IDENTIFICATION OF NATURAL BRAF INHIBITORS AS POTENTIAL ALTERNATIVES TO DABRAFENIB: AN IN SILICO STUDY

A Thesis Submitted

In Partial Fulfilment of the Requirements for the Degree of

MASTER OF TECHNOLOGY

In

Bioinformatics

by

HARSHITA THAKUR

(2K23/BIO/06)

Under the Supervision of

Dr. ASMITA DAS

Associate Professor, Department of Biotechnology

Department of Biotechnology

DELHI TECHNOLOGICAL UNIVERSITY

(Formerly Delhi College of Engineering)

Shahbad Daulatpur, Main Bawana Road, Delhi-110042. India

May, 2025

ACKNOWLEDGEMENTS

I would like to express my deep regards to Dr. Asmita Das for her guidance and support during the course of this project. It was her instructions and help which made things easy and motivated me to complete the work in time. Everything was so simply put forward that actually doing the work became pleasant and interesting. This helped me in doing things and learning new skills. I was very fortunate to have this opportunity to work under her.

I would also like to thank to my friends who have been there by my side through thick and thin, motivating me for doing more and achieving goals I long for. I also thank to all the other people in the department who have made the course of time there beneficial and helped me grasping different concepts.

Nothing is complete without the support of family. They are the ones who have contributed tirelessly throughout. There is no word in the vocabulary to express their efforts and affection. I feel fortunate to have this opportunity to study and work and all this has been made possible my them.

Harshita Thakur

DELHI TECHNOLOGICAL UNIVERSITY
(Formerly Delhi College of Engineering)
Shahbad Daulatpur, Main Bawana Road, Delhi-42

CANDIDATE'S DECLARATION

I Harshita Thakur (2K23/BIO/06) hereby certify that the work which is being presented in the thesis entitled "**Identification of natural BRAF inhibitors as potential alternative to Dabrafenib: An *in silico* study"** in partial fulfillment of the requirements for the award of the Degree of Doctor of Philosophy, submitted in the Department of Biotechnology , Delhi Technological University is an authentic record of my own work carried out during the period from January 2025 to May 2025 under the supervision of Dr. Asmita Das.

The matter presented in the thesis has not been submitted by me for the award of any other degree of this or any other Institute.

Candidate's

Signature

This is to certify that the student has incorporated all the corrections suggested by the examiners in the thesis and the statement made by the candidate is correct to the best of our knowledge.

Signature of Supervisor **Signature of Examiner**

DELHI TECHNOLOGICAL UNIVERSITY
(Formerly Delhi College of Engineering)
Shahbad Daulatpur, Main Bawana Road, Delhi-42

CERTIFICATE BY THE SUPERVISOR

Certified that **Harshita Thakur (**2k23/BIO/06) has carried out their search work presented in this thesis entitled **"Identification of natural BRAF inhibitors as potential alternative to Dabrafenib: An *in silico* study"** for the award of **Master of Technology** from Department of Information Technology, Delhi Technological University, Delhi, under my supervision. The thesis embodies results of original work, and studies are carried out by the student herself and the contents of the thesis do not form the basis for the award of any other degree to the candidate or to anybody else from this or any other University/Institution.

Place: Delhi Technological University, Delhi

Date:

Dr. Asmita Das
Supervisor, Associate Professor
Department of Biotechnology
Delhi Technological University

Prof. Yasha Hasija
Head of Department
Department of Biotechnology

IDENTIFICATION OF NATURAL BRAF INHIBITORS AS POTENTIAL ALTERNATIVES TO DABRAFENIB: AN IN SILICO STUDY

Harshita Thakur

ABSTRACT

Melanoma is the most aggressive form of skin cancer that appears to affect a major section of population. It is the sixth most common form of cancer in the United States itself. UV rays are a common mutant which cause the alterations in multiple genes in the melanin producing melanocytes. The mutations in oncogenes along with loss of cell cycle control result in melanoma. This form of cancer has been associated with age as prolonged exposure to UV rays caused oncogenic mutations leading to cancer. But now, due to changing environmental conditions and altered lifestyle and beauty standards, young people and even children are melanoma patients. There are multiple FDA approved drugs and therapies which are used to treat melanoma. Dabrafenib is one such drug which inhibits the mutated BRAF. It has been proved to be useful over the years but due to multiple underlying interactions, there is a general drug resistance and appearance of side effects like hyperglycemia. In this study, computational tools like virtual screening and molecular docking were used to determine multiple off-target interactions of Dabrafenib. AKT which is also responsible for glucose management was figured out to be a major reason behind instances of hyperglycemia in Melanoma patients. Also, attempts were made to identify the natural compound which can be used as an alternative for Dabrafenib. All this is done using AutoDock Vina as a molecular docking tool. We were able to identify a natural compound, Gericudranin A which can be potentially used as a safer alternative for Dabrafenib as it has shown comparative interactions with the target and relatively less likeliness to cause Hyperglycemia.

Keywords: Melanoma, Dabrafenib, Gericudranins A, BRAF inhibitors, AutoDock Vina, Molecular Dynamics Simulation

PUBLICATIONS

- H. Thakur and A. Das, "Comparative Analysis of in Silico Tools for Drug Side Effect Prediction," 2025 International Conference on Intelligent Control, Computing and Communications (IC3), Mathura, India, 2025, pp. 295-298, doi: 10.1109/IC363308.2025.10956741. keywords: {Drugs;Machine learning algorithms;Reviews;Melanoma;Machine learning;Prediction algorithms;Biology;Compounds;Intelligent control;Cancer;molecular docking;autoDock;swissDock;autoDock vina},

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVATIONS

SC	Skin Cancer
SCC	Squamous Cell Carcinoma
BCC	Basal Cell Carcinoma
βC	B Catenin
NCI	National Cancer Institute
CTD	Comparative Toxicogenomics Database
CMNPD	Comprehensive Marine Natural Products Database
NPACT	Naturally Occurring Plant-based Anticancerous Compound Activity Target Database
NPASS	Natural Product Activity and Species Source
TTD	Therapeutic Target Database
LGP	Liver Glycogen Phosphorylase
HGFR	Hepatocyte Growth Factor Receptor
GAK	Cyclin G- associated Kinase
MITF	Micropthalmia Associated Transcription Factor
TERT	Telomerase Reverse Transcriptase
DVL-Daam1	Dishevelled Associated Activator of morphogenesis
NICD	NOTCH Intracellular Domain
FAERS	FDA Adverse Event Reporting System
CaN	Calcineurin
CAMKII	Calmodulin dependent Kinase II
ROR	RAR related Orphan Receptor
ROCK	Rho Activated Kinase
AP1	Activator Protein-1

