IDENTIFICATION OF POTENTIAL INHIBITORS OF BLOOD CANCER : A MOLECULAR DOCKING STUDY

Under the supervision of Dr. K.S Rishad

Course Coordinator- Gigin Pullemkunnel

UniBiosys Biotech Research Labs

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Submitted by

Ann Mariya Shaju

Student Id Number: UBRL/SR/2023/15

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INTRODUCTION

Cancer is a disease in which some cells of our body grow uncontrollably and can spread to various other parts of the body. As the human body is made up of trillions of cells, cancer can start in any part of the body. Usually, human cells undergo a process called Cell Division in which the human cells grow and multiply, also when the cells grow older they will either become damaged or they die and the new cells replace them. Whereas sometimes this well-organized process breaks down, and those damaged or abnormal cells grow uncontrollably and can form tumors which are basically lumps of tissue. There are two types of tumors that is either cancerous or benign (non-cancerous). Cancerous tumors can travel to different places in the body and can form new tumors and this process is called Metastasis. Therefore cancerous tumors are also called Malignant tumors. Most cancers will form solid tumors, but blood cancer, such as leukemias, generally do not. On the other hand benign tumors do not invade nearby tissues. That's the reason why benign tumors usually don't grow back but cancerous tumors sometimes do. Sometimes, benign tumors in the brain can be life-threatening.

Blood cancer is one of the serious illnesses that can lead to death. The volume of blood is approximately 10% of an adult's weight. Blood cancer affects how the body produces blood cells and the effectiveness of those cells. It starts in the bone marrow, which makes the stem cells that when mature become red blood cells, white blood cells, and platelets. Abnormal blood cells overwhelm normal blood cells in the case of a person who is affected by blood cancer. All blood cancers effect the white blood cells in our body. As per one of the hematologist-oncologist Nicole Lamanna, " It's a blood disorder, and your blood is in your whole body, so the cancer is in your whole body." Unlike many other solid cancers which have lumps or tumors in specific organs or parts of the body and can later spread to other parts of the body, Blood cancers are completely different. It is of three types that is Leukemia, Lymphoma, Myeloma.

Leukemia- It originates in the blood and bone marrow. It is a situation in which the body creates too many abnormal white blood cells and is one of the most common type of cancer among children and teenagers.

Lymphoma- It is a cancer of the lymphatic system, which includes the bone marrow. In this type of cancer, a specific type of white blood cell called a lymphocyte becomes abnormal and multiplies.

Myeloma- It is a cancer that starts in the bone marrow and affects the plasma cells. Multiple myeloma is the most common myeloma type.

The tripartite motif (TRIM) family proteins are involved in a broad range of biological processes, including transcriptional regulation, cell growth, apoptosis, development, and tumorigenesis. The TRIM-containing proteins is defined as a subfamily of the RING type E3 ubiquitin ligase. Some studies show that TRIM proteins are involved in the regulation of nuclear receptors. Promyelocytic leukemia (PML) gene encodes TRIM19 and is involved in the t(15;17) translocation that is specific for acute promyelocytic leukemia (APL). As TRIM19 is localized in PML-nuclear bodies (PML-NBs) in the nucleus and it can regulate the response to several cellular stresses, DNA repair, and viral infection. Emerging clinical evidence has shown that the deregulation of ubiquitin-mediated degradation of oncogene products or tumor suppressors is likely to be involved in the aetiology of carcinomas and leukemias. Several recent studies indicate that some members of TRIM proteins can function as important regulators for carcinogenesis.

Cancer therapy has evolved throughout the years. In the case of solid tumors alongside surgery, they use antitumor drugs and radiation as part of treatment. Chemotherapy and radiotherapy are the most common types of cancer treatments. Nowadays immunotherapy has become an important therapeutic alternative. The use of nanostructures as new therapeutic alternatives for controlled drug delivery has recently arrived on the scene. Gene therapy is also offering promising new methods for treatment. There is a constant demand for new therapies to prevent and treat this life-threatening disease. Recently scientists and researchers are looking for some naturally derived compounds as they are considered to have less toxic side effects compared to other treatments such as chemotherapy. Plants have naturally occurring metabolites which are being investigated for their anticancer activities leading to the development of new clinical drugs. Nanomedicines aim to enhance the anticancer activities of plant-derived by controlling the release of the compound and investigating new methods of administration. There is a wide range of secondary metabolites in medicinal plants which include flavonoids, flavones, anthocyanins, lignans, coumarins, isocatechins, and catechins. These bioactive compounds are mainly responsible for anti-oxidant prosperity of medicinal plants.

The long-used traditional methodology for novel drug discovery and drug development is an immensely challenging, multifaceted, and prolonged process. Therefore to overcome this limitation, a futuristic approach was developed and adopted over time which is known as Computer-Aided Drug Discovery (CADD). With the advancement of computational tools and methods, CADD has accelerated the overall traditional time-consuming process of new drug entity development. Also with the increase in availability and knowledge of biological/ bio-macromolecule structures, along with the exponential increase in computing power, it is now plausible to use these methods effectively. Recently various CADD techniques such as homology modeling, docking, ab initio design, toxicity profile, quantitative structure-activity relationship (QSAR), and quantitative free-energy calculation have been improved. Molecular Docking is widely used in CADD (Computer-Aided Drug Designing), SBDD (Structure-Based Drug Designing), and LBDD (Ligand-Based Drug Designing). It is a method for predicting the binding orientation of one molecule with another, also it can be used for small drug molecule with its protein target, protein-protein binding, or DNA-protein binding and docking is a popular technique due to its predictability. These current methods of CADD are utilized in academic and commercial research, as it has been now an emerging field of interest in drug design and developments.

Some molecular docking studies reveal that the "drug-likeness" of ~400 compounds from African medicinal plants that have shown in vitro and/or in vivo anticancer, cytotoxic, and antiproliferative activities has been explored. To confirm potential binding to anticancer drug targets, the interactions between the compounds and 14 selected targets have been analyzed by *in silico* modeling. Upon carrying docking and binding affinity calculations, in comparison with known anticancer agents comprising ~1500 published naturally occurring plant-based compounds from around the world, the results reveal that African medicinal plants is a good starting point for discovery of anti-cancer drugs. The small data set that was generated is available for research groups working on virtual screening.

