	**Yes**
68	**Acidissiminol**	**2.25e-03 mg/ml ; 5.71e-06 mol/l**	**High**	**Yes**	**Yes**
69	**Azulene**	**5.21e-02 mg/ml ; 4.07e-04 mol/l**	**Low**	**Yes**	**Yes**
70	**Anthraquinone**	**3.14e-02 mg/ml ; 1.51e-04 mol/l**	**High**	**Yes**	**Yes**
71	**Lactic Acid**	**1.19e+02 mg/ml ; 1.32e+00 mol/l**	**High**	**No**	**Yes**

72	**Quinic Acid**	**6.48e+02 mg/ml ; 3.37e+00 mol/l**	**Low**	**No**	**Yes**
73	**Quinoline**	**2.83e-01 mg/ml ; 2.19e-03 mol/l**	**High**	**Yes**	**Yes**
74	**1,4-Benzoquinone**	**2.50e+01 mg/ml ; 2.31e-01 mol/l**	**High**	**No**	**Yes**
75	**Quinine**	**6.32e-02 mg/ml ; 1.95e-04 mol/l**	**High**	**Yes**	**Yes**
76	**Quinolone**	**9.02e-01 mg/ml ; 6.22e-03 mol/l**	**High**	**Yes**	**Yes**
77	**Quinol**	**3.91e+00 mg/ml ; 3.55e-02 mol/l**	**High**	**Yes**	**Yes**
78	**Quinidine**	**6.32e-02 mg/ml ; 1.95e-04 mol/l**	**High**	**Yes**	**Yes**
79	**p-Cymene**	**3.12e-02 mg/ml ; 2.33e-04 mol/l**	**Low**	**Yes**	**Yes**
80	**Terpinolene**	**4.30e-02 mg/ml ; 3.16e-04 mol/l**	**Low**	**Yes**	**Yes**
81	**Beta-Eudesmol**	**6.89e-02 mg/ml ; 3.10e-04 mol/l**	**High**	**Yes**	**Yes**
82	**Gamma-Eudesmol**	**1.14e-01 mg/ml ; 5.15e-04 mol/l**	**High**	**Yes**	**Yes**
83	**Sebacic Acid**	**3.00e+00 mg/ml ; 1.48e-02 mol/l**	**High**	**Yes**	**Yes**
84	**Camphane**	**7.91e-02 mg/ml ; 5.72e-04 mol/l**	**Low**	**Yes**	**Yes**
85	**Alpha-Curcumene**	**6.17e-03 mg/ml ; 3.05e-05 mol/l**	**Low**	**No**	**Yes**
86	**Beta-Pinene**	**6.74e-02 mg/ml ; 4.95e-04 mol/l**	**Low**	**Yes**	**Yes**
87	**Linalool**	**6.09e-01 mg/ml ; 3.95e-03 mol/l**	**High**	**Yes**	**Yes**
88	**Thujone**	**1.08e+00 mg/ml ; 7.11e-03 mol/l**	**High**	**Yes**	**Yes**
89	**Camphene**	**6.18e-02 mg/ml ; 4.54e-04 mol/l**	**Low**	**Yes**	**Yes**
90	**Geraniol**	**2.59e-01 mg/ml ; 1.68e-03 mol/l**	**High**	**Yes**	**Yes**
91	**Limonene**	**4.33e-02 mg/ml ; 3.18e-04 mol/l**	**Low**	**Yes**	**Yes**
92	**Osthenol**	**3.97e-02 mg/ml ; 1.72e-04 mol/l**	**High**	**Yes**	**Yes**
93	**Auraptene**	**4.28e-03 mg/ml ; 1.43e-05 mol/l**	**High**	**Yes**	**Yes**
94	**Osthole**	**2.63e-02 mg/ml ; 1.08e-04 mol/l**	**High**	**Yes**	**Yes**
95	**Stigmasterol**	**1.43e-05 mg/ml ; 3.46e-08 mol/l**	**Low**	**No**	**Yes**
96	**Epoxysuberosin**	**3.24e-01 mg/ml ; 1.32e-03 mol/l**	**High**	**Yes**	**Yes**
97	**Dihydrosuberenol**	**1.98e-01 mg/ml ; 7.54e-04 mol/l**	**High**	**Yes**	**Yes**

98	**Isopimpinellin**	**2.41e-01 mg/ml ; 9.77e-04 mol/l**	**High**	**Yes**	**Yes**
99	**Hautriwaic Acid**	**1.37e-02 mg/ml ; 4.13e-05 mol/l**	**High**	**Yes**	**Yes**
100	**Demethylnobiletin**	**1.90e-02 mg/ml ; 4.90e-05 mol/l**	**High**	**No**	**Yes**
101	**Farnesol**	**1.50e-02 mg/ml ; 6.74e-05 mol/l**	**High**	**Yes**	**Yes**
102	**Flavylium**	**2.02e-02 mg/ml ; 9.77e-05 mol/l**	**High**	**Yes**	**Yes**
103	**Beta-Sitostenone**	**5.67e-06 mg/ml ; 1.38e-08 mol/l**	**Low**	**No**	**Yes**
104	**Kaempferol**	**1.40e-01 mg/ml ; 4.90e-04 mol/l**	**High**	**No**	**Yes**
105	**Quercetin**	**2.11e-01 mg/ml ; 6.98e-04 mol/l**	**High**	**No**	**Yes**
106	**1-Tetratriacontanol**	**1.89e-09 mg/ml ; 3.82e-12 mol/l**	**Low**	**No**	**Yes**
107	**Guaijaverin**	**4.47e-01 mg/ml ; 1.03e-03 mol/l**	**Low**	**No**	**Yes**
108	**Ferulic Acid**	**1.49e+00 mg/ml ; 7.68e-03 mol/l**	**High**	**Yes**	**Yes**
109	**Stigmasta-4-ene-one**	**8.27e-06 mg/ml ; 2.01e-08 mol/l**	**Low**	**No**	**Yes**
110	**Naringetol**	**8.74e-02 mg/ml ; 3.21e-04 mol/l**	**High**	**No**	**Yes**
111	**Eriodictyol**	**1.60e-01 mg/ml ; 5.54e-04 mol/l**	**High**	**No**	**Yes**
112	**Sterculic Acid**	**4.78e-03 mg/ml ; 1.62e-05 mol/l**	**High**	**No**	**Yes**
113	**Malvalic Acid**	**7.71e-03 mg/ml ; 2.75e-05 mol/l**	**High**	**Yes**	**Yes**
114	**8-Nonynoic Acid**	**1.73e+00 mg/ml ; 1.12e-02 mol/l**	**High**	**Yes**	**Yes**
115	**9-Decynoic Acid**	**7.21e-01 mg/ml ; 4.29e-03 mol/l**	**High**	**Yes**	**Yes**
116	**Thiamine**	**1.28e+00 mg/ml ; 4.83e-03 mol/l**	**High**	**no**	**Yes**
117	**Riboflavin**	**1.85e+01 mg/ml ; 4.93e-02 mol/l**	**Low**	**No**	**Yes**
118	**Cyanidin chloride**	**1.61e-01 mg/ml ; 4.99e-04 mol/l**	**High**	**No**	**Yes**
119	**Taraxerol Acetate**	**6.80e-07 mg/ml ; 1.45e-09 mol/l**	**Low**	**No**	**Yes**
120	**Nicotinic Acid**	**6.81e+00 mg/ml ; 5.53e-02 mol/l**	**High**	**Yes**	**Yes**
121	**Stigmast-5-ene-3Beta,4Alpha-diol**	**2.16e-05 mg/ml ; 5.02e-08 mol/l**	**Low**	**No**	**Yes**
122	**D-Glucuronic Acid**	**6.09e+02 mg/ml ; 3.14e+00 mol/l**	**Low**	**No**	**Yes**
123	**Methyl malvalate**	**4.85e-03 mg/ml ; 1.65e-05 mol/l**	**High**	**No**	**Yes**

124	**L-Rhamnose**	**4.72e+02 mg/ml ; 2.88e+00 mol/l**	**High**	**No**	**Yes**
125	**D-Galacturonic Acid**	**4.72e+02 mg/ml ; 2.88e+00 mol/l**	**High**	**No**	**Yes**
126	**D-Galactose**	**2.55e+03 mg/ml ; 1.41e+01 mol/l**	**Low**	**No**	**Yes**
127	**Hibiscetin**	**1.87e-01 mg/ml ; 5.58e-04 mol/l**	**Low**	**No**	**Yes**
128	**Citric Acid**	**4.63e+02 mg/ml ; 2.41e+00 mol/l**	**Low**	**No**	**Yes**
129	**2-Hydroxycinnamic Acid**	**6.93e-01 mg/ml ; 4.22e-03 mol/l**	**High**	**Yes**	**Yes**
130	**d-Tartaric Acid**	**6.14e+02 mg/ml ; 4.09e+00 mol/l**	**Low**	**No**	**Yes**
131	**Gossypetin**	**1.26e-01 mg/ml ; 3.96e-04 mol/l**	**Low**	**No**	**Yes**
132	**Myricetin**	**3.14e-01 mg/ml ; 9.88e-04 mol/l**	**Low**	**No**	**Yes**
133	**Myristic Acid**	**1.11e-02 mg/ml ; 4.86e-05 mol/l**	**High**	**Yes**	**Yes**
134	**Ergosterol**	**7.63e-05 mg/ml ; 1.92e-07 mol/l**	**Low**	**No**	**Yes**
135	**Palmitic Acid**	**2.43e-03 mg/ml ; 9.49e-06 mol/l**	**High**	**Yes**	**Yes**
136	**Dihydrosterculic Acid**	**5.38e-04 mg/ml ; 1.82e-06 mol/l**	**High**	**No**	**Yes**
137	**Acetylursolic Acid**	**9.42e-06 mg/ml ; 1.89e-08 mol/l**	**Low**	**No**	**Yes**
138	**Chrysoeriol**	**2.61e-02 mg/ml ; 8.69e-05 mol/l**	**High**	**No**	**Yes**
139	**Isohydnocarpin**	**3.95e-03 mg/ml ; 8.51e-06 mol/l**	**Low**	**No**	**Yes**
140	**Hydnocarpin**	**2.41e-03 mg/ml ; 5.20e-06 mol/l**	**Low**	**No**	**Yes**
141	**Neohydnocarpin**	**8.11e-03 mg/ml ; 1.75e-05 mol/l**	**Low**	**No**	**Yes**
142	**Beta-Amyrin**	**2.40e-06 mg/ml ; 5.62e-09 mol/l**	**Low**	**No**	**Yes**
143	**Actinodaphnine**	**7.23e-02 mg/ml ; 2.32e-04 mol/l**	**High**	**Yes**	**Yes**
144	**Canthin-6-one**	**8.25e-02 mg/ml ; 3.75e-04 mol/l**	**High**	**Yes**	**Yes**
145	**6H-Indolo(3,2,1-de)(1,5)Naphthyridin-6-one**	**8.79e-02 mg/ml ; 3.51e-04 mol/l**	**High**	**Yes**	**Yes**
146	**Moupinamide**	**2.93e-01 mg/ml ; 9.34e-04 mol/l**	**High**	**No**	**Yes**
147	**Ervoside**	**8.25e-01 mg/ml ; 2.07e-03 mol/l**	**High**	**No**	**Yes**
148	**Syringic Acid**	**2.84e+00 mg/ml ; 1.44e-02 mol/l**	**High**	**No**	**Yes**