CHAPTER 1

INTRODUCTION

1.1 Melanoma: The Skin Cancer

Skin Cancer is the sixth most common cancer in the United States and Melanoma is the most aggressive and lethal cancer of them. The changing life styles and environmental conditions are leading to a surge in number of patients year by year. Skin cancer can exist in different forms where the cell of origin determines the type of skin cancer. It appears to be a simple rash or a small mole and remains unnoticed by the patient and this kind of mis-judgement often leads to and aggravated cancer. The most common cause of cancer or the potent carcinogen responsible for skin cancer is Ultraviolet Light and prolonged exposure (usually years) to UV often leads to this disease. Various skin protectants and products like sunscreens have been used for years to prevent this exposure and reduce the chances of developing cancer. This approach has achieved success in terms of reducing the risk by great numbers but certain risks still persist. Areas of the body like head and scalp are mostly exposed to sunlight and environment and no such product has been developed for protecting the scalp and hence cancer can develop in scalp. Protective coverings like caps or hats can be used to reduce the risk but still trends have shown an increase in younger patients and even babies suffering from skin cancers. SC is biased in the sense that chances of a Caucasian developing SC are way higher than that of a Negroid. This is because of the natural pigments produced by the skin which help in combating the adverse effects of UV. This pigment, which provides color to the skin, is called Melanin. Melanoma, the most aggressive form of SC is result of overproduction and over accumulation of the same pigment. It has been found to metastasize at a very fast rate and the most advanced stage of melanoma that is the stage IV melanoma is found responsible for many other forms of cancer. It can reach the lymph nodes and even reach the brain and hence is regarded as one of the most aggressive cancers. The most commonly associated cancers are lung and breast cancer. Multiple studies have deduced common targets which lead to crosstalk between different organs and spread of cancer.

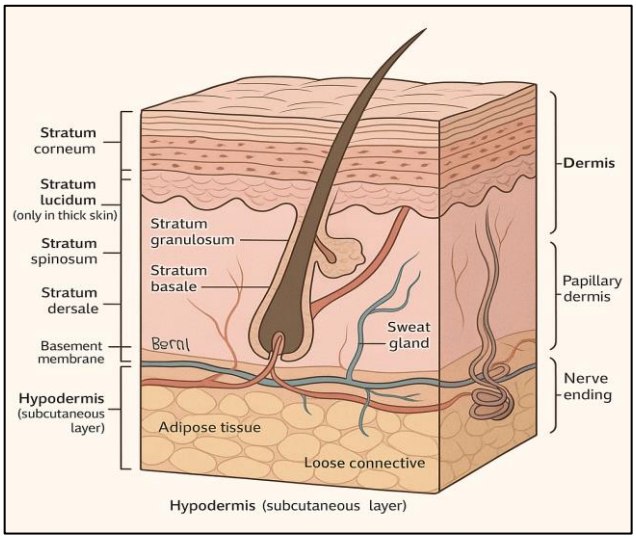

Figure 1 Cross-section of skin

1.1.1 Dabrafenib

Among the different drugs available for Melanoma, Dabrafenib is one such drug which has been approved by the FDA for treatment. It is a BRAF inhibitor which has been used for many years. Melanoma is caused due to mutations in BRAF gene in melanocytes. This leads to uncontrolled growth of these cells. Eventual migration leads to metastases. This is a very risky stage of this cancer. Dabrafenib binds to the mutated BRAF in the MAPK signaling pathway and shields the cells from intensive proliferation.

1.1.2 Rising cases of resistance and Side effects

Due to occurrence of many other mutations impacting other signaling pathways, patients have developed a resistance to this drug. Not only this, there have been reports of certain adverse reactions which patients develop. These side- effects have been discussed in detail in the coming sections.

1.1.3 Natural Compounds: The Healers

Over the years, many natural components have been used to their full potential and it has been discovered that many like resveratrol, curcumin, taxol, vincristine have potential antineoplastic properties. The aim is to find such compounds with similar properties against melanoma and compare if it works as good as Dabrafenib.

1.2 Identifying an Alternative

To identify an alternative to dabrafenib, many databases and tools for Virtual Screening, Molecular Docking and Molecular Dynamics simulation will be used. The compounds with similar target binding behaviors can be considered an alternative. Also, the aim is to identify the reason behind occurrence of side effect. Root cause of the side effect can be identified by considering the off-target associations of the drug.

1.3 What can be the future

To achieve this task, multiple computational tools will be used. This helps in analyzing large data at once and makes the task easy. Through Molecular docking, one can confirm the binding patterns of dabrafenib. Virtual screening can be used for identifying potential natural phytochemicals. The shortlisted compounds can then be used for docking with target sites in order to figure out the potential candidates. This study opens the path to create and discover new compounds which can help save lives and find simpler, safer and effective solutions to a disease like melanoma.

CHAPTER 2

REVIEW OF LITERATURE

2.1 Melanoma

Melanoma is a form of skin cancer which occurs when melanocytes lose the cell cycle control or bear mutations in the signaling pathway genes. These melanocytes are special type of dendritic cells present in skin where they serve the major role of producing melanin, a protective pigment which naturally protects skin from UV rays of sunlight. Melanocytes originate in the neural crest and then migrate extensively to skin and various parts of the body like uveal mucosa, inner ear, rectum etc. If we look at a cross section of skin, it is divided into two major parts, epidermis and the dermis. They are separated by a thin layer of cells called the basal cells organized in a wavy fashion. The outer layer which is epidermis comprises of keratinocytes connected through different types of connective junctions at different levels. Outer layer is made of dead keratinocytes as the cells differentiate and deposit on the outer side of the skin. Melanocytes are dispersed in these keratinocytes. Next layer, the dermis comprises of blood vessels and nerves, hair follicles and several glands. Melanocytes mature in these hair follicles. This is followed up by the layer of fat which gets stored here and serves multiple purposes.

Melanocytes produce melanin which is synthesized and packed in form of small vesicles called melanosomes. These small packets are released and are free to migrate to other cells and get deposited in various squamous cells of the body apart from skin. The main role of this pigment is to absorb UV and protect cell from DNA damage caused due to this UV exposure. For this these melanosomes get deposited near nucleus of other cells such that the melanosomes cover the nucleus up and block nucleus from coming in direct contact of UV rays. This in a way directly acts as a blockage for the normally growing cells (Burge S. a., 2010). To assist the function of melanocytes, sunscreens are applied topically to support body's natural defense. This has helped in reducing the number of melanoma patients over years. But there are still loop holes in this man- made defense as certain parts of the human body aren't always covered. Areas, like head, where sunscreen is not be applied are rendered defense less and hence can develop melanoma over years. Also, various mutations can occur, causing the increase in spread of this disease.