This present project deals with molecular docking of Thioazo compounds, Compounds from *Maclura pomifera, Swertia chirayita, Punica granatum* L., *and Glycyrrhiza glabra* with TRIM3 proteins which function as an important regulator for carcinogenesis. Research shows that the #3 compound from the taken thioazo compounds has better interaction than doxorubicin and paclitaxel and follows Lipinski's rule of 5. Thus it could be a potential lead molecule for inhibiting protein Filamin A in the treatment of oral cancer. *Maclura pomifera,* also known as Osage orange, the inedible fruits contain anti-oxidant and fungicidal compounds.

Swertia chirayita has a wide range of medicinal uses such as for the treatment of chronic fever, malaria, anemia, hepatotoxic disorders. *Punica granatum* L. (pomegranate) has components that have anti-inflammatory, and anti-carcinogenic effects. *Glycyrrhiza glabra* L. (licorice) has anticancerous, anti-inflammatory, and antidiabetic properties. Typical drug discovery organization include target selection, hit identification, lead optimization, preclinical and clinical studies which consume a lot of time, money and effort. Medicinal plants are important sources of structurally novel compounds and thus can be used to develop new drugs. Here we use molecular docking to screen thioazo compounds, phytochemicals in medicinal plants for their potential as inhibitors of these target TRIM proteins.

TRIM proteins are involved in cell growth, development, and cellular differentiation and alteration of these proteins can affect transcriptional regulation, cell proliferation, and apoptosis. With more than 7000 plant species used as medicinal plants, India is a rich source of biodiversity. As cancer is the second leading cause of death worldwide and since there is no complete cure for cancer, finding alternative methods for treatment is critical.

AIM AND OBJECTIVES

The thesis entitled “Identification of potential inhibitors of blood cancer: a molecular docking study” is done with the following objectives.

OBJECTIVES

- Selection of a target molecule for docking studies on Blood Cancer.
- Identification of active site residue of the target.
- Screening and selection of ligands
- Docking of the target with selected ligands and find out lead molecules
- ADME toxicity studies of the selected molecules

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MATERIALS AND METHOD

MATERIALS

The tools used in this study are Autodock 1.5.7, Autodock4, Autogrid4, Chemsketch, Open babel, Chimera 1.16, swiss ADME and molsoft. The ligands used in this study are mostly natural. They were selected from searching different literatures. The structures of these ligands were drawn using ChemSketch.

Thiazo compounds: This project deals with molecular docking of TRIM proteins with thioazo compounds. We took 6 thioazo compounds that is compound 1, 2, 3, 4, 5, 6 and carry out molecular docking of these compounds. Some other research shows that the thioazo compounds 1, 3, 5, and 6 showed best molecular docking interaction as compared to drug doxorubicin. Those data shows that compound #3 has better interaction than the drug doxorubicin and paclitaxel (it is a broad-spectrum anticancer agent, isolated from *Taxus brevifolia*) and follows Lipinski's rule of 5. Therefore, it could be considered as a potential lead molecule for inhibiting Filamin A in the treatment of cancer. Thus we hope molecular docking of TRIM protein with thioazo yield a beneficial results.

Maclura pomifera: It is a small deciduous tree or large shrub, that is native to the south-central United States. It is one of over 1100 species in the Moraceae family's genus Maclura. It is used to treat sore eyes and it has insect-repellent properties. Pomiferin is a prenylated isoflavone that can be found along with osajin in female flowers and fruits of *Maclura pomifera,* it has antioxidant, antimicrobial and anti-cancer activity. *M. pomifera* and its components has several biological activities that is cytotoxic, antitumor, antimicrobial, antibacterial, antiviral activities. Recent studies show that isoflavones isolated from Osage orange have demonstrated to protect brain cells.

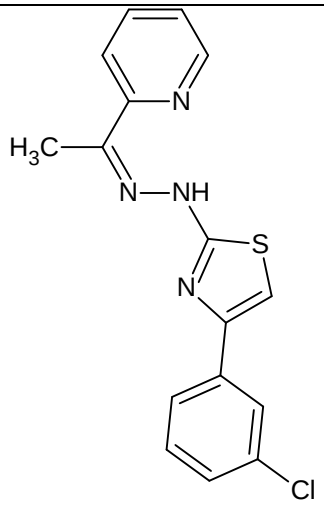
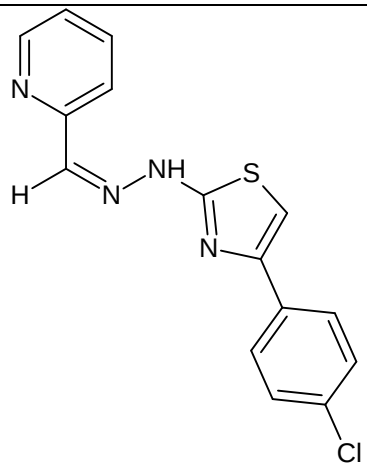
Swertia chirayita: It is a popular medicinal herb that is native to the temperate Himalayas. *Swertia chirayita* is an annual or biennial herb. *Swertia* is a genus in the gentian family and it is used to treat numerous ailments such as liver disorders, malaria, and, diabetes. Its medicinal usage is well-documented in the Indian pharmacological codex. It is an ethnomedicinal herb