149	**10-Hydroxycanthin-6-one**	**1.28e-01 mg/ml ; 5.41e-04 mol/l**	**High**	**Yes**	**Yes**
150	**Stigmasterol Acetate**	**5.11e-06 mg/ml ; 1.12e-08 mol/l**	**Low**	**No**	**Yes**
151	**Glycerol**	**6.22e+02 mg/ml ; 6.76e+00 mol/l**	**High**	**No**	**Yes**
152	**Isoginkgetin**	**3.82e-05 mg/ml ; 6.75e-08 mol/l**	**Low**	**No**	**Yes**
153	**Amentoflavone dimethyl ether**	**2.38e-05 mg/ml ; 4.11e-08 mol/l**	**Low**	**No**	**Yes**
154	**Podolide**	**1.87e-01 mg/ml ; 5.67e-04 mol/l**	**High**	**Yes**	**Yes**
155	**Sugiol**	**1.25e-03 mg/ml ; 4.18e-06 mol/l**	**High**	**Yes**	**Yes**
156	**Totarol**	**2.94e-04 mg/ml ; 1.03e-06 mol/l**	**High**	**Yes**	**Yes**
157	**Podocarpusflavone A**	**6.12e-05 mg/ml ; 1.11e-07 mol/l**	**Low**	**No**	**Yes**
158	**Benzene**	**3.07e-01 mg/ml ; 3.92e-03 mol/l**	**Low**	**No**	**Yes**
159	**Toluene**	**1.58e-01 mg/ml ; 1.72e-03 mol/l**	**Low**	**No**	**Yes**
160	**Palmitoleic Acid**	**5.02e-03 mg/ml ; 1.97e-05 mol/l**	**High**	**Yes**	**Yes**
161	**Oleic Acid**	**1.09e-03 mg/ml ; 3.85e-06 mol/l**	**High**	**No**	**Yes**
162	**Epibetulinic Acid**	**8.87e-06 mg/ml ; 1.94e-08 mol/l**	**Low**	**No**	**Yes**
163	**Ajugacumbin B**	**2.25e-02 mg/ml ; 5.20e-05 mol/l**	**High**	**No**	**Yes**
164	**Linolenic Acid**	**4.64e-03 mg/ml ; 1.67e-05 mol/l**	**High**	**Yes**	**Yes**
165	**9-Decenoic Acid**	**5.91e-01 mg/ml ; 3.47e-03 mol/l**	**High**	**Yes**	**Yes**
166	**Retinol**	**3.91e-03 mg/ml ; 1.37e-05 mol/l**	**High**	**Yes**	**Yes**
167	**Niacin**	**6.81e+00 mg/ml ; 5.53e-02 mol/l**	**High**	**Yes**	**Yes**
168	**Pantothenic Acid**	**1.92e+02 mg/ml ; 8.77e-01 mol/l**	**High**	**No**	**Yes**
169	**Pyridoxine**	**3.86e+01 mg/ml ; 2.28e-01 mol/l**	**High**	**No**	**Yes**
170	**Biotin**	**1.43e+01 mg/ml ; 5.85e-02 mol/l**	**High**	**No**	**Yes**

171	**Phytonadione**	**8.62e-07 mg/ml ; 1.91e-09 mol/l**	**Low**	**No**	**Yes**
172	**Adenine**	**6.98e+00 mg/ml ; 5.16e-02 mol/l**	**High**	**No**	**Yes**
173	**Guanine**	**2.96e+01 mg/ml ; 1.96e-01 mol/l**	**High**	**No**	**Yes**
174	**Cytosine**	**1.13e+02 mg/ml ; 1.01e+00 mol/l**	**High**	**No**	**Yes**
175	**Thymidine**	**4.47e+01 mg/ml ; 1.85e-01 mol/l**	**High**	**No**	**Yes**
176	**Thymine**	**2.38e+01 mg/ml ; 1.89e-01 mol/l**	**High**	**No**	**Yes**
177	**Uracil**	**4.30e+01 mg/ml ; 3.84e-01 mol/l**	**High**	**No**	**Yes**
178	**Adenosine**	**2.36e+01 mg/ml ; 8.83e-02 mol/l**	**Low**	**No**	**Yes**
179	**Nicotinamide**	**1.97e+01 mg/ml ; 1.62e-01 mol/l**	**High**	**No**	**Yes**
180	**Nicotin**	**2.10e+00 mg/ml ; 1.30e-02 mol/l**	**High**	**Yes**	**Yes**
181	**Benzyl isothiocyanate**	**1.28e-01 mg/ml ; 8.55e-04 mol/l**	**High**	**Yes**	**Yes**
182	**Allyl Isothiocyanate**	**1.43e+00 mg/ml ; 1.44e-02 mol/l**	**High**	**Yes**	**Yes**
183	**Thiirane Acetonitrile**	**2.23e+01 mg/ml ; 2.25e-01 mol/l**	**High**	**Yes**	**Yes**
184	**Diallyl Sulfide**	**2.59e+00 mg/ml ; 2.27e-02 mol/l**	**High**	**Yes**	**Yes**
185	**[(Z)-1-[3,4,5-Trihydroxy-6-(Hydroxymethyl)Oxan-2-yl]Sulfanylbut-3-enylideneamino]Sulfate**	**4.25e+01 mg/ml ; 1.19e-01 mol/l**	**Low**	**No**	**Yes**
186	**Cardenolide 2**	**2.55e-01 mg/ml ; 4.79e-04 mol/l**	**Low**	**No**	**Yes**
187	**Sinigrin**	**2.70e+01 mg/ml ; 6.79e-02 mol/l**	**Low**	**No**	**Yes**
188	**3-Butenyl Isothiocyanate**	**1.02e+00 mg/ml ; 9.02e-03 mol/l**	**High**	**Yes**	**Yes**
189	**Glucotropaeolin**	**4.61e+00 mg/ml ; 1.13e-02 mol/l**	**Low**	**No**	**Yes**
190	**Aspirin**	**2.54e+00 mg/ml ; 1.41e-02 mol/l**	**High**	**Yes**	**Yes**
191	**Metronidazole**	**1.72e+01 mg/ml ; 1.00e-01 mol/l**	**High**	**No**	**Yes**
192	**2-Furoic Acid**	**5.19e+00 mg/ml ; 4.63e-02 mol/l**	**High**	**Yes**	**Yes**
193	**Echitamine**	**8.50e-01 mg/ml ; 2.20e-03 mol/l**	**High**	**No**	**Yes**

194	**Squalene**	**8.35e-07 mg/ml ; 2.03e-09 mol/l**	**Low**	**No**	**Yes**
195	**5,7-Dihydroxy-3,6,8-trimethoxyflavone**	**2.37e-02 mg/ml ; 6.88e-05 mol/l**	**High**	**No**	**Yes**
196	**Araneosol**	**2.18e-02 mg/ml ; 5.82e-05 mol/l**	**High**	**No**	**Yes**
197	**Helipyrone**	**2.85e-01 mg/ml ; 8.90e-04 mol/l**	**High**	**No**	**Yes**
198	**Anisodamine**	**2.18e+00 mg/ml ; 7.13e-03 mol/l**	**High**	**No**	**Yes**
199	**Scopine**	**3.27e+01 mg/ml ; 2.11e-01 mol/l**	**High**	**No**	**Yes**
200	**Tropine**	**9.16e+00 mg/ml ; 6.49e-02 mol/l**	**High**	**No**	**Yes**
201	**Scopoline**	**3.27e+01 mg/ml ; 2.11e-01 mol/l**	**Low**	**no**	**Yes**
202	**Scopoletin**	**6.70e-01 mg/ml ; 3.48e-03 mol/l**	**High**	**Yes**	**Yes**
203	**Chlorogenic Acid**	**8.50e+00 mg/ml ; 2.40e-02 mol/l**	**Low**	**No**	**Yes**
204	**Caffeic Acid**	**2.32e+00 mg/ml ; 1.29e-02 mol/l**	**High**	**No**	**Yes**
205	**Cuskhygrine**	**5.68e+00 mg/ml ; 2.53e-02 mol/l**	**High**	**Yes**	**Yes**
206	**Cuscohygrine**	**5.68e+00 mg/ml ; 2.53e-02 mol/l**	**High**	**Yes**	**Yes**
207	**Scopolin**	**1.39e+01 mg/ml ; 3.92e-02 mol/l**	**Low**	**No**	**Yes**
208	**Caffeine**	**6.50e+00 mg/ml ; 3.35e-02 mol/l**	**High**	**No**	**Yes**
209	**Cocaine**	**2.76e-01 mg/ml ; 9.09e-04 mol/l**	**High**	**Yes**	**Yes**
210	**Morphine**	**1.43e+00 mg/ml ; 5.02e-03 mol/l**	**High**	**Yes**	**Yes**
211	**Heroin**	**3.48e-01 mg/ml ; 9.41e-04 mol/l**	**High**	**Yes**	**Yes**
212	**Methamphetamine**	**7.92e-01 mg/ml ; 5.31e-03 mol/l**	**High**	**Yes**	**Yes**
213	**Lysergic Acid diethylamide**	**6.20e-02 mg/ml ; 1.92e-04 mol/l**	**High**	**Yes**	**Yes**
214	**Alpha-Pyrrolidinopentiophenone**	**9.67e-02 mg/ml ; 4.18e-04 mol/l**	**High**	**Yes**	**Yes**
215	**Papaverine**	**4.47e-02 mg/ml ; 1.32e-04 mol/l**	**High**	**Yes**	**Yes**
216	**Tetraphylline**	**4.15e-02 mg/ml ; 1.08e-04 mol/l**	**High**	**Yes**	**Yes**
217	**Serpentine (alkaloid)**	**4.77e-02 mg/ml ; 1.37e-04 mol/l**	**High**	**Yes**	**Yes**

218	**Reserpiline**	**3.68e-02 mg/ml ; 8.91e-05 mol/l**	**High**	**Yes**	**Yes**
219	**Deserpidine**	**1.21e-03 mg/ml ; 2.08e-06 mol/l**	**High**	**No**	**Yes**
220	**Ajmalicine**	**4.63e-02 mg/ml ; 1.31e-04 mol/l**	**High**	**Yes**	**Yes**
221	**Isorauhimbine**	**3.43e-02 mg/ml ; 9.69e-05 mol/l**	**High**	**Yes**	**Yes**
222	**Yohimbine**	**3.43e-02 mg/ml ; 9.69e-05 mol/l**	**High**	**Yes**	**Yes**
223	**Corynanthine**	**3.43e-02 mg/ml ; 9.69e-05 mol/l**	**High**	**Yes**	**Yes**
224	**Tubotaiwine**	**5.56e-02 mg/ml ; 1.71e-04 mol/l**	**High**	**Yes**	**Yes**
225	**Tetrahydroalstonine**	**4.63e-02 mg/ml ; 1.31e-04 mol/l**	**High**	**Yes**	**Yes**
226	**Akuammigine**	**4.63e-02 mg/ml ; 1.31e-04 mol/l**	**High**	**Yes**	**Yes**
227	**Rauniticine**	**4.63e-02 mg/ml ; 1.31e-04 mol/l**	**High**	**Yes**	**Yes**
228	**Rauwolscine**	**3.43e-02 mg/ml ; 9.69e-05 mol/l**	**High**	**Yes**	**Yes**
229	**Beta-Yohimbine**	**3.43e-02 mg/ml ; 9.69e-05 mol/l**	**High**	**Yes**	**Yes**
230	**Ajmaline**	**2.46e-01 mg/ml ; 7.53e-04 mol/l**	**High**	**Yes**	**Yes**
231	**Vincoside lactam**	**3.87e-01 mg/ml ; 7.76e-04 mol/l**	**Low**	**No**	**Yes**
232	**Ajmalidine**	**1.25e-01 mg/ml ; 3.86e-04 mol/l**	**High**	**Yes**	**Yes**
233	**18-Beta-hydroxy-3-Epi-Alpha-Yohimbine**	**1.21e-01 mg/ml ; 3.26e-04 mol/l**	**High**	**No**	**Yes**
234	**Isosandwicine**	**2.46e-01 mg/ml ; 7.53e-04 mol/l**	**High**	**Yes**	**Yes**
235	**Ajmalicidine**	**3.73e-02 mg/ml ; 1.01e-04 mol/l**	**High**	**Yes**	**Yes**
236	**Indoline**	**6.14e-01 mg/ml ; 5.15e-03 mol/l**	**High**	**No**	**Yes**
237	**12-Hydroxyajmaline**	**3.52e-01 mg/ml ; 1.03e-03 mol/l**	**High**	**No**	**Yes**
238	**3,4,5,6-Tetradehydroyohimbine**	**3.64e-02 mg/ml ; 1.04e-04 mol/l**	**High**	**Yes**	**Yes**
239	**17-O-acetylajmaline**	**9.46e-02 mg/ml ; 2.57e-04 mol/l**	**High**	**Yes**	**Yes**
240	**1,2-Dihydrovomilenine**	**1.67e-01 mg/ml ; 4.74e-04 mol/l**	**High**	**Yes**	**Yes**
241	**Raunescine**	**1.20e-03 mg/ml ; 2.12e-06 mol/l**	**High**	**No**	**Yes**
242	**7-Epiloganin**	**3.44e+01 mg/ml ; 8.82e-02 mol/l**	**Low**	**No**	**Yes**