2.1.1 Early stages may be asymptomatic

The conversion of a normal melanocyte involves multiple stages and intermediates. A simple benign nevus doesn't convert to a melanoma very often. It is the location of the affected cells which make the system susceptible to melanoma. When the benign nevus originates near the basal cells or the epidermal-dermal junction, it becomes more likely to develop into a melanoma. This arises due to multiple mutations in the melanocytes. The early melanoma tends to grow radially and hence is termed as radial growth phase of melanoma. At this stage, the cells rarely cross the basement layer. This stage can persist for many years without causing any serious ailment and can stay un noticed. The vertical growth phase begins when the cells pile up and cross the basement membrane. This gives a raised- up appearance to melanoma. This is the stage where the melanoma starts to become metastatic. This location and clonal change causes metastasis. The metastatic melanoma migrates from the dermal-epidermal junction and reach up to liver, lungs and even brain through lymph nodes. This is the most advanced stage of cancer and it can be very difficult to trace and treat once it has metastasized.

2.2 Can SC be prevented?

There are multiple studies being carried to figure out the way human body can be protected against the ill effects of UV rays. Several awareness programs have also been initiated to apprise people about the repercussions of prolonged UV exposure, be it natural or the indoor UV exposure. Sun blockers with significant SPFs have been in use for a long time but how far are they effective in preventing melanoma or any other form of skin cancer is lesser known. Sunscreens have been found to work significantly in preventing squamous cell carcinoma and they may be effective against melanoma and basal cell carcinoma. There has not been any significant advancement in this area of research but this doesn't rule out the necessity to wear an effective sun blocker. The other ways for photoprotection involves understanding the way UV radiations affect body and what possible changes they make. It has been found that the vitamins and their derivatives can play a major role in preventing melanomagenesis (Sample A, 2018). Vitamin A, B, D directly can influence the functioning of melanocytes. Vitamin D3 is majorly absorbed in the lower layers of dermis after interaction with UVB rays. Active forms of vitamin D3 have been linked to be associated with lower chances of developing malignant melanoma. Vitamin B3 plays a major role in regulating oxidative/ reductive activity of a large number of cells in form of enzymes in form of nicotinamide adenine dinucleotide (NAD). Nicotinamide has been proven to be effective as a chemo-protectant by some studies. Retinoids which are derivatives of Vitamin A has been used earlier for treating bladder cancer and liver and breast cancer. Administration of acitretin can help in chemoprevention of some forms of skin cancer. Topical application of tretinoin has been tried for malignant melanoma but yet not much has been researched. β- carotene is another photo-protectant which has been used

previously to deal with photosensitivity (Hyeraci, 2023). Many such compounds have shown to be effective. Their incorporation in diet or consumption as supplements can prove effective and help in avoiding the terror of melanoma and other skin cancers.

2.3 Mutational Aspects of the Cancer

Different genes have been associated with localized form of melanoma. The major site of mutation is the tyrosine receptor kinase in the MAPK Kinase pathway. The major genes involved are KIT, RAF and RAS. The major mutation occurs in the RAF and RAS in case of cutaneous melanoma where UV rays cause the major damage resulting in the typical C>T point mutation. Mucosal melanoma on the other hand arises due to mutations in c-Kit (Davis, 2018). Other erroneous mutations which can possibly give rise to melanoma include PTEN, PI3K, TERT, PPP6C etc. It has been found that melanoma has more sequence per mega base of DNA compared to most other cancers. Mutation occurs in either the DNA giving rise to proteins functioning in balance of cell cycle or cell cycle checkpoints. This means that cell growth pathways of melanocytes are inflicted due to the occurrence of mutations. To understand this entire pathogenesis, it is crucial to know how these orchestrated events manage normal working and what all conditions give rise to melanoma. There are several signaling pathways and check point inhibitors which monitor is the cell is growing and dividing normally. These pathways involve a cascade of events and several small proteins are involved in maintaining normal replication. When even a single protein moiety gets mutated, its function gets disrupted and this destroys the entire network of a normal replicative machinery. Most of the pathways involved are interconnected and hence a modification at even one step can alter the entire microenvironment of the cell. This can hence give rise to cancer. Melanoma also involves such disruption and multiple pathways are involved in this. Mutation in any one can cause a serious after effect. Many pathways are disrupted in melanocytes when they transform into an oncogenic cell. Here major affected pathways and mutations associated with them are discussed in brief (Guo, 2021).

2.3.1 RAS-RAF-MAP Kinase Pathway: Activation of ERK1/ 2 kinases occurs due to signaling by RAS/RAF. This pathway regulates a variety of proteins. MITF is one of the TFs present in melanocytes, which is under the control of ERK signaling. Prevalence of activating MAPK pathway mutations across many tumor types has been discovered (Burotto, 2014). RAS is a family of GTPases which acts as proto-oncogenes. The common RAS proteins occurring in cellular machinery are KRAS, NRAS and HRAS. Mutations associated with NRAS give rise to metastatic melanoma whereas mutations in HRAS don't lead to metastasis. RAF is a family of serine/threonine kinases which acts as oncogenes. Common RAF proteins include ARAF, BRAF and CRAF. Mutations in BRAF are central to melanoma. V600E and V600K are most common mutations which lead to melanoma. This alteration can

increase the catalytic activity of BRAF upto 200 times but BRAF, when activated can't lead to cancer beyond the preliminary stages of tumor. Mutations in BRAF and other mutations combined lead to the formation of complexed forms of melanoma, for example, loss of PTEN causes invasive melanoma. MEK mutations are rare in melanoma many such inhibitory compounds have been tested which work against melanoma caused due to this mutation (Alqathama, 2020). NF1 is a tumor suppressor gene which undergoes inactivating mutations. It codes a neurofibromin (RAS GAP) which normally negatively controls RAS signaling by cleaving RAS-GTP. Loss of NF1 leads to dysregulated RAS signaling. MALT1, MKK4/7 and JNK/AP1 signaling cascade promotes melanoma cell proliferation and migration whereas CYLD inhibits it (Yajima, 2012).

2.3.2 Cell Cycle Regulators: The entire cell cycle is under control of RB signaling pathway. At times, absence or deletion of RB locus is has been associated with occurrence of melanoma (DeVita, 2023). Germline mutations in this pathway (CDKN2A, CDK4) are detected in melanoma. CDKN2A locus is associated with familial melanoma. Loss of p^{16} causes increased activation of CDK 4/6 cyclin D1 complex. Loss of ARF down modulates p53 by increased activation of MDM2. Downregulation of two tumor suppressor pathways is caused due to deletion of locus. Protein's interaction with INK4A is disrupted due to a point mutation in CDK4. INK4A is bona fide genetic dysregulation of p53 pathway seems obligatory for melanoma genesis. Somatic amplification of CDK4 observed in sporadic melanoma. CDK4 drives cell through G1/S checkpoint. Some CDK4 inhibitors have entered the clinical trials for therapy. CCND1 encodes cyclin D1 kinase which forms a complex with CDK4 and CDK6. Amplification of CCND1 has been observed in rare events in melanoma. Mutation in TP53 locus occurs in >50% 0f tumors. Amplification in MDM2 which inhibits p53 has also been detected in melanoma (DeVita, 2023). Loss of p53 coordinates with BRAF and activated HRAS. PI3K-AKT pathway signaling coordinates RAS/RAF/MAPK activation in some melanoma. Loss of PTEN can result in increased AKT activity in many sorts of cancers including melanoma. This occurs with complementation of BRAF. AKT and PI3K are attractive targets for melanomas. Copy number gain of AKT3 locus has been found in melanoma. AKT can be activated by point mutations that affect pleckstrin homology domains of protein (Hung, 2025). RTK c-KIT and its ligands (stem cell factor) contribute in melanocyte development. Loss of c-Kit expression and the conversion of benign primary and metastatic melanoma has been linked. Activating mutations and amplifications of KIT gene have been identified in melanoma. Alterations in KIT can lead to upregulation of multiple signaling pathways whereas inhibition of KIT can cause growth inhibition and eventually apoptosis. ERBB4 mutation may affect 20% of melanoma (Li W. S., 2006).