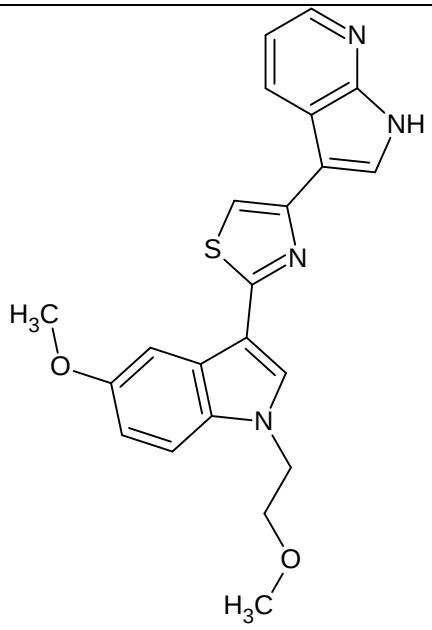
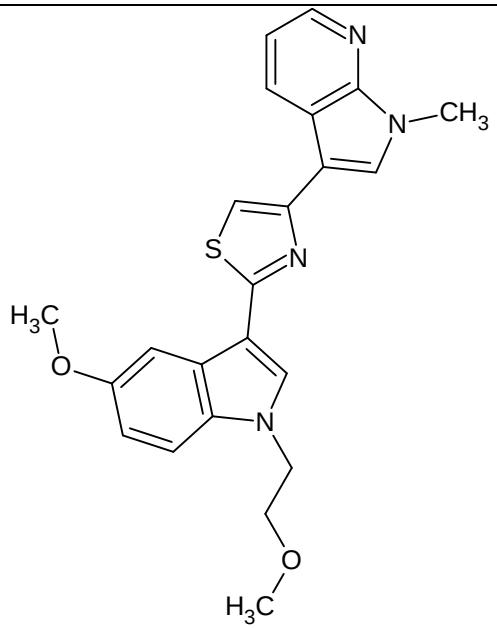
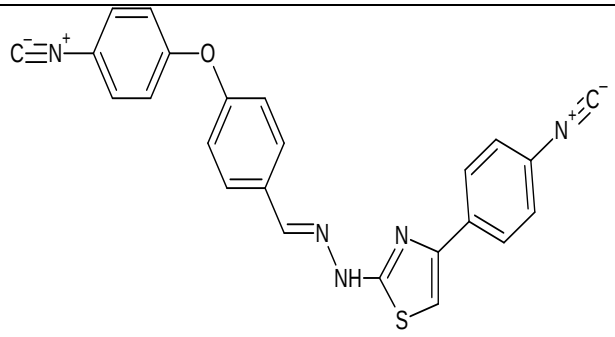
known for its bitter taste due to the presence of different bioactive compounds that are associated with human health welfare. Traditionally, the decoctions of this species has various antimalarial, anti-inflammatory, antiaging, antibacterial activities. Also studies shows the anticancer and apoptotic efficacy of *S. chirayita* ethanolic extract on small cell lung cancer.

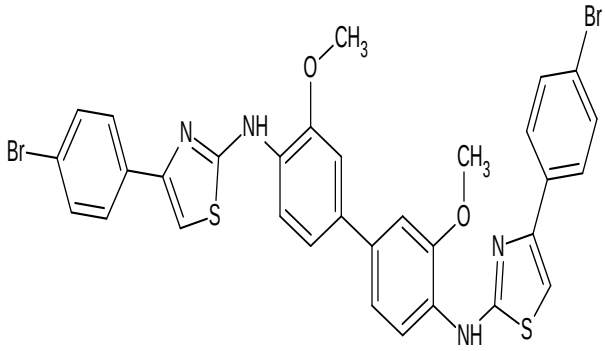
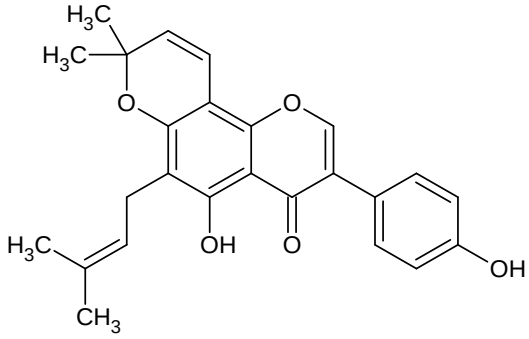
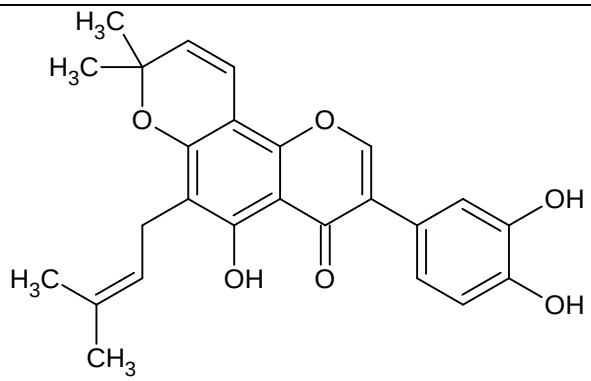
***Punica granatum* L.:** It is commonly known as pomegranate. It is a fruit-bearing deciduous shrub in the Lythraceae family. Research shows that there are abundant phytochemicals in pomegranate juice including ellagitannins, whereas the peel is high in polyphenols, catechins, and prodelphinidins. The seed oil contains punicic acid, palmitic acid. Oleic acid and so on. Various data reveals that pomegranate has several health benefits such as it can prevent and treat various risk factors including high blood pressure, high cholesterol, hyperglycemia, and inflammatory activities. Also certain components of pomegranate such as polyphenols have antioxidant and anticarcinogenic effects. Pomegranate fruit extract prevents cell growth and induces apoptosis.

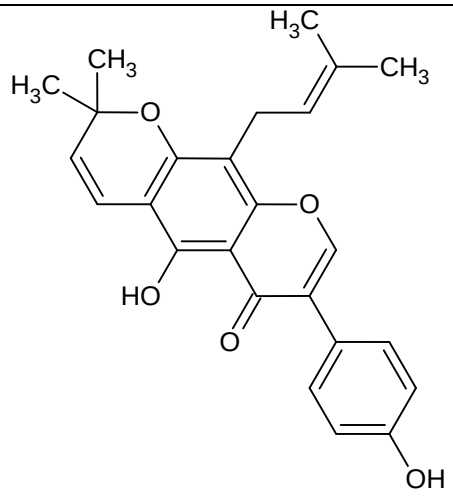
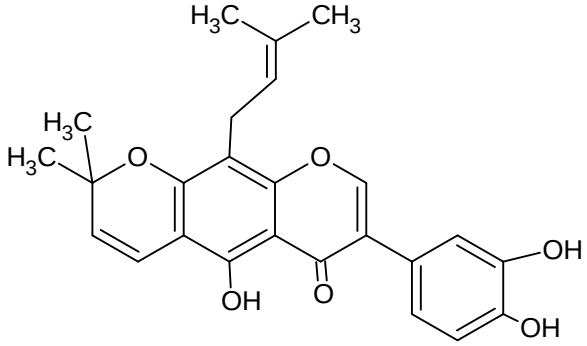
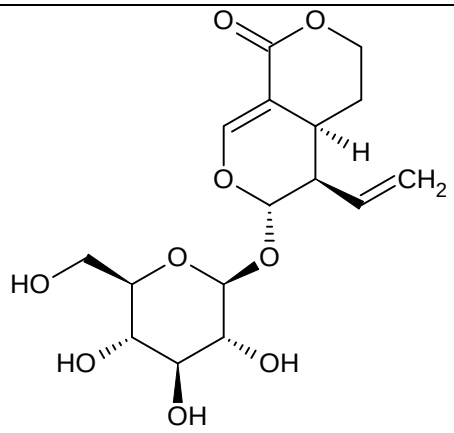
***Glycyrrhiza glabra* L.:** Licorice is the common name of *G. glabra*. It is a flowering plant of Fabaceae family, from the root of which a sweet, aromatic flavouring can be extracted. Licorice flavor is found in variety of candles or sweets. In the Netherlands, licorice confectionery is one of the popular forms of sweets. The essential oils present in licorice inhibit growth of *Aspergillus flavus.* The chemical composition of licorice are glycyrrhizin, glycyrrhetic acid, isoliquiritin, isoflavones and its derivatives. It has several pharmacological effects such as antidiabetic, anti-inflammatory, and anticancer activities.