243	**Alstonine**	**4.77e-02 mg/ml ; 1.37e-04 mol/l**	**High**	**Yes**	**Yes**
244	**Normacusine B**	**1.78e-01 mg/ml ; 6.04e-04 mol/l**	**High**	**Yes**	**Yes**
245	**7-Dehydrositosterol**	**1.26e-05 mg/ml ; 3.05e-08 mol/l**	**Low**	**No**	**Yes**
246	**Thebaine**	**1.89e-01 mg/ml ; 6.06e-04 mol/l**	**High**	**Yes**	**Yes**
247	**Geissoschizol**	**1.39e-01 mg/ml ; 4.69e-04 mol/l**	**High**	**Yes**	**Yes**
248	**Secoxyloganin**	**5.90e+01 mg/ml ; 1.46e-01 mol/l**	**Low**	**No**	**Yes**
249	**Diisobutyl phthalate**	**3.94e-02 mg/ml ; 1.42e-04 mol/l**	**High**	**Yes**	**Yes**
250	**Loganic Acid**	**5.54e+01 mg/ml ; 1.47e-01 mol/l**	**Low**	**No**	**Yes**
251	**Reserpine N-Oxide**	**3.14e-02 mg/ml ; 7.88e-05 mol/l**	**High**	**Yes**	**Yes**
252	**Yohimbic Acid**	**1.49e+00 mg/ml ; 4.38e-03 mol/l**	**High**	**No**	**Yes**
253	**Isorauhimbinic Acid**	**1.49e+00 mg/ml ; 4.38e-03 mol/l**	**High**	**No**	**Yes**
254	**2,6-Dimethoxy-1,4-benzoquinone**	**3.26e+01 mg/ml ; 1.94e-01 mol/l**	**High**	**No**	**Yes**
255	**18-Hydroxyepialloyohimbine**	**1.21e-01 mg/ml ; 3.26e-04 mol/l**	**High**	**No**	**Yes**
256	**Isoajmaline**	**2.46e-01 mg/ml ; 7.53e-04 mol/l**	**High**	**Yes**	**Yes**
257	**6Alpha-Hydroxyraumacline**	**3.41e-01 mg/ml ; 9.97e-04 mol/l**	**High**	**Yes**	**Yes**
258	**Aricine**	**4.15e-02 mg/ml ; 1.08e-04 mol/l**	**High**	**Yes**	**Yes**
259	**Isoreserpiline**	**3.68e-02 mg/ml ; 8.91e-05 mol/l**	**High**	**Yes**	**Yes**
260	**3,4,5-Trimethoxybenzoic Acid**	**1.68e+00 mg/ml ; 7.92e-03 mol/l**	**High**	**Yes**	**Yes**
261	**Allo-Yohimbine**	**3.43e-02 mg/ml ; 9.69e-05 mol/l**	**High**	**Yes**	**Yes**
262	**Cadaverine**	**1.46e+02 mg/ml ; 1.43e+00 mol/l**	**High**	**No**	**Yes**
263	**Trimethylamine**	**2.52e+01 mg/ml ; 4.26e-01 mol/l**	**Low**	**No**	**Yes**
264	**Dimethyl Sulfide**	**1.03e+01 mg/ml ; 1.66e-01 mol/l**	**High**	**Yes**	**Yes**
265	**Capsaicin**	**9.00e-02 mg/ml ; 2.95e-04 mol/l**	**High**	**Yes**	**Yes**

266	Tetramethylenebis[di(2-cyanoethyl)phosphine]	1.06e+02 mg/ml ; 3.16e-01 mol/l	High	No	Yes
267	Phosgene	2.45e+00 mg/ml ; 2.48e-02 mol/l	High	Yes	Yes
268	Clionasterol	5.23e-06 mg/ml ; 1.26e-08 mol/l	Low	No	Yes
269	Pyrimidine	1.20e+01 mg/ml ; 1.50e-01 mol/l	High	No	Yes
270	Purine	9.73e+00 mg/ml ; 8.10e-02 mol/l	High	No	Yes
271	Cannabiscitrin	5.93e-01 mg/ml ; 1.23e-03 mol/l	Low	No	No
272	Acetoside	8.36e-01 mg/ml ; 1.34e-03 mol/l	Low	No	No
273	Jaceoside	5.60e-02 mg/ml ; 1.14e-04 mol/l	Low	No	No
274	Sophoraflavonoloside	7.97e-01 mg/ml ; 1.31e-03 mol/l	Low	No	No
275	Orientin	9.00e-01 mg/ml ; 2.01e-03 mol/l	Low	No	No
276	Isoquercitrin	4.23e-01 mg/ml ; 9.10e-04 mol/l	Low	No	No
277	Eruberin B	8.03e-01 mg/ml ; 1.25e-03 mol/l	Low	No	No
278	Eruberin C	3.61e-01 mg/ml ; 5.51e-04 mol/l	Low	No	No
279	Quercitrin	2.08e-01 mg/ml ; 4.64e-04 mol/l	Low	No	No
280	Aconitine	2.63e-01 mg/ml ; 4.07e-04 mol/l	Low	No	No
281	Veratrine	1.28e-01 mg/ml ; 2.17e-04 mol/l	Low	No	No
282	Nicotiflorin	9.31e-03 mg/ml ; 1.57e-05 mol/l	Low	No	No
283	Narcissin	1.92e-01 mg/ml ; 3.07e-04 mol/l	Low	No	No
284	Rutin	3.08e-01 mg/ml ; 5.05e-04 mol/l	Low	No	No
285	Meratin	2.44e+00 mg/ml ; 3.89e-03 mol/l	Low	No	No
286	Spiraeoside	1.07e-01 mg/ml ; 2.29e-04 mol/l	Low	No	No
287	Hyperoside	4.23e-01 mg/ml ; 9.10e-04 mol/l	Low	No	No
288	Quercetin 3-Sambubioside	1.23e+00 mg/ml ; 2.06e-03 mol/l	Low	No	No
289	Quercimeritrin	4.23e-01 mg/ml ; 9.10e-04 mol/l	Low	No	No

290	**Cyanin**	**1.35e+01 mg/ml ; 2.21e-02 mol/l**	**Low**	**No**	**No**
291	**Cyanidin 3-sophoroside**	**1.83e+00 mg/ml ; 2.99e-03 mol/l**	**Low**	**No**	**No**
292	**Quercetin 3-diglucoside**	**2.44e+00 mg/ml ; 3.89e-03 mol/l**	**Low**	**No**	**No**
293	**Cyanin chloride**	**2.74e+00 mg/ml ; 4.23e-03 mol/l**	**Low**	**No**	**No**
294	**Alpha-Carotene**	**4.19e-09 mg/ml ; 7.80e-12 mol/l**	**Low**	**No**	**No**
295	**Quercetin-3,7-diglucoside**	**1.49e+00 mg/ml ; 2.38e-03 mol/l**	**Low**	**No**	**No**
296	**Kaempferol 3-xylosylglucoside**	**1.02e+00 mg/ml ; 1.76e-03 mol/l**	**Low**	**No**	**No**
297	**Gossypitrin**	**5.93e-01 mg/ml ; 1.23e-03 mol/l**	**Low**	**No**	**No**
298	**Hydnowightin**	**1.67e-04 mg/ml ; 2.60e-07 mol/l**	**Low**	**No**	**No**
299	**Amentoflavone**	**9.63e-05 mg/ml ; 1.79e-07 mol/l**	**Low**	**No**	**No**
300	**Ajugamacrin B**	**1.96e-02 mg/ml ; 3.31e-05 mol/l**	**Low**	**No**	**No**
301	**Ajugapantin A**	**1.87e-01 mg/ml ; 3.39e-04 mol/l**	**Low**	**No**	**No**
302	**Folic Acid**	**1.09e+01 mg/ml ; 2.48e-02 mol/l**	**Low**	**No**	**No**
303	**Reserpine**	**1.08e-03 mg/ml ; 1.77e-06 mol/l**	**High**	**No**	**No**
304	**Rescinnamine**	**4.97e-04 mg/ml ; 7.82e-07 mol/l**	**High**	**No**	**No**
305	**Strictosidine**	**3.72e-01 mg/ml ; 7.00e-04 mol/l**	**Low**	**No**	**No**
306	**Glomeratose A**	**1.44e+01 mg/ml ; 2.56e-02 mol/l**	**Low**	**No**	**No**
307	**Swertiaside**	**1.03e+00 mg/ml ; 2.07e-03 mol/l**	**Low**	**No**	**No**
308	**Rescinnamidine**	**7.53e-04 mg/ml ; 1.18e-06 mol/l**	**High**	**No**	**No**

Table SM 2: Binding affinity of the ligands (i.e. phytochemicals) with the chosen receptors.

Sl. No.	Phytochemical Name	Interaction with Proteins		
		VEGFR2 Binding Energy (in kcal/mol)	VEGFR1 Binding Energy (in kcal/mol)	EGFR Binding Energy (in kcal/mol)
1	Myrcene	-4.8	-4.8	-5.1
2	Tricyclene	-5.6	-6.6	-5.6
3	Citronellyl Acetate	-5.0	-6.4	-5.6
4	d-Borneol	-5.8	-5.3	-5.8
5	Geranyl Acetate	-4.8	-6.9	-6.1
6	Beta-Phellandrene	-5.6	-6.7	-5.8
7	Camphor	-5.3	-5.3	-5.7
8	Alpha-Pinene	-7.0	-5.4	-5.6
9	O-Cymene	-5.6	-5.5	-5.6
10	Thymol methyl ether	-4.7	-5.8	-5.6
11	Isogermacrene D	-6.9	-6.3	-6.6
12	Vanillic Acid	-5.3	-6.2	-6.1
13	Naphthalene	-5.9	-7.1	-5.9
14	Syringin	-9.4	-9.1	-9.5
15	Tannic Acid	-9.3	-8.3	-9.5
16	Mannitol	-4.4	-5.0	-4.7
17	2-C-Methyl-D-Erythritol	-4.3	-4.5	-4.5
18	Hyoscine	-7.5	-7.3	-7.3
19	Hyoscyamine	-5.8	-5.8	-6.4
20	Betulin	-8.3	-8.4	-8.5
21	Alpha-Amyrin	-9.8	-9.2	-9.9
22	Beta-Sitosterol	-7.8	-7.5	-8.7
23	N,N-Dimethyl-5-Methoxytryptamine	-6.0	-5.5	-6.2
24	Linoleic Acid	-4.9	-6.5	-5.8
25	Digitolutein	-8.2	-7.7	-8.8

26	**Digitoxigenin**	**-7.8**	**-9.0**	**-8.2**
27	**Ursolic Acid**	**-9.5**	**-8.8**	**-9.8**
28	**Ellagic Acid**	**-7.7**	**-6.9**	**-8.8**
29	**Betulinic Acid**	**-7.5**	**-8.2**	**-8.5**
30	**Cadalene**	**-7.6**	**-6.4**	**-7.6**
31	**Hexadecane**	**-4.7**	**-3.2**	**-4.7**
32	**Chrysanthenone**	**-5.1**	**-5.3**	**-6.1**
33	**Carvacrol**	**-7.6**	**-7.3**	**-6.0**
34	**Geranylacetone**	**-5.6**	**-5.2**	**-5.7**
35	**Jasmone**	**-5.5**	**-5.7**	**-6.0**
36	**Ilicic Acid**	**-6.9**	**-6.2**	**-7.3**
37	**3-Octanol**	**-5.5**	**-5.3**	**-4.4**
38	**3-Octanone**	**-5.4**	**-5.2**	**-4.4**
39	**Acetophenone**	**-6.2**	**-6.2**	**-5.2**
40	**Eucalyptol**	**-5.3**	**-5.5**	**-5.6**
41	**Byakangelicin**	**-5.9**	**-6.0**	**-7.8**
42	**Coumarin**	**-7.3**	**-6.0**	**-6.0**
43	**Limonin**	**-8.7**	**-9.5**	**-9.0**
44	**Ostruthin**	**-5.8**	**-4.8**	**-6.2**
45	**Ascorbic Acid**	**-4.3**	**-5.3**	**-5.6**
46	**Luteolin**	**-10.3**	**-8.3**	**-8.7**
47	**Apigenin**	**-7.7**	**-7.9**	**-8.9**
48	**Vitexin**	**-8.1**	**-7.7**	**-9.8**
49	**Lycorenine**	**-6.8**	**-6.8**	**-8.2**
50	**Isovitexin**	**-8.4**	**-8.2**	**-9.4**
51	**4-Hydroxybenzoic Acid**	**-6.0**	**-6.0**	**-6.3**
52	**Hellebrigenin**	**-7.7**	**-7.9**	**-7.8**
53	**Dtxsid10942442**	**-8.2**	**-8.9**	**-8.1**
54	**Corytuberine**	**-7.4**	**-6.4**	**-8.5**
55	**Magnoflorine**	**-6.6**	**-7.0**	**-8.7**
56	**Methoxsalen**	**-6.7**	**-5.4**	**-6.9**
57	**Luvangetin**	**-7.9**	**-6.0**	**-7.6**
58	**Umbelliferone**	**-6.0**	**-7.3**	**-6.3**
59	**Obacunone**	**-8.1**	**-9.1**	**-9.0**