2.3.3 Melanin Synthesis Pathways: MITF is a gene which encodes transcription factor whose function is crucial for survival of normal melanocytes. Amplification of

MITF in melanoma has proved the central role of this transcription factor in melanoma. MITF is essential for survival of melanocyte. E318K is a variant of MITF which can be an indicator of melanoma. ETS transcription factor positively regulates MITF expression in melanoma (ETV1) (Chauhan, 2022). Genetically, red hair color, pale skin phenotypes (RHC) phenotypes is linked to variant alleles of melanocyte specific melanocortin I receptor gene (MCIR) which is central to melanin synthesis. The ligand for G protein coupled MCIR is MSH peptide which activates downstream signaling consisting of a cAMP-CREB/ATF-1 cascade, culminating in induced expression of MITF. Keratinocytes respond to UV by strongly upregulating expression of MSH (Nguyen, 2019). RAC1 is a GTPase which regulates cytoskeletal reorganization and cell identity in melanocytes (Watson, 2014). Mutations in this enzyme, which predominantly is a P29S substitution, can risk the normal growth and development of the cells. It is a very common gene mutation found in melanoma. Two mutations affecting TERT (which encodes a key catalytic component of telomerase enzymes complex). Both mutations generate consensus ETS transcription factor binding motifs in setting of an identical 11 nucleotide stretch suggesting a gain of function effect. High frequency of TERT promoter mutation is found in melanoma and other tumor types (DeVita, 2023) (Yardman-Frank, 2021).

2.3.4 Nuclear Factor-Kappa β Pathway: Activated NFK β translocates to nucleus and leads to transcription of genes involved in cell survival and anti -apoptotic (Carrà, 2020). UV irradiation promotes inflammatory response and cytokine production and these cytokines have NFK β as downstream target (DeVita, 2023).

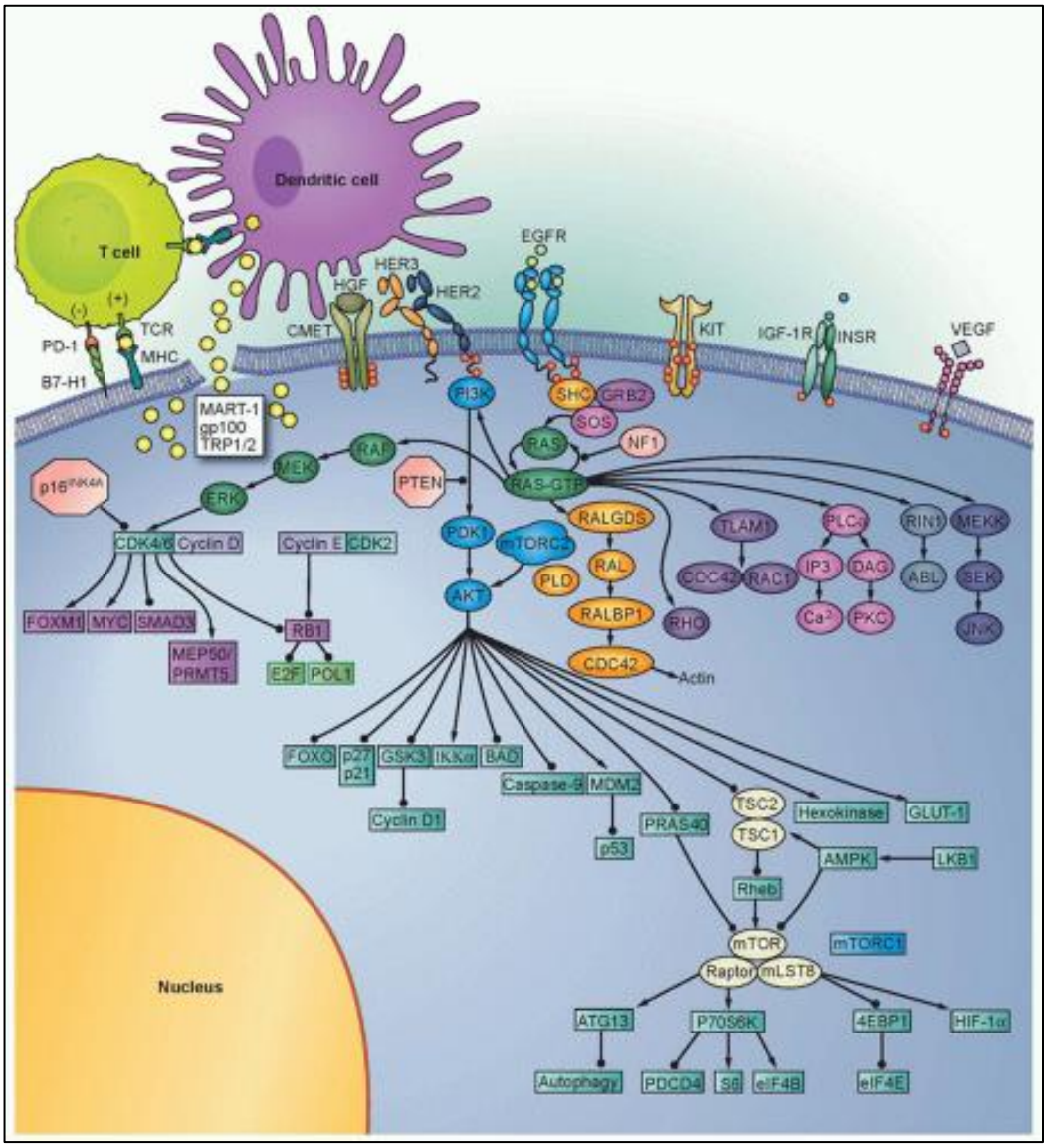

Figure 2 Molecular Basis of Melanoma (Source: Sullivan RJ, Lorusso PM, Flaherty KT. Clinical Cancer Research. Vol. 19. Philadelphia, PA: American Association for Cancer Research; 2013:5286 (DeVita, 2023))