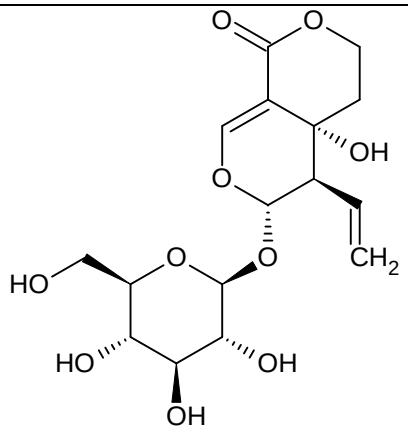
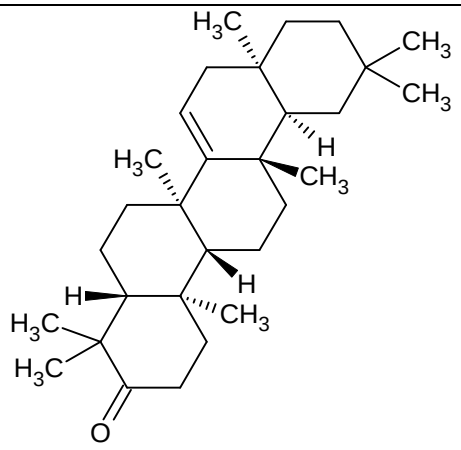
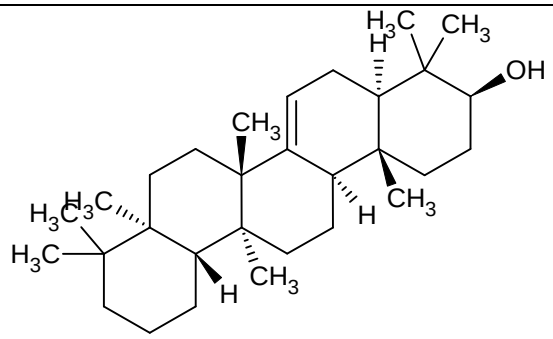
TABLE 1: LIGAND SELECTION

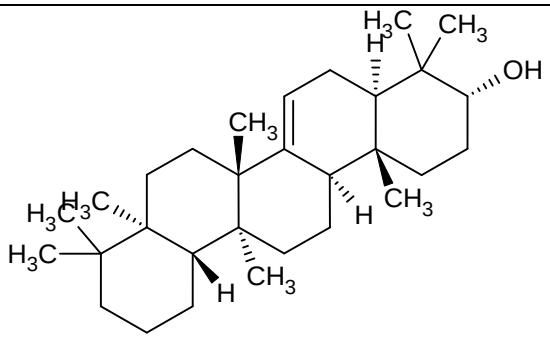
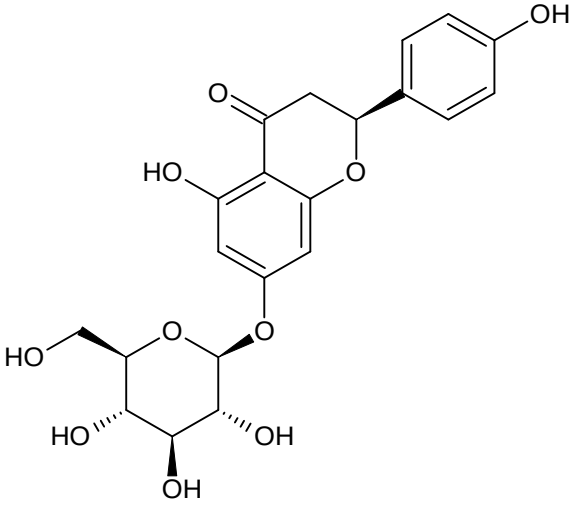
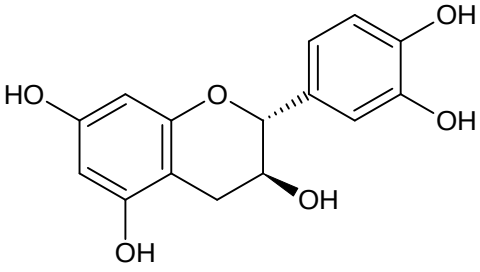
LIGAND NO.	LIGAND NAME	PLANT NAME	STRUCTURE	MOLECULAR FORMULA
1	COMPOUND 1 (THIOAZO COMPOUND -1)			
2	COMPOUND 2 (THIOAZO COMPOUND-2)			

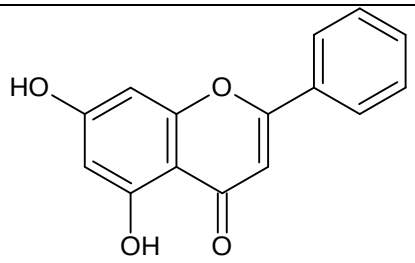
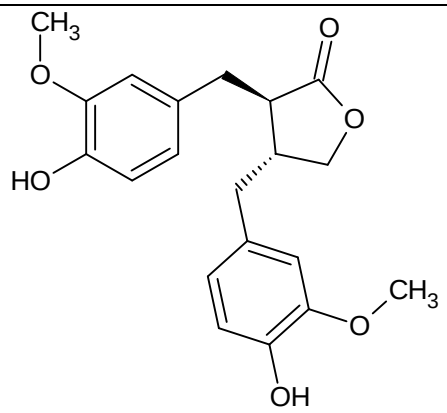
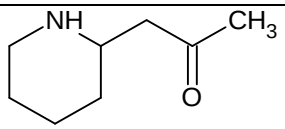
3	COMPOUND 3 (THIOAZO COMPOUND-3)			
4	COMPOUND 4 (THIOAZO COMPOUND-4)			
5	COMPOUND 5 (THIOAZO COMPOUND-5)			