60	**4-Methoxy-1-Methylquinolin-2-one**	**-6.0**	**-5.1**	**-6.3**
61	**Bergapten**	**-6.8**	**-6.5**	**-7.0**
62	**Psoralen**	**-6.4**	**-6.3**	**-6.9**
63	**Marmesin**	**-6.4**	**-7.8**	**-8.0**
64	**Lupeol**	**-9.0**	**-8.6**	**-9.2**
65	**Suberosin**	**-5.9**	**-6.1**	**-7.5**
66	**Lauric Acid**	**-9.7**	**-6.0**	**-8.4**
67	**Acidissiminol**	**-5.3**	**-8.1**	**-8.2**
68	**Azulene**	**-7.6**	**-6.2**	**-5.9**
69	**Anthraquinone**	**-6.5**	**-6.5**	**-8.0**
70	**Lactic Acid**	**-3.7**	**-4.3**	**-3.9**
71	**Quinic Acid**	**-5.5**	**-5.4**	**-6.0**
72	**Quinoline**	**-6.9**	**-5.8**	**-5.8**
73	**1,4-Benzoquinone**	**-5.3**	**-4.4**	**-4.9**
74	**Quinine**	**-6.6**	**-6.8**	**-7.3**
75	**Quinolone**	**-4.9**	**-5.4**	**-6.0**
76	**Quinol**	**-5.3**	**-5.1**	**-5.1**
77	**Quinidine**	**-6.8**	**-6.7**	**-7.5**
78	**p-Cymene**	**-7.3**	**-6.7**	**-5.5**
79	**Terpinolene**	**-7.2**	**-5.9**	**-5.6**
80	**Beta-Eudesmol**	**-7.2**	**-7.0**	**-7.7**
81	**Gamma-Eudesmol**	**-7.6**	**-6.8**	**-7.4**
82	**Sebacic Acid**	**-4.8**	**-4.1**	**-4.6**
83	**Camphane**	**-6.0**	**-5.2**	**-5.4**
84	**Alpha-Curcumene**	**-5.6**	**-6.6**	**-6.7**
85	**Beta-Pinene**	**-5.5**	**-5.6**	**-5.6**
86	**Linalool**	**-4.1**	**-5.1**	**-5.3**
87	**Thujone**	**-5.4**	**-4.7**	**-5.8**
88	**Camphene**	**-6.3**	**-5.3**	**-5.6**
89	**Geraniol**	**-5.1**	**-5.2**	**-5.5**
90	**Limonene**	**-5.4**	**-6.6**	**-5.7**
91	**Osthenol**	**-7.4**	**-6.4**	**-7.5**
92	**Auraptene**	**-5.7**	**-6.1**	**-7.5**
93	**Osthole**	**-5.8**	**-6.2**	**-6.4**

94	**Stigmasterol**	**-8.3**	**-8.3**	**-9.9**
95	**Epoxysuberosin**	**-5.4**	**-6.6**	**-6.1**
96	**Dihydrosuberenol**	**-5.9**	**-7.0**	**-7.2**
97	**Isopimpinellin**	**-5.6**	**-5.1**	**-6.5**
98	**Hautriwaic Acid**	**-7.8**	**-6.1**	**-7.8**
99	**Demethylnobiletin**	**-6.7**	**-7.0**	**-8.0**
100	**Farnesol**	**-5.1**	**-5.6**	**-6.2**
101	**Flavylium**	**-10.2**	**-7.5**	**-8.2**
102	**Beta-Sitostenone**	**-5.5**	**-5.8**	**-8.7**
103	**Kaempferol**	**-7.8**	**-7.9**	**-8.7**
104	**Quercetin**	**-7.6**	**-7.1**	**-8.9**
105	**1-Tetratriacontanol**	**-8.8**	**-9.1**	**-6.3**
106	**Guaijaverin**	**-8.3**	**-7.7**	**-9.7**
107	**Ferulic Acid**	**-6.0**	**-6.0**	**-6.3**
108	**Stigmasta-4-ene-one**	**-9.6**	**-7.4**	**-8.9**
109	**Naringetol**	**-7.7**	**-8.2**	**-8.6**
110	**Eriodictyol**	**-7.9**	**-7.9**	**-8.6**
111	**Sterculic Acid**	**-5.2**	**-4.2**	**-5.5**
112	**Malvalic Acid**	**-4.4**	**-5.5**	**-5.4**
113	**8-Nonynoic Acid**	**-3.7**	**-3.4**	**-4.5**
114	**9-Decynoic Acid**	**-3.6**	**-3.5**	**-4.2**
115	**Thiamine**	**-5.5**	**-5.8**	**-6.4**
116	**Riboflavin**	**-5.9**	**-6.1**	**-7.0**
117	**Cyanidin chloride**	**-7.5**	**-6.8**	**-8.4**
118	**Taraxerol Acetate**	**-9.9**	**-9.6**	**-9.5**
119	**Nicotinic Acid**	**-4.4**	**-5.2**	**-5.3**
120	**Stigmast-5-ene-3Beta,4Alpha-diol**	**-7.9**	**-8.2**	**-9.0**
121	**D-Glucuronic Acid**	**-5.3**	**-5.5**	**-5.8**
122	**Methyl malvalate**	**-3.9**	**-4.1**	**-5.2**
123	**L-Rhamnose**	**-5.3**	**-5.1**	**-5.3**
124	**D-Galacturonic Acid**	**-5.3**	**-5.5**	**-5.9**
125	**D-Galactose**	**-5.0**	**-5.0**	**-5.5**
126	**Hibiscetin**	**-8.8**	**-8.0**	**-8.8**
127	**Citric Acid**	**-5.2**	**-5.0**	**-5.6**

128	2-Hydroxycinnamic Acid	-6.9	-6.0	-6.1
129	d-Tartaric Acid	-4.4	-4.5	-4.8
130	Gossypetin	-7.9	-8.2	-8.9
131	Myricetin	-7.9	-6.9	-8.9
132	Myristic Acid	-4.5	-4.4	-5.2
133	Ergosterol	-9.3	-8.9	-9.3
134	Palmitic Acid	-3.7	-4.1	-4.6
135	Dihydrosterculic Acid	-4.7	-4.6	-5.9
136	Acetylursolic Acid	-9.5	-8.8	-9.5
137	Chrysoeriol	-8.1	-8.7	-9.0
138	Isohydnocarpin	-8.3	-8.9	-9.1
139	Hydnocarpin	-9.2	-8.0	-9.4
140	Neohydnocarpin	-8.2	-7.8	-7.8
141	Beta-Amyrin	-9.5	-8.9	-9.3
142	Actinodaphnine	-6.8	-6.9	-9.2
143	Canthin-6-one	-7.9	-6.2	-8.1
144	6H-Indolo(3,2,1-de)(1,5)Naphthyridin-6-one	-6.1	-6.1	-8.1
145	Moupinamide	-7.9	-6.3	-8.0
146	Ervoside	-7.8	-7.2	-8.9
147	Syringic Acid	-5.4	-4.7	-5.7
148	10-Hydroxycanthin-6-one	-8.0	-6.5	-8.1
149	Stigmasterol Acetate	-9.3	-7.6	-9.2
150	Glycerol	-3.4	-3.6	-3.9
151	Isoginkgetin	-9.3	-8.5	-10.1
152	Amentoflavone dimethyl ether	-9.5	-8.5	-8.5
153	Podolide	-7.3	-7.5	-8.8
154	Sugiol	-8.0	-8.3	-8.2
155	Totarol	-8.1	-6.7	-8.4
156	Podocarpusflavone A	-9.5	-9.2	-9.7

157	**Benzene**	**-4.8**	**-4.6**	**-3.8**
158	**Toluene**	**-5.5**	**-5.3**	**-4.5**
159	**Palmitoleic Acid**	**-4.7**	**-4.8**	**-5.2**
160	**Oleic Acid**	**-6.0**	**-4.6**	**-5.2**
161	**Epibetulinic Acid**	**-8.5**	**-8.2**	**-8.6**
162	**Ajugacumbin B**	**-7.8**	**-7.4**	**-7.4**
163	**Linolenic Acid**	**-7.4**	**-4.7**	**-5.8**
164	**9-Decenoic Acid**	**-4.5**	**-3.6**	**-5.0**
165	**Retinol**	**-6.1**	**-6.0**	**-7.7**
166	**Niacin**	**-5.4**	**-4.6**	**-5.3**
167	**Pantothenic Acid**	**-4.3**	**-4.2**	**-5.5**
168	**Pyridoxine**	**-4.5**	**-4.5**	**-5.1**
169	**Biotin**	**-4.9**	**-4.6**	**-6.4**
170	**Phytonadione**	**-5.3**	**-6.6**	**-7.0**
171	**Adenine**	**-4.8**	**-5.1**	**-5.4**
172	**Guanine**	**-4.9**	**-5.0**	**-5.2**
173	**Cytosine**	**-3.9**	**-4.3**	**-4.9**
174	**Thymidine**	**-5.8**	**-6.2**	**-7.2**
175	**Thymine**	**-4.6**	**-4.8**	**-5.2**
176	**Uracil**	**-4.1**	**-4.0**	**-4.6**
177	**Adenosine**	**-6.7**	**-6.5**	**-7.1**
178	**Nicotinamide**	**-4.3**	**-4.6**	**-5.1**
179	**Nicotin**	**-5.4**	**-5.4**	**-5.6**
180	**Benzyl isothiocyanate**	**-4.0**	**-4.0**	**-4.0**
181	**Allyl Isothiocyanate**	**-2.5**	**-2.7**	**-3.1**
182	**Thiirane Acetonitrile**	**-3.5**	**-3.8**	**-3.6**
183	**Diallyl Sulfide**	**-3.9**	**-3.3**	**-3.4**
184	**[(Z)-1-[3,4,5-Trihydroxy-6-(Hydroxymethyl)Oxan-2-yl]Sulfanylbut-3-enylideneamino]Sulfate**	**-6.2**	**-6.3**	**-6.9**
185	**Cardenolide 2**	**-7.9**	**-9.7**	**-8.6**
186	**Sinigrin**	**-5.7**	**-5.5**	**-7.2**