2.3.5 WNT Signaling: It is a special pathway of regulation which works in canonical and non-canonical modes. In canonical pathway, normally level of β catenin (βC) is due to a destruction complex of AXINI, APC, GSK3β, CKIα. B-TrCP tags βC for ubiquitination and proteasomal degradation. WNT signal initiated by binding at FZD receptor and LRP5/6. This inhibits βC degradation. DVL is phosphorylated after interaction with FZD by PAR1/CK1E/MAK/PKC and phosphorylated DVL interacts with destruction complex and removes AXINI. This released AXINI binds to phosphorylated LRP5/6 (phosphorylated by GSK3β). Apart from this a leucin rich repeat containing GPCR5/a root specific spondin complex (LGR5/RSPO) is present that works along with FZD/LRP5/6. This neutralizes RNF43, ZNRF3, transmembrane

E3 ligase. This leads to accumulation of βC in cytoplasm. This translocates to nucleus by associating with nucleoporins and building nuclear pore complex (NPC). It displaces transcriptional repressor Groucho and associates with multiple proteins to link its N terminal with PYGO. Then it acts as transcriptional regulator of the target genes. Mutated βC, because of mutation in CTNNB1 causes melanoma. Mutations alter the phosphorylation pattern of βC making the protein resistant to proteasomal degradation. Apart from this, downregulation of antagonists like DKK1/2/3 have also been found responsible for melanoma (Kovacs, 2016). WNT signalling assists in migration of neural crest cells and drives them towards melanoma onset (differentiation of melanoblast to melanocyte) by activating MITF. WNT1 and WNT3A are crucial for bypassing melanocyte senescence. The non canonical pathway works by using various methods and by this planar cell polarity is maintained (Yongfeng Chen, 2021). The WNT signalling here, is involved in regulation of cell motility and modification of actin cytoskeleton structures. The frizzled receptor complex comprises of FZD receptor and tyrosine kinase coreceptors: Protein tyrosine kinase 7 (PTK7), RAR related orphan receptor (ROR) and receptor like tyrosine kinase (RYK) (Bengoa-Vergniory, 2015). They are activated by binding of WNT5A (WNT5A long and short), WNT7A and WNT11. This activates DVL which forms dishevelled associated activator of morphogenesis I (DVL- Daam1) complex which acts on and activates RHO-GTPase. This acts on and forms ROCK (RHO activated kinase). This helps in modification of actin cytoskeleton and cytoskeletal rearrangements. The other route this pathway follows is by using the JNK-Jun signalling pathway. Here, DVL activates RAC GTPase, JNK, c-Jun and then this activates AP genes which are responsible for modification of actin cytoskeleton structures. The WNT calcium ion signalling helps in modulating canonical WNT signalling. It also helps in controlling the motility of cells but uses different mechanism to operate. Frizzled receptors and WNT ligands activate phospholipase C which in turn through the conventional path activates the calcium calmodulin dependent kinase II (CAMKII) and calcineurin (CaN) (Martinez-Marin, 2025). To inhibit the transcriptional activity of WNT signalling through canonical pathway, NLK gets activated due to phosphorylation of TAKI by CAMKII. CaN activates NFAT which translocates to nucleus resulting in expression of genes pertaining to motility and cytoskeleton organisation. Low level of βC is associated with metastatic melanoma. FZD3 blocking agents may enhance efficacy of melanoma treatment (Gajos-Michniewicz, 2020).

2.3.6 NOTCH Pathway: This signalling machinery comprises a set of different ligands and receptors. α 5- nicotinic acetylcholine receptors (α5- nAchRs) increase in melanoma cell lines and Notch1 signalling pathway is its downstream target. CHRNA5/A3/B4 is associated with lung cancer and some studies show its role in melanoma as well (Improgo, 2010). α 5- nAchR assists in movement and invasion of tumorigenic cells. Its knockdown induces apoptosis in melanoma cells by altering the way apoptotic proteins are produced, it is involved in phosphorylation of PI3K/AKT and ERK1/2. α 5- nAchR affects transcription factor activity, transferase activity, calcium ion binding and notch binding in melanoma cells (Cai Jiaying, 2025). It has

been found out that presence of NOTCH signalling proteins is linked with declining melanoma prognosis so it can have a preventive role (Mikheil, 2023). Notch mutations can be predictive biomarkers for immune checkpoint blockade therapy. Canonical and non -canonical pathways exist in notch signalling. In the canonical notch signalling, mature notch receptor on membrane is a heterodimer which has undergone S1 cleavage in GC. Binding to ligand initiates endocytosis where S2 cleavage occurs. S2 cleavage binding site is exposed due to conformational changes. NICD binding change conformation of CSL repressing complex and recruits activating partners to promote transcription (Zhou, 2022).

2.4 How are Melanoma patients treated?

Most of the preliminary phases of Skin cancer and melanoma are curable and can easily be treated. Both, surgical and topical methods are available and are often used together to bring out the best effect and prevent recurrence of melanoma. For treating such cancers, some topical creams and medicines are used. Here is a list of some of them.

- **Imiquimod**: Imidazolaquinoline promotes cytokine synthesis leading to a specific immune response which generally is cell mediated.
- **5- Fluorouracil**: It inhibits DNA synthesis by disrupting enzymes. On its use, patients can experience some on site reactions like edema, erythema, pain, ulceration and bleeding.
- **Diclofenac**: This can inhibit cyclooxygenase which can increase as a result of melanoma.
- **Retinoids**: Melanoma patients are topically and orally administered with retinoids. They downregulate expression of AP1 response genes, and activate transcription of AP1 which curb development and induce apoptosis and differentiation.
- **Ingenol Mebutate**: It induces apoptosis in tumorigenic cells and helps in generating effector immune response (Burge S. R., 2016) (DeVita, 2023).

These were some of the topically used medicines and therapies. They are useful at stages zero to three. When melanoma progresses further, it doesn't make use of these chemicals solely. Instead, drugs are administered to patients. The National Cancer Institute (NCI) has a list of therapies and drugs which are used to treat melanoma patients. Most of them are used to deal with patients in which mutations are sole cause of melanoma.