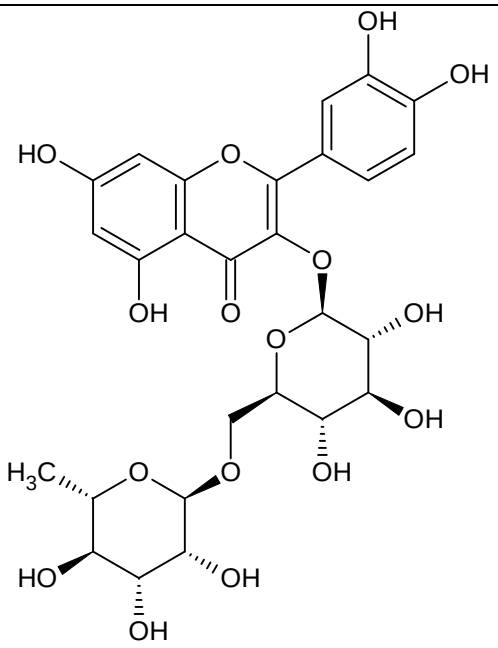
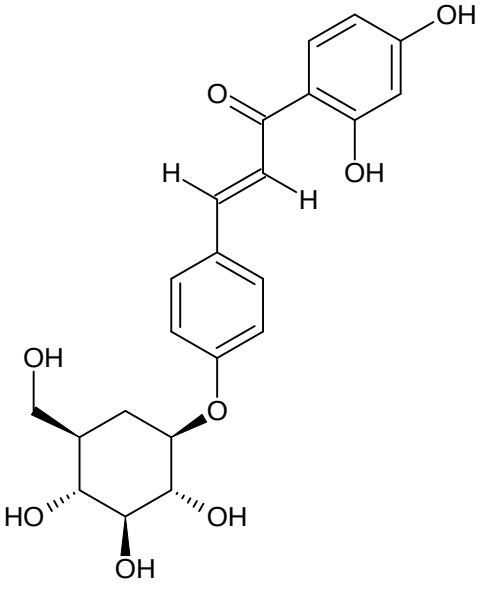
6	COMPOUND 6 (THIOAZO COMPOUND-6)			
7	OSAJIN	*Maclura pomifera*		C25H24O5
8	POMIFERIN	*Maclura pomifera*		C25H24O6

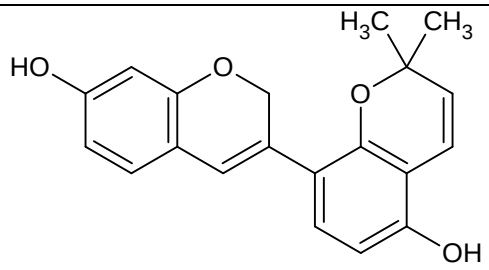
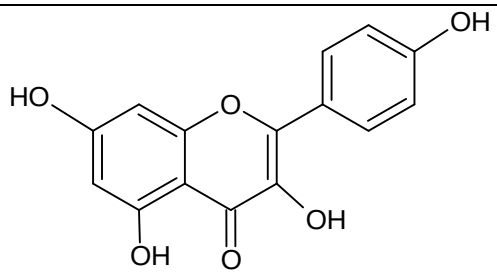
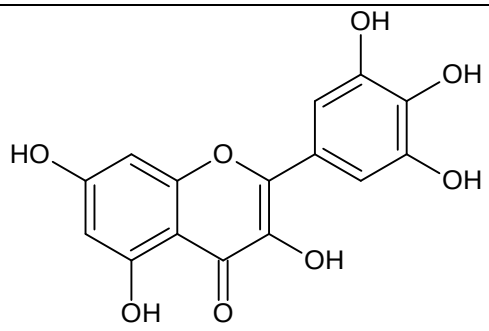
9	SCANDENONE	*Maclura pomifera*		C25H24O5
10	AURICULASIN	*Maclura pomifera*		C25H24O6
11	SWEROSIDE	*Swertia chirayita*		C16H22O9

12	SWERTIAMARIN	*Swertia chirayita*		C16H22O10
13	TARAXERONE	*Swertia chirayita*		C30H48O
14	SWERTENOL	*Swertia chirayita*		C30H50O

15	EPISWERTENOL	*Swertia chirayita*		C30H50O
16	PRUNIN	*Punica granatum* L.		C21H22O10
17	CATECHIN	*Punica granatum* L.		C15H14O6

18	CHRYSIN	*Punica granatum* L.		C15H10O4
19	MATAIRESINOL	*Punica granatum* L.		C20H22O6
20	ISOPELLETIERINE	*Punica granatum* L.		C8H15NO

21	RUTIN	*Punica granatum* L.		C27H30O16
22	ISOLIQUIRITIN	*Glycyrrhiza glabra* L.		C21H22O9

23	GLABRENE	*Glycyrrhiza glabra* L.		C20H18O4
24	KAEMPFEROL	*Glycyrrhiza glabra* L.		C15H10O6
25	MYRICETIN	*Glycyrrhiza glabra* L.		C15H10O8

METHOD

Draw the ligands using ChemSketch

↓

Save the format of structure as MDL molfiles using open babel program

↓

Download the TRIM3 protein (PDB Id- 7QRW) from protein databank

↓

Remove the Heteroatoms attached to the protein

↓

Protein was then undergone molecular docking using autodock4

↓

Glg and dlg files are created

↓

Molecules with minimum binding energy are selected by observing RMSD values

↓

Visualized using UCSF chimera

↓

Quality evaluation of selected lead molecules

TRIM3 protein was selected as target on the basis of literature reading. 25 ligands were selected for screening.

Protein preparation:

The three-dimensional structure of TRIM3 was obtained from the pdb(www.rcsb.org). The base structure of the protein was prepared by removing all the heteroatoms attached to the TRIM3 protein. The binding pocket of TRIM3 was optimized by excluding the coordinates of heteroatom molecule. The UCSF Chimaera was used to visualize the 3d structure of the protein and its energy was minimized for further docking studies.