187	**3-Butenyl Isothiocyanate**	**-2.8**	**-3.1**	**-3.5**
188	**Glucotropaeolin**	**-6.8**	**-7.1**	**-8.1**
189	**Aspirin**	**-5.1**	**-5.7**	**-6.3**
190	**Metronidazole**	**-4.8**	**-4.6**	**-5.3**
191	**2-Furoic Acid**	**-5.0**	**-4.7**	**-4.8**
192	**Echitamine**	**-6.7**	**-7.4**	**-7.2**
193	**Squalene**	**-4.3**	**-5.2**	**-6.6**
194	**5,7-Dihydroxy-3,6,8-trimethoxyflavone**	**-7.3**	**-6.6**	**-7.7**
195	**Araneosol**	**-7.5**	**-7.0**	**-7.6**
196	**Helipyrone**	**-7.3**	**-7.1**	**-6.3**
197	**Anisodamine**	**-7.5**	**-6.4**	**-7.5**
198	**Scopine**	**-4.1**	**-4.7**	**-5.6**
199	**Tropine**	**-4.7**	**-5.2**	**-5.3**
200	**Scopoline**	**-5.3**	**-4.7**	**-5.2**
201	**Scopoletin**	**-5.3**	**-5.9**	**-6.4**
202	**Chlorogenic Acid**	**-6.1**	**-6.7**	**-7.8**
203	**Caffeic Acid**	**-5.9**	**-7.0**	**-6.1**
204	**Cuskhygrine**	**-5.6**	**-4.3**	**-6.0**
205	**Cuscohygrine**	**-4.7**	**-4.5**	**-4.6**
206	**Scopolin**	**-7.4**	**-6.7**	**-8.9**
207	**Caffeine**	**-5.5**	**-5.0**	**-6.2**
208	**Cocaine**	**-7.2**	**-5.5**	**-7.0**
209	**Morphine**	**-7.4**	**-7.4**	**-7.8**
210	**Heroin**	**-8.0**	**-6.9**	**-8.5**
211	**Methamphetamine**	**-5.5**	**-5.6**	**-5.3**
212	**Lysergic Acid diethylamide**	**-7.6**	**-6.8**	**-8.4**
213	**Alpha-Pyrrolidinopentiophenone**	**-6.5**	**-5.3**	**-6.7**
214	**Papaverine**	**-5.7**	**-5.9**	**-7.4**
215	**Tetraphylline**	**-7.1**	**-7.2**	**-8.6**
216	**Serpentine (alkaloid)**	**-6.5**	**-7.1**	**-8.9**
217	**Reserpiline**	**-6.8**	**-6.8**	**-8.5**
218	**Deserpidine**	**-7.7**	**-8.5**	**-8.5**

219	**Ajmalicine**	**-6.6**	**-7.0**	**-8.7**
220	**Isorauhimbine**	**-6.9**	**-6.6**	**-8.6**
221	**Yohimbine**	**-7.4**	**-7.7**	**-9.4**
222	**Corynanthine**	**-6.8**	**-7.9**	**-7.9**
223	**Tubotaiwine**	**-6.1**	**-6.6**	**-7.1**
224	**Tetrahydroalstonine**	**-7.6**	**-8.1**	**-8.6**
225	**Akuammigine**	**-6.5**	**-8.0**	**-8.6**
226	**Rauniticine**	**-8.3**	**-6.9**	**-8.2**
227	**Rauwolscine**	**-7.7**	**-7.6**	**-8.1**
228	**Beta-Yohimbine**	**-8.9**	**-7.7**	**-8.9**
229	**Ajmaline**	**-8.7**	**-7.7**	**-8.3**
230	**Vincoside lactam**	**-8.1**	**-9.7**	**-9.4**
231	**Ajmalidine**	**-6.8**	**-8.1**	**-8.8**
232	**18-Beta-hydroxy-3-Epi-Alpha-Yohimbine**	**-7.0**	**-7.0**	**-8.8**
233	**Isosandwicine**	**-8.9**	**-6.9**	**-8.6**
234	**Ajmalicidine**	**-8.4**	**-7.1**	**-8.6**
235	**Indoline**	**-6.2**	**-5.2**	**-5.3**
236	**12-Hydroxyajmaline**	**-7.8**	**-6.4**	**-8.4**
237	**3,4,5,6-Tetradehydroyohimbine**	**-9.5**	**-7.6**	**-9.8**
238	**17-O-acetylajmaline**	**-7.2**	**-7.3**	**-8.5**
239	**1,2-Dihydrovomilenine**	**-7.7**	**-7.8**	**-8.8**
240	**Raunescine**	**-8.2**	**-8.5**	**-9.0**
241	**7-Epiloganin**	**-6.8**	**-6.4**	**-7.7**
242	**Alstonine**	**-7.0**	**-7.5**	**-9.0**
243	**Normacusine B**	**-8.5**	**-8.3**	**-8.6**
244	**7-Dehydrositosterol**	**-8.5**	**-7.9**	**-8.9**
245	**Thebaine**	**-7.4**	**-6.7**	**-7.8**
246	**Geissoschizol**	**-8.2**	**-7.0**	**-8.4**
247	**Secoxyloganin**	**-5.3**	**-6.1**	**-6.4**
248	**Diisobutyl phthalate**	**-5.4**	**-5.5**	**-6.9**
249	**Loganic Acid**	**-6.4**	**-6.6**	**-7.6**
250	**Reserpine N-Oxide**	**-8.5**	**-7.9**	**-8.3**

251	**Yohimbic Acid**	**-9.0**	**-7.7**	**-9.7**
252	**Isorauhimbinic Acid**	**-8.7**	**-7.9**	**-9.0**
253	**2,6-Dimethoxy-1,4-benzoquinone**	**-4.4**	**-4.9**	**-5.3**
254	**18-Hydroxyepialloyohimbine**	**-6.8**	**-6.8**	**-8.5**
255	**Isoajmaline**	**-8.9**	**-7.3**	**-8.7**
256	**6Alpha-Hydroxyraumacline**	**-7.1**	**-7.2**	**-7.1**
257	**Aricine**	**-6.7**	**-7.2**	**-8.8**
258	**Isoreserpiline**	**-7.7**	**-7.0**	**-8.8**
259	**3,4,5-Trimethoxybenzoic Acid**	**-4.7**	**-5.1**	**-5.8**
260	**Allo-Yohimbine**	**-9.0**	**-8.7**	**-8.9**
261	**Cadaverine**	**-3.7**	**-3.9**	**-4.0**
262	**Trimethylamine**	**-2.2**	**-2.3**	**-2.2**
263	**Dimethyl Sulfide**	**-1.8**	**-1.8**	**-1.8**
264	**Capsaicin**	**-6.4**	**-5.3**	**-6.3**
265	**Tetramethylenebis[di(2-cyanoethyl)phosphine]**	**-3.6**	**-3.9**	**-2.9**
266	**Phosgene**	**-2.9**	**-2.8**	**-2.8**
267	**Clionasterol**	**-7.6**	**-8.2**	**-9.1**
268	**Pyrimidine**	**-3.6**	**-3.6**	**-3.6**
269	**Purine**	**-4.3**	**-4.6**	**-5.0**

ABSTRACT

Understanding how ligands will attach to receptors is crucial for both molecular biology and medication development. Due to its ability to anticipate ligand-receptor interactions precisely, this approach necessitates the use of the computational method known as molecular docking. In order to evaluate several phytochemicals as prospective anti-cancer medications and take into account their potential applications, this thesis will look at them. A new comparative investigation reveals that just 3.4% of cancer treatments are effective, compared to a success rate of 20.9% for all oncology medications. Although there were numerous anti-cancer medications available at the time, the basic issue is that they are less effective than other oncology drugs, which have a success rate of 20.9%. In addition, not all cancer drugs that pass Phase III trials necessarily offer a therapeutic benefit to a wider population. The immune system is also stimulated by such treatments, which has a number of negative consequences including anemia, diarrhea, appetite loss etc. To find more potent anti-cancer drugs, further investigation is being done. These phytochemicals are produced by a wide variety of plants and have beneficial medicinal properties. These plants are mentioned in Ayurveda as well. The names of several medicinal plants may also be found in Indian Medicinal Plants, Phytochemistry and Therapeutics. There are 4010 Indian medicinal plants, 17967 phytochemicals, and 1095 therapeutic uses present in the IMPPAT database. Our objective was to find phytochemicals that may combat cancer more successfully and with fewer side effects. To achieve this, molecular docking is a great method for examining the bonds between protein and phytochemicals. The most well-liked and useful tool for molecular docking is AutoDock Vina. SwissADME is a tool that allows us to assess the ligand's ADMET qualities, such as its solubility, BB penetration, and GI absorption level, as well as whether the ligand (in this example, a phytochemical) violates Lipinski's rule of five for the possibility that a molecule is a medication.

Keywords: cancer, phytochemical, ADMET, multi-target, molecular docking, VEGFR1, VEGFR2, EGFR

CHAPTER 1:

INTRODUCTION

1.1 BACKGROUND:

Finding the disease's causes would help researchers create plans for early detection, precise diagnosis, efficient treatment, and ultimately eradication. The government provides the majority of funding for cancer research that is conducted in academic, research, and commercial contexts.

History: The father of contemporary chemotherapy is considered as Sidney Farber. For millennia, scientists have been studying cancer. Early studies centred on cancer's causes (Wong C.H. et al., 2019). In 1775, Percivall Pott discovered the first environmental cause of cancer, chimney soot, and in 1950, lung cancer was linked to smoking cigarettes. Early cancer therapies concentrated on honing surgical methods for tumor removal. In the 1900s, radiation therapy gained popularity. The 20th century saw the development and improvement of chemotherapy. According to Hay, M., et al. (2014), the United States proclaimed a "War on Cancer" in the 1970s and expanded funding and support for cancer research. The Hallmarks of Cancer by Douglas Hanahan and Robert Weinberg, published in 2000, and Hallmarks of Cancer: The Next Generation, released in 2011, are two of the most cited and significant research studies. Over 30,000 academic papers have cited these articles collectively.

1.2 RESEARCH OBJECTIVES:

Human body is made of organs and tissues. Organs and Tissues are made of Cells. Old cell dies and new cell take place of that new cell as a natural process. When there is any disturbance in this natural order like virus, cell mutation, carcinogenic chemical etc, the old cell may develop cancerous property i.e, it does not die and starts to divide uncontrollably and diverts the nutrients of the body to itself for its own growth like a parasite or a separate organism. Our cells have several mechanisms for cell death like Apoptosis and Pyroptosis. Due to previous mentioned reasons this process may be hampered and Cancer starts to develop. This thesis intends to identify and assess phytochemicals with Anti-Cancer characteristics using computational methods, particularly molecular docking. Anti-Cancer characteristic may be defined as inhibition of cancer growth, death of existing cancer cell. The main goal is to find the potential ligands which can alter target proteins involved in cancer growth, in the process of uncontrolled cell division. The study also aims to evaluate the therapeutic potential of the identified phytochemicals and clarify the molecular mechanisms underlying their Anti-Cancer effects.

The following research questions are addressed in the thesis:

- Which phytochemicals have the maximum binding affinity and have the greatest potential in Cancer Treatments?
- What are the main molecular interactions and processes through which these phytochemicals influence the pathways leading to Cancer?

1.3 RESEARCH ISSUES:

Manual work of finding random phytochemicals, finding its 3-D structure in SDF format, Converting it to (.pdb), Modifying it to (.pdbqt) format and then individually docking with each protein is very much time consuming and succession is also dependent on the processor of PC. Added to it, simulation cannot be done in normal PC, because it may take week to month. That's why high power Super Computer is needed simulation, which is not accessible to everyone.

CHAPTER 2:

LITERATURE REVIEW

As part of the drug discovery process, a particular chemical molecule with the required biological activity on the target can be picked. This platform employs many techniques to investigate compounds and targets from various perspectives. As medication development and discovery are both labor- and resource-intensive procedures, so they provide a number of challenges for researchers working on varied illnesses including different forms of cancer. As a result, the use of new technologies may help finding new-age drugs which have excellent therapeutic potential. This would be a huge development in the treatment of disease. Compound screening assays, that can help with grand discovery, verification, creating prospects, procedure improvements are covered. One of the approaches for that are Evaluation of the effects of the compounds on the therapeutic objective. As a result of technology improvements and the fusion of computational methods with biological and pharmacological investigations, methods like virtual screening are routinely utilized in drug developing and discovery.