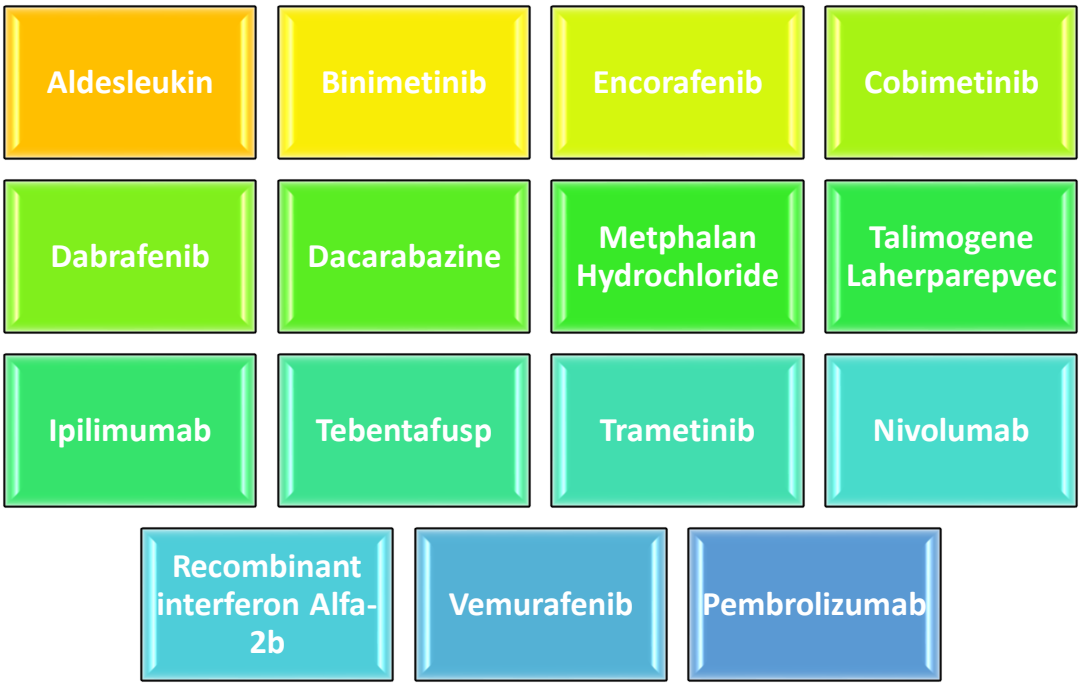

Figure 3 List of FDA Approved Drugs

Of these enlisted methods, some are checkpoint inhibitors that is antibodies which have been approved for treatment and some are chemical compounds known to cure melanoma. BRAF is the major target for most of these drugs and they have been used to design them. They are administered in patients with invasive melanoma. They are used in combination or individually to treat cancer patients. Major BRAF inhibitors are Vemurafenib (Bollag, 2012), Dacarbazine (Abdullah A. Al-Badr, 2016), Trametinib (Zeiser R, 2018), Dabrafenib (Garzón-Orjuela N, 2020). Vemurafenib is the most common drug used to treat Melanoma patients but over time, it has been observed that many patients have developed resistance to this drug and in general to most other BRAF inhibitors as the other mutations are also responsible for the diseased condition compensate for the mutated BRAF correction. Other drugs also used for similar effects and have been approved by FDA. The drugs for overcoming effects of mutations other than those in BRAF are still under trials and none of them have been able to make it up to the market and public use.

2.5 BRAF inhibitors and their efficiency

BRAF V600E mutation is the major cause of this disease. This impacts the MAPK pathway and alters signalling through it. The mutated BRAF has an increased kinase activity. Melanocytes somehow escape the upstream control of RAS and tyrosine kinase receptors due to this, making them capable of independently functioning

(replicating and proliferating). This finding helped in designing suitable BRAF inhibitors which can bind and block mutated BRAF. Vemurafenib, Dabrafenib, Trametinib are some of the widely used $BRAF^{V600E}$ blockers. Dabrafenib is one such drug approved by the FDA. It is reversible and competitive kinase inhibitor which has shown to block the activity of $BRAF^{mut}$. Initial trials revealed that dabrafenib is not only effective against $BRAF^{mut}$, but also can to some extent target the metastasized cancer particularly, in the brain. Insignificant toxicities and adverse events were recorded in the preliminary stages of trials. Studies also propose the use of dabrafenib as an adjunct for brain metastases treatment due to satisfactory intracranial activity and less toxicities. A study conducted to analyse the long-term effects of using Dabrafenib and trametinib in early-stage melanoma shows how this combination is helpful in not only eliminating the tumor but also renders patients relapse free. The 5 year- long study calculated a 65% relapse free survival in the early stage III melanoma (Reinhard Dummer, 2020). BRAF mutations have been elucidated as the lead cause of melanoma, but is has been figured out that it is responsible for the initial stages of this cancer. The later stages involve a complex interplay of several underlying mutations. Metastases is a result of $BRAF^{mut}$ along with others like disruption of PTEN or Rab signaling. This is the reason behind resistance of these BRAF blockers in melanoma patients. Several other differences in genes coding for other house- keeping proteins join hands with mutations in BRAF to give rise to metastasis which is in fact the most lethal form of skin cancer. Multiple drugs have been used together to achieve better results. Other checkpoint therapies are also used in addition to the given kinase inhibitors to achieve better results. Many such therapies proved to be effective in early stages of use but often have to be discontinued due to unknown reasons. There has been no substantial evidence to establish relationship between the observed adverse effects and factors like sex, age, body mass. This finding rejects the concept of pharmacokinetics and therefore monitoring doses or changing them will have no impact on the adverse events observed upon administration of dabrafenib or any of its combination therapy (Isberner, 2022).

2.6 Adverse Drug Events of Dabrafenib

As many other drugs, Dabrafenib also has possible ill effects which have made it difficult for the oncologists to prescribe it. Initially, it was found that the drug is not associated with serious side effects or toxicities. But after its use over the time, many cases of side effects have been reported. They mostly arise due to long term administration of the drug. Side effects occur due to non- target interactions of a chemical compound. As a drug in administered in the body, it can bind at multiple locations making the body susceptible to any sort of adverse effect. The fact that dabrafenib is a kinase inhibitor and it is administered orally, make it possible for the drug to bind to a non- target receptor. Though dabrafenib binds to mutated form of the serine/threonine kinase, it can also associate with the wild type form as well. But the prescribed dosage for the drug to associate with wild type is not apt. It would require nearly 5 times of the dosage of dabrafenib to do so (Menzies, 2014). This can be the reason why no immediate side effects are observed upon administration. Prolonged