PDB(protein databank)- It is a single international repository for all information about the structure of large biological molecules. The data, typically obtained by x-ray crystallography, NMR spectroscopy, or, increasingly, cryo-electron microscopy, and submitted by biologists and biochemists from around the world, are freely accessible on the internet via the websites of its member organisations (pdbe, pdbj, and rcsb).PDB is a primary database. These primary data may include atomic coordinates, information related to the chemistry of the macromolecule, the small-molecule ligands, some data collection details, structure refinement, and some structural descriptors. A PDB entry may contain about 400 unique items of data. Pdb is a repository of the 3-dimensional structural data of large biological macromolecules such as protein and nucleic acid or their complexes. The pdb is the key resource for structural biotechnologists. About 12% of structures are determined by protein NMR. The file format that was used by the pdb was called the pdb file format. The individual pdb files can easily be downloaded into graphics packages using web addresses. By convention, the names of each pdb files start with a number followed by three letters like 1smt. This is also called the pdb id.

***In silico* generation of ligands:**

The available ligand structures were drawn using Chemsketch. The openbabel server was used to convert the sdf files of the ligands to pdb format providing details on the coordinates of the ligand.

ChemSketch: ACD/ChemSketch is an open source software developed by American Chemistry Department Lab which is primarily used for educational purpose. It is a popular

structure drawing software with over 2 million downloads worldwide. It is a molecular modeling program that is used to draw and modify images of chemical structures. One can also calculate the molecular properties such as molecular weight, density, molar refractivity and so on. Also it can clean up the structure and view it in 2D and 3D.

Open babel: Open babel is a chemical toolbox designed to speak the many languages of chemical data. It's a free and open, collaborative project allowing anyone to search, analyze, or store data from molecular modeling, chemistry, solid-state materials, biochemistry, or related areas. It is a version of the babel chemistry file translation program. Open babel is a project designed to pick up where babel left off, as a cross-platform program and library designed to interconvert between many file formats used in molecular modeling, computational chemistry, and many related areas.Open babel includes two components, a command-line utility and a c++ library. The command-line utility is intended to be used as a replacement for the original babel program, to translate between various chemical file formats. The c++ library includes all of the file-translation code as well as a wide variety of utilities to foster development of other open source scientific software.The original babel is hosted by smog.com on a babel homepage, by the computational chemistry list (ccl) and of course by open babel at sourceforge.net. Along the way, the two original authors started a rewrite of babel into c++ they called obabel,openbabel has two main pieces.

1. Ready to use programs for interconverting, searching, modifying and analysing chemical files.
2. A complete programmer's tool kit to allow easy chemistry software development.

It can read, write and convert over 110 chemical file formats and also filter and search molecular files using smarts and other methods.

Molecular docking studies:

Autodock4 was used to predict how substrates or drug candidates, bind to a receptor of known 3d structure. It was used to create gpf-grid parameter file and dpf-dock parameter for adding polar hydrogen, kollman charges and atoms , edit option was available. These were added to the receptor for the preparation of protein in docking simulation. Autodock requires precalculated grid maps. This grid must surround the region of interest(active site) in the macromolecule. The grid centre was set to 13.18,19.983,16.29 for x, y ,and z respectively, which covered all the aminoacid residues in the considered active pocket. Docking software

autodock 4.2.6 program supplied with autogrid 4.0 and autodock 4.0 was used to produce grid maps. The lamarckian genetic algorithm (lga) was chosen to search for the best conformers. During the docking process, a maximum of 10 conformers was considered for each compound. The dlg file showed docked structure at different runs with different binding energy(B.E.). The poses of the docked structure at the run with the least binding energy were finally selected. The Lamarckian genetic algorithm (lga) was chosen to search for the best conformers. The highest-ranked ligands were compared with the known experimental structure using the standard cartesian root-mean-square deviation (RMSD) measure (between similar atoms in the pose and experimental structure). The pose for the ligand-receptor complex was analyzed three dimensionally for hydrogen bond-based interactions at the active site of TRIM3 protein using the software UCSF Chimera. The selected ligand was highlighted. The drug likeness, ADME properties and toxicity of the selected ligands were further analyzed. In the case of ADME toxic structures, computer-assisted search for alternate drug candidates was also evaluated.

Autodock: Autodock is a suite of c programs used to simulate interactions between small flexible ligands and macromolecules of known structure. Docking is achieved through a search of conformational space using a Lamarckian genetic algorithm coupled with energy assessments using a method based on the amber force field. The combination of these two functions produces a family of molecular coordinates detailing possible docked ligand conformations which can then be used as a starting point for theoretical ligand design and study. Confidence in the docked conformation is represented by an energy value based on both quantum and molecular mechanical modelling of atomic forces. The genetic algorithm used in autodock defines a ligand's "chromosome" as having seven standard genes accounting for the ligand's cartesian coordinates, and four variables specifying its orientation. Once the genes have been defined the genetic algorithm starts by creating a population of random individuals confined within a user specified box also containing the protein. For each individual the three translation genes (x,y,z) are given a random value between the minimum and maximum of the search area, the four genes describing the orientation given a random quaternion consisting of a unit vector and rotation angle, whilst the torsion angle genes (if any) are given random values between -180º and 180º. These gene values are then converted into a corresponding phenotype that enables the assessment of each individual's "fitness" measured by interactions both within the ligand and between the ligand and the protein. This assessment is followed by a selection procedure that decides which individuals will be allowed to progress into the next refinement round. Autodock also performs a limited local search based on the energy phenotype of each

resulting chromosome, followed by reverse-transcription of the optimized phenotype back into the genome in much the same way as hypothesized by the discredited Lamarckian evolutionary theory.