2.1 MECHANISMS OF CANCER:

Years of research have shown that improving patient outcomes requires a thorough understanding of the fundamental mechanics of cancer, including how it develops, why it persists, and how it spreads throughout the body. Patients will benefit from new fields of fundamental cancer research that examine the differences between individual cells with tumors, the effects of the environment on tumor growth, and the effectiveness of an individual's immune system in mounting a defense. Currently, cancer researchers are using novel methods, technologies, and instruments to increase their understanding of the mechanisms behind cancer. Researchers are looking into minute differences that affect the behavior of cancer cells, not just between individuals or cancer kinds but also within the various cell types that make up a single tumor. At the same time, scientists are shifting their attention from tumors to other parts of the body to understand how those elements affect a patient's sickness. Studies of cancer biology have until now mostly concentrated on how tumor cells vary from healthy cells. But it is now obvious that different tumor cells can exist even within a single tumor. The ability to divide and support the tumor's growth may only be present in a tiny subset of a tumor's cells. Given that this diversity has significant clinical repercussions, it will be crucial to comprehend human cancer on a cell-by-cell basis, we now know. Researchers can now analyze the DNA, RNA, and proteins of thousands of individual cells using recently developed high-throughput technologies to describe this heterogeneity and learn how it impacts tumor growth, metastasis, and patients' responses to treatment. It is

now clear that a tumor's ability to grow is influenced by factors other than the characteristics of its own cells. Equally important are the milieu in which a tumor develops and the ferocity with which the body's immune system detects and combats malignancies. Understanding the connections between tumors and their microenvironments is a difficult task. At some point, we will need to understand the signals that tumors transmit to adjacent immune cells and identify the environmental factors that influence whether a tumor remains small and benign or spreads rapidly. **Figure-1** illustrates that under a microscope how a malignant tissue uses the circulatory system of its host to grow. Three enzymes or proteins are the key growth factors in the human body's cancer-causing mechanism. These are listed below:

1. **VEGFR1 (PDB CID: 3HNG)**
2. **VEGFR2 (PDB CID: 3VHE)**
3. **EGFR (PDB CID: 1M17)**

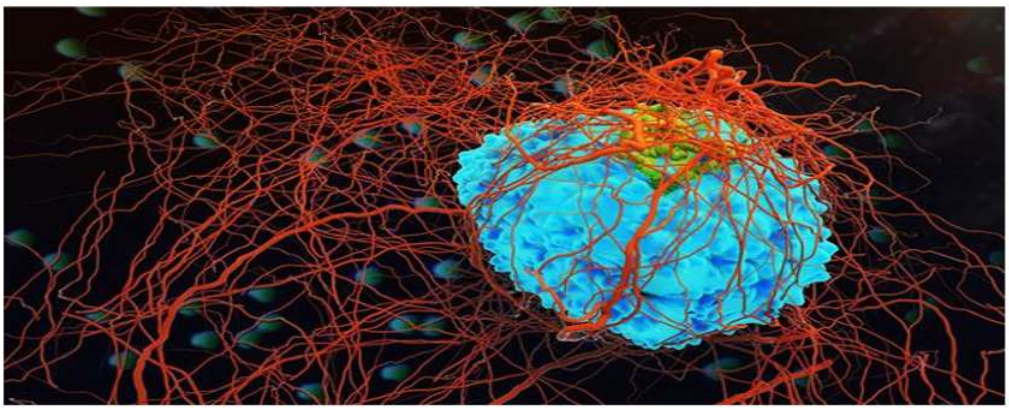


Figure-1: Cancerous Tissue

It makes sense that targeted medicines would be developed to hinder certain molecular functions that are essential for the survival, development, or growth of malignancies. A variety of targeted drugs with anti-tumor action provide objective responses like delay the progression of illness, prolong patient survival with advanced malignancies in human cancer cell lines and xenograft models. VEGF, HER2, and EGFR are validated targets for cancer therapy based on preclinical and clinical evidence and they continue to be the focus of intense research. EGFR and HER2 are known to be targets on cancer cells, but VEGF is a target that works in the tumor microenvironment. While other research examines if various strategies for blocking certain targets will be more advantageous, clinical research focuses on the best ways to incorporate targeted therapy into current treatment programs.The outcomes of targeted medicines to date are encouraging, but they also highlight the need for more preclinical and clinical research.

The primary source of new blood vessel creation brought on by malignancies is microvascular endothelial cells (EC) of the host organ, and the microvasculature of the liver and lung are quite different. VEGF is thought to stimulate tumor angiogenesis, and it is thought that the VEGFR-2 plays a significant part in this process. In this study, although the VEGFR-1 had no effect, the VEGFR-2 dramatically decreased the development of lung metastases of RenCa renal cell carcinoma by 26%. VEGFR-2 neutralization had little effect on RenCa liver metastases, despite VEGFR- reduced liver metastases by 31%. Both VEGFR-1 and VEGFR-2 inhibition was required to prevent the formation of CT26 colon cancer liver metastases. Instead of preventing the growth of micrometastases, inhibition of VEGFR-1 or VEGFR-2 decreased tumor burden by lowering vascularization and proliferation of micrometastases by 55% and 43%, respectively. VEGF enhanced the phosphorylation of VEGFR-1 and VEGFR-2 in ECs from the liver and lungs, respectively. For lung EC and liver EC, inhibiting VEGFR-2 and VEGFR-1 more successfully decreased EC migration, proliferation, and capillary tube formation in vitro. Overall, our results demonstrate that, due to the distinct VEGFR activity patterns of liver EC and lung EC, liver metastases are more dependent on VEGFR-1 than lung metastases to promote angiogenesis. As a result, the targeted metastatic disease regions should be considered while developing medications that block certain VEGFRs.

2.2 ANTI-CANCER CHEMICALS:

While cultures in Asia and Africa have used medicinal plants for thousands of years in traditional medicines. Developed nations uses the therapeutic benefits of compounds obtained from natural sources, some nations remain primarily rely on therapies that are plant-based.

a. Polyphenols: The polyphenolic compounds are all known to have anticancer effects. Red wine, grapes, and peanuts are a few examples of foods that contain resveratrol. Gallacatechins are found in green tea. Because polyphenols are natural antioxidants, it is thought that include them in one's diet can improve one's health and reduce the chance of developing cancer.

b. Flavonoids: Flavonoids are a diverse family of plant secondary metabolites and a subclass of polyphenolic compounds, with 10,000 known structural variants. They are plant chemicals with physiological activity that are receiving a lot of scientific attention for their possible health benefits.

c. Brassinosteroids: Brassinosteroids (BRs) are naturally occurring compounds found in plants that serve a number of purposes, such as controlling hormone communication to

control cell development and differentiation, lengthening stem and root cells. BRs are also used to manage the senescence of plants. They are essential for the growth and development of plants. Another chemical with therapeutic potential in the battle against cancer is BRs.

d. Plant-based cancer treatment options Plant-based medications are utilized to treat cancer because they are secure and convenient. They are simple to give the patient orally as part of their diet. Due to the fact that they are naturally occurring compounds derived from plants, they are frequently more tolerable and non-toxic to healthy human cells. A few taxanes, lectins, saponins, lignans, and cyanogenetic glycosides are exceptions to this rule, though. Methytransferase inhibitors, antioxidants that prevent DNA damage, histone deacetylases (HDAC) inhibitors, and mitotic disruptors are the four classes into which plant-derived drugs may be divided depending on their activity. As a control medicine for our thesis, we employed already-approved anti-cancer medications Trastuzumab Deruxtecan, Ribociclib, Sunitinib, and Ibrutinib.

2.3 TECHNIQUES FOR MOLECULAR DOCKING:

A popular computer method for analyzing and predicting the interactions between ligands (phytochemicals) and target proteins is molecular docking. Docking techniques make use of scoring functions to determine the binding affinity and find optimal binding conformations. The docking program attempts to compute binding energy at various locations while doing many docking runs, just like for the same protein and ligand. The position and binding energy of that maximal pass are taken as the major data among all the findings.The popular molecular docking programs AutoDock and Vina offer a selection of search strategies and scoring choices. These techniques provide valuable data on ligand-receptor interactions and have been beneficial in lead optimization and virtual screening.

The goal of virtual screening in this case is to use mathematical calculations to examine and choose a few chemicals from vast list micro-molecules. One virtual screening technique utilized in structure-based (SBVS), which tries to simulate and assess the functional bond configuration between a micro-molecule and a macro-molecule is the molecular docking method. The most efficient and stable state of the ligand-receptor complex may be predicted using the most advanced computational drug design technique, molecular docking. The major objective of the entire process is to comprehend the three-dimensional structures of the target and ligand molecules. As a consequence, several methods may be used to determine the molecular structure of substances as well as to develop supporting tools for the development of medications. Molecular docking has two crucial elements of docking programs, searching algorithms and scoring functions. A method that might lead to the examination of the well-liked and effective is searching algorithms.

2.4 BENEFITS OF MOLECULAR DOCKING IN RESEARCH ON CANCER:

For investigations on anti-cancer agents, molecular docking provides a number of advantages, including the ability to search through enormous chemical databases in search of potential anti-cancer compounds. The computational approach is useful for both the investigation of structure-activity correlations and the rational creation of anti-cancer medicines.

The Organization (2020) and Vineis and Wild (2014) both rank cancer among the most dangerous and prevalent causes of death worldwide. On December 14, 2020, there were 19.3 million new instances of the illness and 10.3 million fatalities attributable to cancer, according to the most recent. Given the fast improvement of oncology research and the development of innovative biotechnology techniques, knowing many elements of cancer progression can lead to better cancer prognoses and treatment alternatives (Goyal et al., 2006; Charmsaz et al., 2018; Pucci et al., 2019). As a result, a full understanding of tumor heterogeneity can aid in the development of new cancer treatments and provide a complete picture of the progression of cancer (Cajal et al., 2020). Tumor heterogeneity, as defined by Prager et al. (2019), is a condition in which tumor cells differ in a range of biological traits, such as function, differentiation, carcinogenesis, and sensitivity to anti-cancer therapy. Furthermore, heterogeneous groupings of tumor cells may contain comparable or dissimilar genetic contents depending on the degree of heterogeneity (Prager et al., 2019). In addition, a variety of factors, including genetics, epigenetics, and several microenvironmental traits, can contribute to it (Wang et al., 2015). In fact, a subpopulation of cancerous tumor cells called CSCs display their stemness traits similarly to normal stem cells. For instance, they may self-renew to produce daughter cells that are exactly like them and can differentiate into several cell lineages that lead to tumors. The quiescence state may potentially contribute to the growth of cancer and the emergence of resistance to therapy. This is one trait (Hung et al., 2019; Lee et al., 2020) that separates malignant stem cells from healthy stem cells. Because they are resistant to chemotherapy and radiation therapy, CSCs can make the healing process even more difficult. The expression of multidrug resistance proteins (MRPs), different signaling pathways, efficient DNA damage resistance mechanisms, and the epithelial-to-mesenchymal transition (EMT) procedure are a few of the components and mechanisms that may be in charge of the aforementioned therapeutic resistance (Phi et al., 2018). According to several cellular and molecular level studies, CSCs exhibit multiple metabolic activities (Chae and Kim, 2018; Yadav et al., 2020). For the purpose of identifying CSC behaviors and creating specialized therapeutic strategies for various cancer types, the science of metabolomics as well as an understanding of changes related to metabolic

processes may be helpful (Gilany et al., 2018; Rahim et al., 2018; Arjmand, 2019a, 2019b; Goodarzi et al., 2019; Larijani et al., 2019; Tayanloo-Beik et al., 2020). The development of tailored therapy modalities for various cancer types may benefit from an understanding of metabolic process alterations in addition to CSC activity (Cuyàs et al., 2017). Scientists have also been compelled to employ customized methods for treating cancer as a result of problems with CSCs resistance to treatment strategies. Docking is essential in the creation of novel medications and pharmaceutical research. This mathematical algorithm-based strategy for computer-assisted drug design enables the assessment of the real biological binding arrangement between the ligand and the target protein. In fact, the molecular structure serves as the basis for the aforementioned medication designing since it allows for the modeling and prediction of molecular interactions as well as the evaluation of biochemical processes (Meng et al., 2011; Phillips et al., 2018).

2.5 MOLECULAR DOCKING:

The bonding energy of a ligand interacting with a macromolecule is predicted through molecular docking. Additionally, it forecasts which side of the macromolecule the ligand will bind to. With the exception of a solid commitment or bond, information can be mounted in any direction of rotation. By affinity, two molecules connect to one another. The human body relies heavily on molecules including proteins, peptides, nucleic acids, carbohydrates, and lipids for signal transmission. In addition, the couples' relative orientations when engaging the kind of signal that forms may be impacted. Since docking may alter a molecule's workflow and serve as a medicine, it aids in the prediction of potency to target certain macromolecules **Figure-2**.