use of dabrafenib may cause certain off-target interactions and lead to some other condition which we call a side effect. Multiple cutaneous adverse events have been reported due the use of dabrafenib. These include photosensitivity, inflammatory dermatoses, lesions like actinic keratoses, alopecia (Gençler, 2016) (Macdonald, 2015). Similar conditions can also be observed upon administration of other pathway blockers and therapies. Diarrhoea, vomiting, nauseas and even gastric polyps are some of the reported gastrointestinal side effects of administering dabrafenib (Sloot, 2014). These are some of the cases reported in literature. Once the drug is made available for public use, it can have an immense number of reactions in different populations. All such events have to be recorded and addressed in order to carry out further developments. There are multiple databases which keep a record of reported adverse events of the approved drugs and those under trials. Large amount of data is available on these databases which can help in analysis the effects of a particular drug and comparing multiple drugs. All the adverse events are recorded for analysis. Comparative Toxicogenomics Database (CTD), SIDER, MetaADEDB, PharmGKB, DrugBank are some of the prominent databases where one can get a plethora of facts and details about any desired drug either approved or under trial. CTD helps in analysing how the chemical compounds interact with genes and corresponding proteins. SIDER provides with information regarding the observed side effects with the underlying stats. SIDER is one of the significant tools which helped in identifying the adverse reactions. MetaADEDB is supported by multiple platforms which record the adverse events caused due to a drug. These databases helped in identifying multiple adverse events that can arise due to prolonged use. Some of them include Lymphopenia, nausea, hyperglycemia, hyponatraemia, pyrexia, athralgia, fatigue and even neoplasm progression. Data available on these databases is obtained from the various authorised reporting bodies like FDA Adverse Event Reporting System and Canada Vigilance. In order to actually understand how are these side effects are caused, one needs to get into how a drug interacts within the body. For that, all of its interactions have to be analysed and determined all possible bindings. This will, in return help in determining the underlying cause of some symptoms. A list of all identified side effects has been mentioned here in Table 3.

Table 1 List of predicted off- targets using databases (Daina A. M., 2019) (Daina A. a., 2024)

Off- Targets					
Drug Bank	**TTD**	**SwissTarget**			
Serine/threonine- protein kinase B-raf	Serine/threonine-protein kinase RIPK2 (RIPK2)	Serine/threonine-protein kinase A-Raf	Tyrosine-protein kinase JAK3	Tyrosine-protein kinase JAK3	Nerve growth factor receptor Trk-A
RAF proto-oncogene serine/threonine-protein kinase	Serine/threonine-protein kinase A-Raf (ARAF)	Serine/threonine-protein kinase RAF	Adenosine A1 receptor	Sodium channel protein type IX alpha subunit	Phosphatidylinositol-4-phosphate 3-kinase C2 domain-containing subunit gamma
Serine/threonine- protein kinase SIK 1	Receptor-interacting serine/threonine-protein	TGF-beta receptor type I	Adenosine A2a receptor	Cell division cycle 2-like protein kinase 6	DNA topoisomerase I

	kinase 3 (RIPK3)				
Serine/threonine- protein kinase Nek 11	MLK-related kinase (MLTK)	Serine/threonine-protein kinase B-raf	Phosphodiesterase 4B	Bradykinin B1 receptor	Cyclophilin A
LIM domain kinase 1	Vascular endothelial growth factor receptor 2 (KDR)	Adenosine A2b receptor	Adenosine A2b receptor	Prostanoid EP3 receptor	Beta-1,4-mannosyl-glycoprotein 4-beta-N-acetylglucosaminyltransferase
	Smoothened homolog (SMO)	Receptor protein-tyrosine kinase erbB-4	Adenosine A3 receptor	Orexin receptor 1	Cathepsin L
		Tyrosine-protein kinase BTK	Nuclear receptor ROR-gamma	L-lactate dehydrogenase B chain	MAP kinase ERK2
		Tyrosine-protein kinase LCK	Estrogen receptor beta	Cholecystokinin B & A receptor	p53-binding protein Mdm-2
		Tyrosine-protein kinase Lyn	Tyrosine-protein kinase JAK1 & JAK 2	Tyrosine-protein kinase TIE-2	Endothelin receptor ET-B
		Activin receptor type-2B	Purinergic receptor P2Y1	Mitogen-activated protein kinase kinase kinase 14	Serine/threonine-protein kinase GAK
		Carbonic anhydrase II	TRAF2- and NCK-interacting kinase	Serine/threonine-protein kinase AKT	Bromodomain-containing protein 4
		L-lactate dehydrogenase A chain	Orexin receptor 2	Carbonic anhydrase IV	Receptor protein-tyrosine kinase erbB-2
		Serine/threonine-protein kinase mTOR	Thrombin and coagulation factor X	Peroxisome proliferator-activated receptor alpha	Cytochrome P450 19A1
		PI3-kinase p110-beta subunit	Endothelin receptor ET-A	Peroxisome proliferator-activated receptor gamm	Purinergic receptor P2Y12
		Serine/threonine protein phosphatase PP1-alpha catalytic subunit	Cathepsin (B and K) Ephrin type-B receptor 1	Serine/threonine-protein kinase ILK-1 Ephrin type-A receptor 1	Dual specificity mitogen-activated protein kinase kinase 1
		Hepatocyte growth factor receptor	Kelch-like ECH-associated protein 1	Cathepsin K	Prostanoid EP4 receptor
		Matrix metalloproteinase 13	Solute carrier family 22 member 12	Liver glycogen phosphorylase	Vascular endothelial growth factor receptor 3
		Estradiol 17-beta-dehydrogenase 1 and dehydrogenase 2	C-C chemokine receptor type 9	Histone deacetylase 1	Inhibitor of nuclear factor kappa B kinase beta subunit
		Kinesin-1 heavy chain/ Tyrosine-	Mammalian target of	DNA-dependent protein kinase	Inhibitor of NF-kappa-B kinase (IKK)

protein kinase receptor RET	Rapamycin (mTORC1)

Hyperglycemia is one such side effect which has been observed during many cancer treatments. There are many incidents reported where diabetes has been a major cause of health deterioration across different cancer types. Everything begins with insulin resistance and can potentially lead to diabetes. Even a paediatric study revealed that patients administered with dabrafenib over some time develop hyperglycemia. Apart from those who are already predisposed to it, hyperglycemia is prevalent in otherwise healthy patients as well (Jalal, 2025). Hyponatraemia was also one of the major side-effect in this study. To determine the reason behind such unforeseen symptoms, we have to determine off target interactions. Many possible binding sites were obtained from databases like SwissTarget in order to determine the off- target interactions a drug can have. Such information can also be obtained from CTD. Multiple possible off-targets predicted by SwissTarget are given here. This significantly helped in shaping the entire study and is a starting point of search. To establish relationship between these sites and drugs, molecular docking can be performed and compared with the target. Multiple such sites have been identified with possible interactions. To confirm that tools like AutoDock Vina are used. Here we seek to determine if hyperglycemia is possible ADE of dabrafenib and if this is so, what is the reason behind it.