UCSF Chimera: It is an extensive program for interactive visualization and analysis of molecular structures and related data. Chimera is developed for biocomputing visualization informatics at the University of California, San Francisco. It is also known as chimera. It's development is funded at national institute of health. UCSF Chimera X is a next generation program under development, and is not yet released. Chimera is segmented into a core that provides basic services and visualization, and extensions that provide most higher-level functionality. This architecture ensures that the extension mechanism satisfies the demands of outside developers who wish to incorporate new features. Two unusual extensions are presented: multiscale, which adds the ability to visualize large-scale molecular assemblies such as viral coats, and collaboratory, which allows researchers to share a chimera session interactively despite being at separate locales. Other extensions include multalignviewer, for showing multiple sequence alignments and associated structures; viewdock, for screening docked ligand orientations; movie, for replaying molecular dynamics trajectories; and volume viewer, for display and analysis of volumetric data. Chimera includes full user documentation, and is free to academic and nonprofit users, and is available for Microsoft Windows.

Molsoft: Molsoft was established in 1994 and is located in San Diego. It was privately owned – founded by Rubena Bagyan (UCSD). Molsoft is a leading provider of tools, databases, and consulting services in the area of structure prediction, structural proteomics, bioinformatics, cheminformatics, molecular visualization and animation, and rational drug design. Molsoft offers complete solutions customized for a biotechnology or pharmaceutical company in the areas of computational biology and chemistry. Molsoft is building unique technologies for structure prediction that improves our understanding of the spatial organization of biological molecules and their interactions with each other, their biological substrates, and drug-like molecules at the atomic level. The molsoft molecular modeling technology is based on the internal coordinate mechanics (ICM) approach which gives a general modeling and structure prediction framework for many tasks of structural biology and rational drug design. The ICM project was initiated by the founder in 1985, and is being continuously developed ever since.

RESULTS

Docking of TRIM3 was done with several ligand compounds. The ligands are 6 Thioazo compounds that is compound 1, compound 2, compound 3, compound 4, compound 5, compound 6; Osajin, Pomiferin, Scandenone, Auriculasin, Sweroside, Swertiamarin, Taraxerone, Swertenol, Episwertenol, Prunin, Catechin, Chrysin, Matairesinol, Isopelletierine, Rutin, Isoliquiritin, Glabrene, Kaempferol, Myricetin.

Fig 1: 3D view of TRIM3 protein (https://www.rcsb.org/3d-view/7QRW)

Among these ligands, Sweroside and Matairesinol were selected on the basis of drug-likeliness score and they also obey Lipinski's rule .The binding of ligands with TRIM3 protein is shown below :

Table 2 : Minimum Binding energy and run of ligands

Ligand name	Binding energy	Run
Compound 1 (Thioazo Compound 1)	-8.88	43
Compound 2 (Thioazo Compound 2)	-8.84	43
Compound 3 (Thioazo Compound 3)	+5.60	29
Compound 4 (Thioazo Compound 4)	+7.19	40
Compound 5 (Thioazo Compound 5)	+19.24	47
Compound 6 (Thioazo Compound 6)	+373.77	50
Osajin	-3.68	44
Pomiferin	-3.17	38
Scandenone	-4.26	43
Auriculasin	-2.26	38
Sweroside	-13.31	14
Swertiamarin	-14.34	49
Taraxerone	+3.67	15
Swertenol	+0.15	34
Episwertenol	+0.30	25
Prunin	-8.20	6
Catechin	-11.57	8
Chrysin	-10.28	2
Matairesinol	-10.25	38
Isopelletierine	-6.84	6
Rutin	+32.62	5
Isoliquiritin	-9.98	47
Glabrene	-5.50	8
Myricetin	-12.48	17