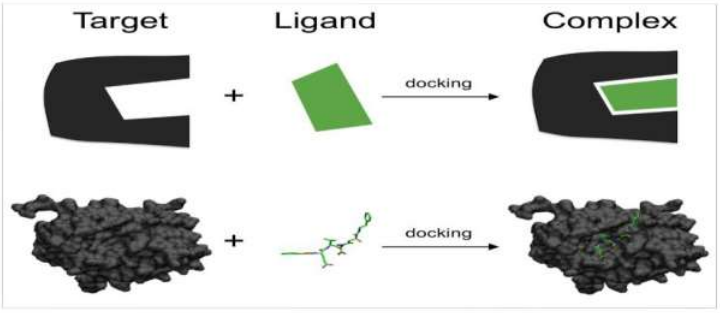


Figure-2: Molecular Docking

2.6 MECHANISM OF DOCKING WITH ITS IMPORTANCE:

Through the use of molecular binding methods, the atomic level interactions between minute substances and proteins may be modeled. This explains how tiny molecules behave at the binding site. The joining process comprises just two basic steps. determining the ligand's shape, placement, and orientation inside these sites (commonly referred to as postpositions), as well as the binding affinity. These two acts have to deal with sampling methods and scoring systems. Knowing the location of the binding point before docking greatly improves the efficiency of docking. When the ligand binds, the binding site is typically already known. Comparing the target protein to a protein that crystallizes with a protein family or another ligand with a related function can also reveal information about the location.

THEORY OF DOCKING: The goal of molecular docking is to predict the structure of the ligand receptor complex using computational techniques. Two interconnected phases can complete the docking process. Next, rank these conformations according to a scoring system.

IMPORTANCE OF MOLECULAR DOCKING: 1. Predicting the binding affinity (scoring function) 2. Identifying the ligands in binding sites. 3. Designing of drugs rationally

RECEPTOR SELECTION AND PREPRATIONS: First we have to identify macromolecule responsible for some disease or the important macromolecule for the workflow of the disease. In case of cancer, we observe that VEGFR1, VEGFR2 and EGFR are being expressed more than normal.

BULIDING THE RECEPTORS: It is recommended to get the 3-D receptor structures in (.pdb) file format from the RCSB official website. Processing of the uncleaned(Ligand/Water Molecule may be present) structures is required. The receptors ought to be stable and biologically active.

ASSESSMENT OF THE ACTIVE SITE: It is important to locate the receptors' active location. Although the receptors may have several active sites, the active site will be the one with the highest amount of binding energy.

SELECTION OF LIGAND: It may be obtained from a number of databases, including PubChem, etc. Following docking of the ligands onto the receptors, interactions are evaluated. The scoring algorithm then determines the scores based on which ligand is the best match.

THE USE OF AUTODOCK: A quick gradient-optimized conformational tool and a

straightforward scoring function constitute the foundation of the computer-assisted docking application AutoDock Vina. Drug-like ligands can be efficiently and quickly docked to proteins. This docking software for molecules is available for free. Its initial conception and execution took place at the Molecular Graphics Lab. The following are the justifications given by AutoDock Vina for docking:

1. Accuracy: AutoDock Vina significantly improves the typical accuracy of the result predictions.
2. 2. Easy to use: All that's needed is that the structures of the molecules being docked and the specification of the search area including the binding site.

2.7 DIFFERENT TYPES OF DOCKING:

RIGID DOCKING: The internal geometry of both the ligands and receptors are treated as rigid. These are also known as lock and key.

FLEXIBLE DOCKING: Generally, smaller molecules are counted as they rotate, and after each revolution, energy is computed to determine the best position. Protein-ligand, protein-protein, and protein-nucleotide interactions may all be docked. There are several troops operating at the moment.

Both type of docking shown in **Figure-3.**

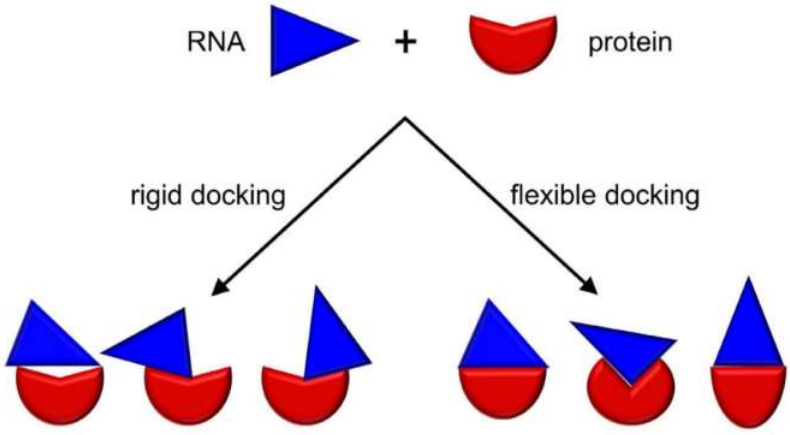


Figure-3: Rigid and flexible docking

CHAPTER 3:

METHODOLOGY

Flowchart of Molecular Docking process shown in **Figure-4** (Ahmad F Eweas, 2014).

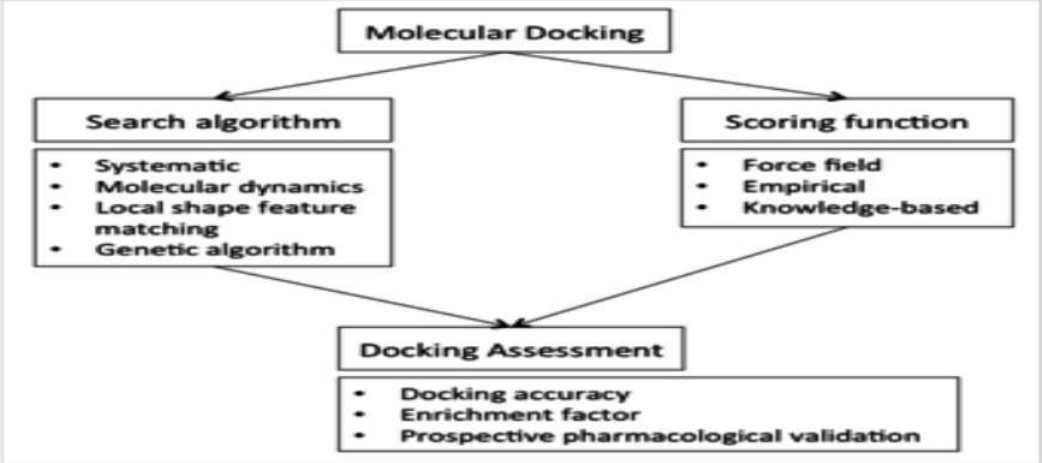


Figure-4: Flowchart of Molecular Docking

3.1 PHYTOCHEMICAL DATABASE SELECTION:

A broad and varied database of phytochemicals is necessary to undertake the screening of Anti-Cancer phytochemicals. Compounds are selected randomly from IMPPAT and the availability of structural data are among the selection criteria for the phytochemical database. For gathering the required molecules, well-known databases like PubChem phytochemical databases might be an invaluable resource. In PubChem we can also find canonical smiles for individual compound.

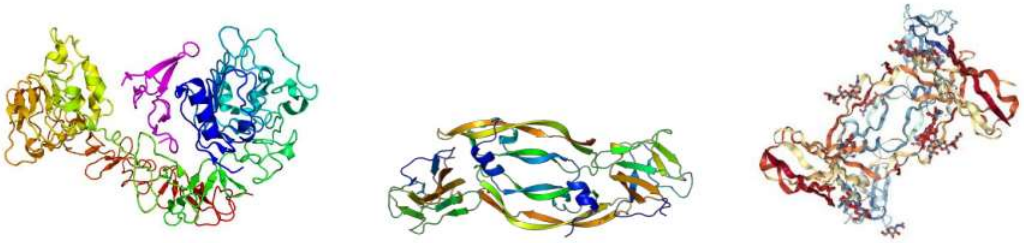
ADMET properties: ADMET Properties of the ligands can be found by searching the canonical smiles of that ligand in SwissADME application.

3.2 SELECTION OF PROTEIN TARGETS:

It is crucial to locate significant protein targets linked to cancerous cells for the screening process. Target proteins should include important enzymes involved in the production and control of cancerous cell or important in structural configuration, such as VEGFR1, EGFR, and VEGFR2. In the thesis paper we have taken those three types of protein such as:

1. VEGFR1 (PDB CID: 3HNG) 2. VEGFR2 (PDB CID: 3VHE) 3. EGFR (PDB CID: 1M17)

These proteins are potential locations for the control of cancer and play crucial functions in the cancer development process especially in skin cancers. **Figure-5** shows the structure of EGFR, VEGFR1 and VEGFR2 (Left to Right).



EGFR **VEGFR1** **VEGFR2**

Figure-5: The structures of the chosen receptor molecules

3.3 PROTOCOL FOR MOLECULAR DOCKING:

STEP-1: Getting the complex PDB.

STEP-2: Cleaning the complex by removing H2O molecule and extra ligands.

STEP-3: Adding the missing hydrogels/side chain atoms (Poler).

STEP-4: Adding Kollman charges.

STEP-5: Distributing the charge.

STEP-6: Grid Preparation For that macromolecule.

STEP-7: Saving the Macromolecule as (.pdbqt) Format.

STEP-8: Preparing Configuration file for docking.

STEP-9: Selecting the Ligand.

STEP-10: Downloading Ligand Structure in (.sdf) 3-D format.

STEP-11: Converting Ligand to (.pdb) format.

STEP-12: Modifying the Ligand and Saving in (.pdbqt) format.

STEP-13: Running the docking code in CMD prompt.

STEP-14: Analyzing the results of docking.

These steps have been shown in **Figure-6**.

The docking code used in command prompt is as follows:

cd {Location Of MM and Ligand as (.pdbqt) format in the file explorer}"

{Location of (vina.exe) in file explorer}\vina.exe" --receptor MM_File_Name.pdbqt --ligand Ligand_File_Name.pdbqt --config Configuration_File_Name.txt --log Log_File_Name.txt --out Output_File_Name.pdbqt

(*MM stands for Macromolecule)

3.4 PREPARATION OF LIGAND:

The phytochemicals from the chosen database need to be prepared as ligands prior to docking simulations. Only those ligands will be taken in action which does not violate Lipinski's rule of five for drug likeliness of a molecule. In order to make a ligand, molecule geometry must be optimized. For ligand preparation chores, software tools like Open Babel and AutoDock tool can be employed.

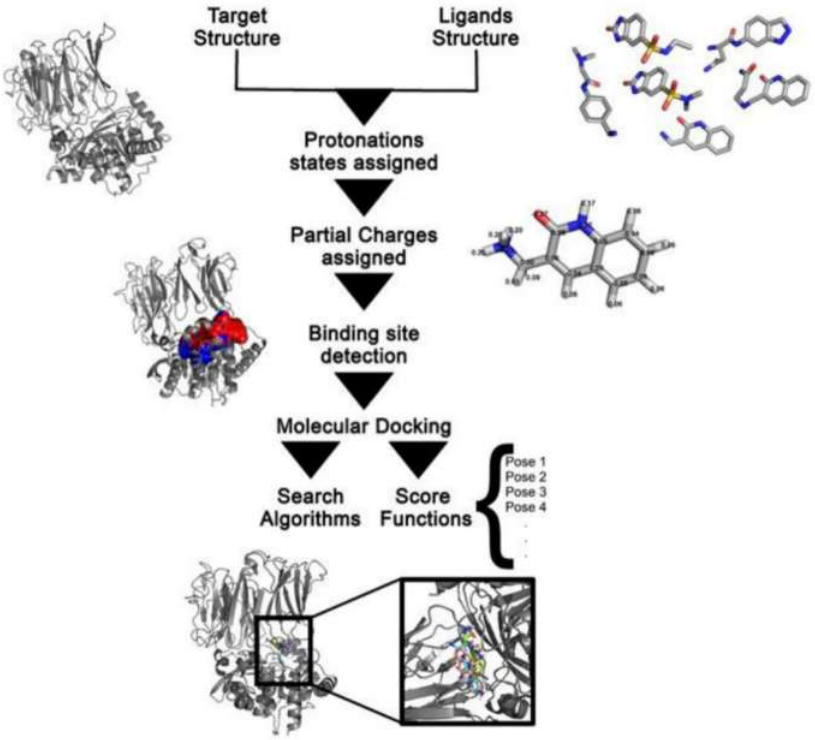


Figure-6: Basic Steps of Docking

3.5 PREPARATION OF PROTEIN:

Prior to running docking simulations, the chosen protein structures must be ready (for example, from the Protein Data Bank). In order to prepare proteins, water molecules and extra ligand must be removed, Poler Hydrogen atoms must be added, Partial Charge (Kollman Charge) must be assigned, distributed and then the protein structure must be optimized. After that protein file is saved in (.pdbqt) format. For the preparation of proteins, we utilized AutoDock Tools.