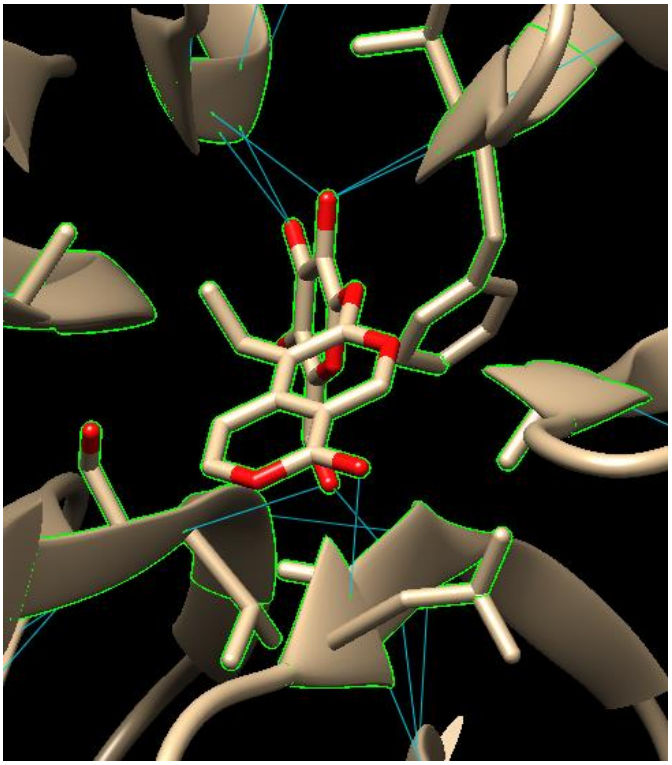


Fig 2: Image showing binding of Sweroside with TRIM3 protein

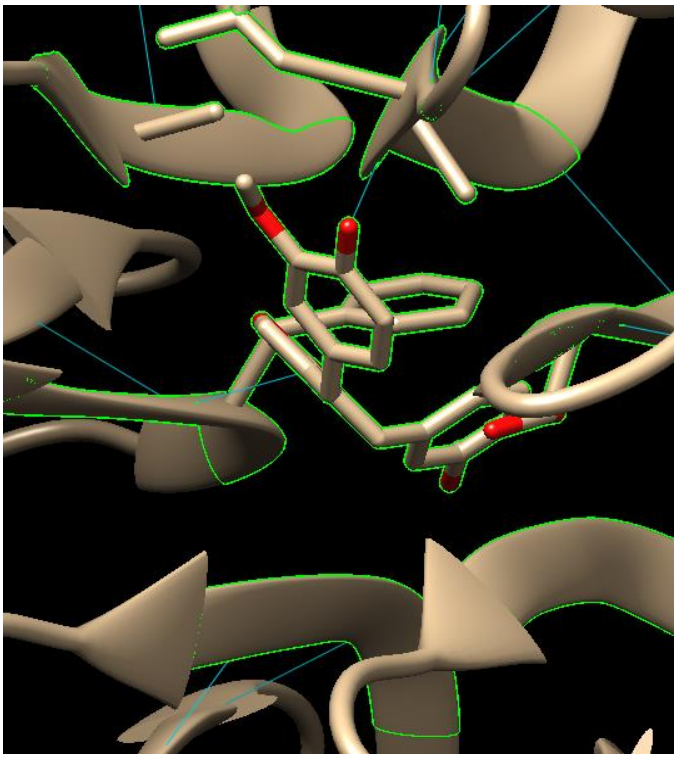
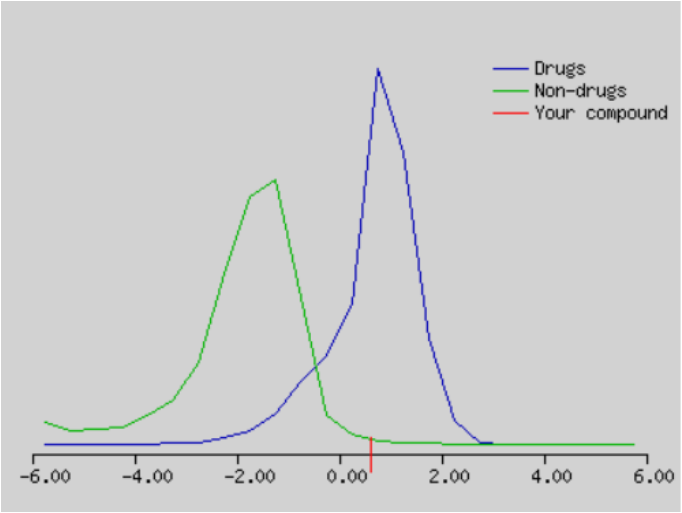


Fig 3: Image showing binding of Matairesinol withTRIM3 protein.

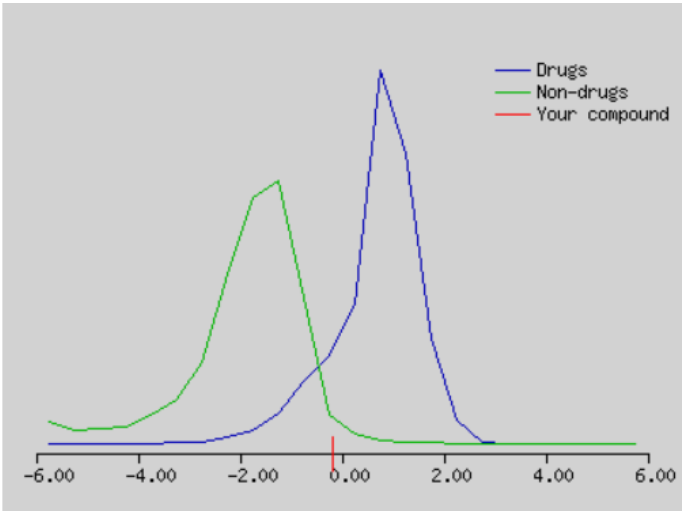
The above figures are of ligands which formed H bonding with the TRIM3 protein in the active site. All other ligands which does not form bonds were rejected for further analysis.

Drug likeness score:

Drug likeness is a qualitative concept used in drug design for how "druglike" a substance is with respect to factors like bioavailability. It is estimated from the molecular structure before the substance is even synthesized and tested.



Drug-likeness model score: 0.63 Fig 4: Sweroside



Drug-likeness model score: -0.17 Fig 5: Matairesinol

The results of drug-likeness score of Sweroside is 0.63 and Matairesinol is -0.17. .Although these two are good, Sweroside has a good score when compared to other one. A molecule is considered as the best drug as it show value close to the drug region in the graph.

Lipinski rule of five

Lipinski's rule of five also known as the pfizer's rule of five or simply the rule of five (ro5) is a rule of thumb to evaluate druglikeness or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans. The rule was formulated by Christophera.Lipinski in 1997, based on the observation that most medication drugs are relatively small and lipophilic molecules.

Table: 3 showing Lipinski rule of five with additional parameters

MOLECULAR FORMULA	**MOLECULAR WEIGHT (g/mol)**	**NO: OF HBA**	**NO:OF HBD**	**MOL LOG P**	**MOL LOG S**	**MOL PSA**	**MOL VOL**
C16H22O9	358.13	9	4	-0.95	-1.00	111.17	334.71
C20H22O6	358.14	6	2	2.03	-2.57	70.90	347.39

ADME properties

ADME is an abbreviation in pharmacokinetics and pharmacology for absorption, distribution, metabolism and excretion. Optimization of the ADME (Absorption, Distribution, Metabolism, and Excretion) properties of the drug molecule is often the most difficult and challenging part of the whole drug discovery process. The ADME profile will also have a major impact on the likelihood of success of a drug.

Table:4 showing ADME properties

ADME	**Sweroside**	**Matairesinol**
BBB permeant	No	No
Bioavailability score	0.56	0.55
GI absorption	Low	High
Skin permeation (cm/s)	-9.14	-6.17
PAIN alerts	0	0

CONCLUSION

Drug design, often referred to as rational drug design or simply rational design, is the inventive process of finding new medications based on the knowledge of a biological target. The drug is most commonly an organic small molecule that activates or inhibits the function of a biomolecule such as a protein, which in turn results in a therapeutic benefit to the patient. Drug design frequently but not necessarily relies on computer modeling techniques. This type of modeling is often referred to as computer-aided drug design (CADD).In recent years the field of Computer-Aided Drug Design (CADD) has grown rapidly enhancing our understanding of complex biological processes and protein-ligand interactions. The main objective of this work was to find the inhibitors of TRIM3 protein for Blood Cancer. Ligands were docked using the autodock tool and 2 molecules that can be used as a drug is found out. They are Sweroside and Matairesinol. The best drug was selected according to their drug-likeness score, Lipinski's rule of 5, H-bonds and ADME properties. Docking studies were done with 25 compounds. Sweroside and Matairesinol showed hydrogen bonds with 7QRW.These molecules follow Lipinski rule of 5 as well as ADME properties. Sweroside from *Swertia chirayita* and Matairesinol from *Punica granatum* L. can potentially inhibit the overproduction of TRIM3 proteins, thus these traditional medicinal plants play an important role in cancer treatment. From the study, it is clear that these 2 molecules are potential inhibitors for TRIM3 protein as the target for Blood Cancer and can act as a drug candidate yet pharmacological study will yet confirm it to be promising.