3.6 GRID GENERATION:

To specify the area where ligand binding should take place, a docking grid is created around the target protein. The active site or pertinent binding pockets, where ligands are anticipated to interact with the protein, are covered by the grid.To guarantee thorough sampling while retaining computational efficiency, the grid size and spacing parameters should be properly specified. **Figure-7** Shows How grid is selected for a specific protein.

3.7 SCORING AND DOCKING SIMULATION:

By putting the ready-made ligands inside the created docking grid, docking simulations are carried out. While looking for the ideal binding pose, the docking program investigates various ligand conformations and orientations. Ranking algorithms assess the ligands' anticipated binding energies and rank them according to their binding affinities. To improve sampling and capture ligand flexibility, we have used several dockings (run number was set to 9).

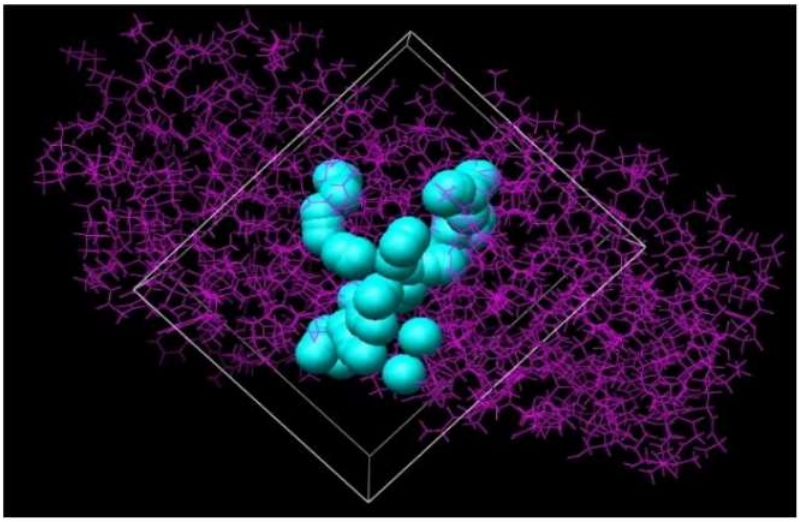


Figure-7: Grid Box

3.8. EVALUATION AND ANALYSIS:

The results of the docking simulations are examined to find top-ranked ligands that may have cancer-killing potential. Focusing on important residues and binding motifs, the molecular interactions between the ligands and target proteins are investigated. Molecular Docking is done for control drugs with VEGFR1, VEGFR2 and EGFR. The binding affinity of the phytochemicals is compared with that of the control drugs to highlight the compound that can multitarget cancer receptors with low inhibition constant.

CHAPTER 4:

RESULTS AND ANALYSIS

4.1 VIRTUAL SCREENING:

We have initially chosen 308 phytochemicals as our compound database after taking into account several medicinal plants that are said to have anti-cancer properties. 270 phytochemicals passed Lipinski's rule of five (for drug likeliness of chemical compounds) when ADMET attributes were predicted using SWISSADME. Compounds 271 to 308 were in violation of Lipinski's criterion and were thus excluded from consideration in our future docking investigation, according to the data provided in the supplemental material (**Table SM 1**).

By employing molecular docking to check the phytochemical database against the selected protein targets, a set of docking findings are generated. The results of the docking provide information on the predicted binding modalities and affinities of the ligands with the target proteins. The extent of the link between the ligand and the protein is demonstrated by the binding affinities, which are frequently provided as docking scores or binding energies. The next step is to identify the ligands from the outcomes of this experiment with the highest binding affinities that may have anti-cancer potential.

The affinity of the selected phytochemicals for the cancer receptors EGFR, VEGFR1 and VEGFR2 is shown in **Table SM 2**. **Table 2** lists the possible multi-targeted inhibitors of EGFR, VEGFR1, and VEGFR2 and highlights the phytochemicals that display significant protein-ligand interaction (similar to the outcomes of conventional anti-cancer medications shown in **Table 1**). These phytochemicals exhibited a binding affinity value of higher or close to that of standard drug compounds with all the chosen three receptors. However, the stability of these protein-ligand complexes under physiological settings will be determined by further molecular dynamics modeling.

Table 1: Existing Drug (Control) Docking Result and Threshold Calculations

Sl. No.	Existing Cancer Drug Name	Interaction with Proteins		
		VEGFR2 Binding Energy (in kcal/mol)	VEGFR1 Binding Energy (in kcal/mol)	EGFR Binding Energy (in kcal/mol)
1	Trastuzumab Deruxtecan	-8.7	-8.4	-8.2
2	Ribociclib	-7.7	-8.8	-8.6
3	Sunitinib	-8.3	-7.9	-8
4	Ibrutinib	-8.7	-9.3	-9.4

Table 2: Phytochemicals that are highlighted as potential candidates for anti-cancer agents

Sl. No.	Phytochemical Name	Interaction with Proteins Binding Energy (in kcal/mol)		
		VEGFR2	VEGFR1	EGFR
1	Syringin	-9.4	-9.1	-9.5
2	Tannic Acid	-9.3	-8.3	-9.5
3	Betulin	-8.3	-8.4	-8.5
4	Alpha-Amyrin	-9.8	-9.2	-9.9
5	Ursolic Acid	-9.5	-8.8	-9.8
6	Limonin	-8.7	-9.5	-9
7	Luteolin	-10.3	-8.3	-8.7
8	Isovitexin	-8.4	-8.2	-9.4
9	Dtxsid10942442	-8.2	-8.9	-8.1
10	Obacunone	-8.1	-9.1	-9
11	Lupeol	-9	-8.6	-9.2
12	Stigmasterol	-8.3	-8.3	-9.9
13	Taraxerol Acetate	-9.9	-9.6	-9.5
14	Hibiscetin	-8.8	-8	-8.8
15	Gossypetin	-7.9	-8.2	-8.9
16	Ergosterol	-9.3	-8.9	-9.3
17	Acetylursolic Acid	-9.5	-8.8	-9.5
18	Chrysoeriol	-8.1	-8.7	-9
19	Isohydnocarpin	-8.3	-8.9	-9.1
20	Hydnocarpin	-9.2	-8	-9.4
21	Beta-Amyrin	-9.5	-8.9	-9.3
22	Isoginkgetin	-9.3	-8.5	-10.1
23	Amentoflavone dimethyl ether	-9.5	-8.5	-8.5
24	Sugiol	-8	-8.3	-8.2
25	Podocarpusflavone A	-9.5	-9.2	-9.7
26	Epibetulinic Acid	-8.5	-8.2	-8.6
27	Cardenolide 2	-7.9	-9.7	-8.6
28	Beta-Yohimbine	-8.9	-7.7	-8.9
29	Ajmaline	-8.7	-7.7	-8.3
30	Vincoside lactam	-8.1	-9.7	-9.4
31	Raunescine	-8.2	-8.5	-9
32	Normacusine B	-8.5	-8.3	-8.6
33	Allo-Yohimbine	-9	-8.7	-8.9

4.2 ANALYSIS OF MOLECULAR INTERACTIONS:

The analysis's primary objective is to examine specific molecular bonding between top-ranked ligands and the target proteins. Among the interactions are stacking interactions, electrostatic interactions, hydrogen bonds, and hydrophobic contacts. 33 phytochemicals are included in **Table 2** that can targets EGFR, VEGFR1 and VEGFR2 respectively (based on the binding affinity values shown in **Table 1). Figures 8** and **9** show, respectively, the 2D binding pocket and 2D interaction diagram of the anti-cancer medication trastuzumab deruxtecan and the phytochemical syringin with EGFR. Comparing the two compounds reveals that they have comparable interaction residues, which suggests a similar mode of action on EGFR.The identification of important residues involved in ligand-protein interactions highlights the binding motifs and potential hotspots. We now have a better comprehension of the molecular mechanisms by which the ligands affect the target proteins and inhibit malignancy. Rankings of potential anti-cancer medicines are determined by molecular interactions, or binding affinities. Highest binding affinities, strong molecular interactions, and favourable structural traits make ligands the most promising candidates. Using further computational methods or experimental testing, potential anti-cancer effects of those the selected candidates can be verified.

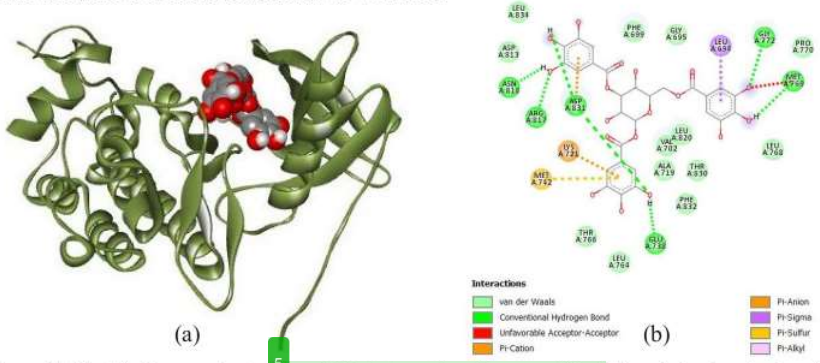


Figure 8: The binding pocket (a) and 2D interaction diagram (b) of the phytochemical syringin with EGFR

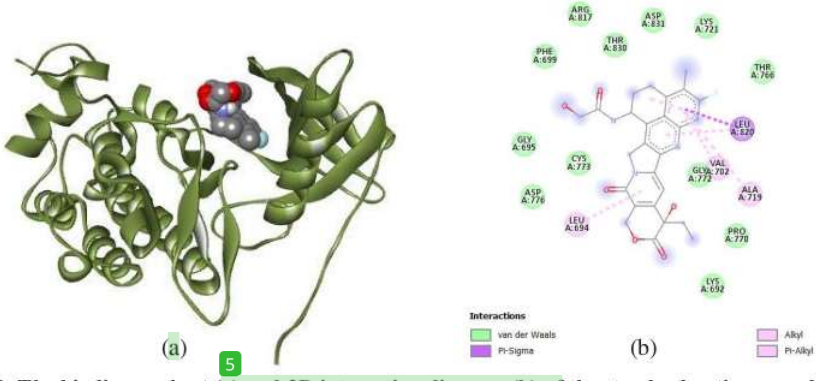


Figure 9: The binding pocket (a) and 2D interaction diagram (b) of the standard anti-cancer drug trastuzumab deruxtecan with EGFR

CHAPTER 5:

SUMMARY AND FUTURE SCOPE

New genomic and computational methods have significantly sped up the hunt for information regarding the molecular abnormalities that underlie cancer, even though there is still much to discover. Researchers can now classify and analyze hundreds of patient tumors, allowing them to find characteristics that affect cancer risk even when they are uncommon or have a minimal overall impact. It is hoped that identifying these characteristics would help us identify crucial cancer pathways and novel areas for intervention.

Our researchers are in a good position to continue understanding the underlying cellular pathways that underlie all forms of cancer by building on the CCR's long-standing excellent portfolio of basic research and the freedom of CCR main scientists to freely pursue fundamental topics in biology. We are also looking at the genetically distinct but uncommon malignancies that may be model systems for understanding more universally relevant cancer processes. As in the past, inquiries into the fundamental processes of cancer promise to accelerate the discovery of new and improved diagnostic and treatment techniques.

We identified thirty-three phytochemicals in our thesis that may be able to treat cancer. THis selection is based on the binding affinity values- phytochemicals exhibiting ΔG values higher or close to that of standard compounds are identified as hit molecules. Syringin, Tannic Acid, Betulin, Alpha-Amyrin, Ursolic Acid, Limonin, Luteolin, Isovitexin, Dtxsid10942442, Obacunone, Lupeol, Stigmasterol, Taraxerol Acetate, Hibiscetin, Gossypetin, Ergosterol, Acetylursolic Acid, Chrysoeriol, Isohydnocarpin, Hydnocarpin, Beta-Amyrin, Isoginkgetin, Amentoflavone dimethyl ether, Sugiol, Podocarpusflavone A, Epibetulinic Acid, Cardenolide 2, Beta-Yohimbine, Ajmaline, Vincoside lactam, Raunescine, Normacusine B, Allo-Yohimbine are those phytochemicals with anti-cancer properties. However, that may be verified in future following modelling, in vivo and in vitro testing, and clinical trials.

Avik Majumdar Final Edited Paper

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