2.6.1 What can cause Hyperglycemia?

Hyperglycemia is a medical condition where the blood glucose level exceeds beyond the acceptable range. This may occur due to insulin resistance in the body or when body is incapable of utilising the insulin. Mostly Type II Diabetes is the result of such insulin resistance. Glucose isn't used as energy source. This is prevalent in many cancer patients other than melanoma as well. Multiple factors can cause this. Elevated cortisol levels is one of the reasons. Immune checkpoint inhibitors can also disrupt the normal sugar uptake (Gauci, 2018). It has also been found that drugs like mTOR inhibitors (Vergès, 2015), or PI3K/AKT inhibitors can accelerate the insulin resistance and hence cause hyperglycemia. This is a problematic situation as there is no solution to this. The only possible way to prevent this "side-effect" is to stop administration of drug which anyways is dangerous for the patient (LA, 2021). It is seen that AKT1 is a potential off-target of Dabrafenib which implies that Dabrafenib can also block AKT1 which can disrupt the pathway of glucose uptake. This can be associated with the pathway of insulin resistance where AKT1 acts on AS160, a substrate which is phosphorylated by AKT. This in turn is a prerequisite for translocation of GLUT4 (glucose transporter) (Mîinea, 2005). The RabGAP domain of AS160 is actually phosphorylated by AKT and when AKT is engaged or blocked by a drug like Dabrafenib, it can't function and hence leads to hyperglycemia (Bingxian Xie, 2016).

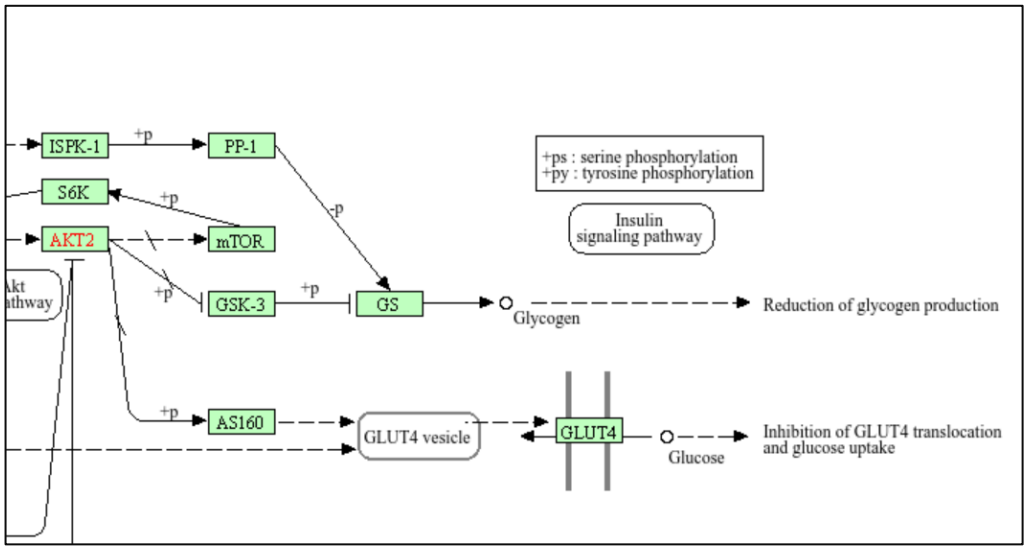

Figure 4 Role of AKT is Glucose metabolism and IR

2.7 Can we develop natural chemotherapeutics?

Many different cultures have been using plants and other components of nature to cure many diseases. Not only they are used as therapeutic compounds but, they have a preventive ability against many diseases. Chemo- preventive potential of many compounds has been tested and many edible items like turmeric which are readily available in household have shown promising outcomes. Plant products, marine compounds, insect products and even compounds form many animals have been tested for their potential (Han, 2022). Any cancer patient when exposed to radiotherapy suffers a great deal of after- effects. Radiation can lead to weakening of the immune system and increased inflammation in the body, leaving a long recovery period for patients. Natural medicines or Traditional Chinese Medicines can help in eliminating tumors by inducing senescence (Liu Y, 2020). Though they need a comparatively longer duration to work, but reduction in tumorigenic cells is feasible in minimum damage to the body with long term benefits. Senescence can be induced through many ways. There can be a change in tumor microenvironment, a change or damage in the DNA sequence or inhibition of telomerase activity. There are several classes of natural compounds which have shown promising results in inducing senescence. Flavonoids, terpenoids, phenolics, alkaloids are some of the major classes. Many of these compounds have proven their efficiency in controlling the growing tumor and curbing the reckless cell division. There ae multiple ways a compound can help prevent or cure cancer. They can assist in senescence, as discussed earlier, through multiple pathways (Naeem, 2022). Cells can be blocked from reproducing, growth can be inhibited, apoptosis pathways can be upregulated, immune system can be assisted in identifying the abnormal cells and eliminating them. Such proteins can be targeted which support the tumor growth, also the signalling pathways which may be oncogenic can be regulated. Mutations can be corrected or such targets can be identified which are causing abnormalities in these pathways and they can be selectively blocked. There

are multiple options available and correct method for cancer treatment can be derived through proper genetic testing of the patients. There are multiple such compounds which have been associated with chemotherapeutic properties. Some of the examples are discussed briefly. Taxol, Vinblastin and Vincristin are some of the earliest antineoplastic compounds to be discovered and their role in eradicating cancer has been well studied. They assist in cell lysis by interfering with the microtubule synthesis in cancerous cells particularly in case of breast cancer and lymphoma (Shaik, 2022). Many derivatives from these compounds have been used to treat different carcinomas. Not only plants, but such compounds can be microbial and marine in origin. Actinomycin D, Mitomycin C, anthracylcin are some microbial compounds which have been approved by the FDA for use as antineoplastics (G., 2020). Many compounds have been tested in the animal models for different types of skin cancer. Hinokitiol is such compound which has proved anti -cancer effect against SCC. *Azadirachta indica* is an important plant used throughout the Indian subcontinent for its antimicrobial properties. It has always been a topic of research for its valuable compounds. Research finds that the leaf extracts of neem have potential as carcinopreventive against SCC. This has been proven in animal model (Mali, 2023). Capsaicin is another component which has been found to suppress protooncogenic pathways in breast cancer. Apigenin is flavonoid found to have significant anticancer effect in multiple cell lines. It is known to work for various types of cancers including melanoma. It targets the Erk/MAPK pathway and is also known to be effective in regulating many signalling pathways. These compounds may be toxic but only when they are consumed in high concentrations and such thresholds are usually high for the green compounds. The natural compounds have been combined with many FDA approved drugs in order to achieve a complete eradication of the disease. The combination therapies can help in avoiding tumor relapse. They are an adjuvant to conventional treatment methods and can work by destroying the cancer stem cells, preventing angiogenesis and hence restricting tumor growth (Sheema Hashem, 2022). These compounds hence prove to be of immense use in targeting melanoma as it is known for its metastatic nature and the main aim is to prevent this. The main issue with such NPs is the way they interact in the body and how is the delivery at specific sites possible. Bioavailability has been an issue with them. To solve this, nanoparticles can be used and other delivery methods can be identified which make compound more soluble and bioavailable so that administration is not hindered.

There are multiple databases like CMNPD (Lyu, 2021), NPACT (Mangal, 2013), NPASS (Hui Zhao, 2023), DrugBank, PubChem available where information pertaining to such compounds is available freely. Comprehensive Marine Natural Products Database contains a large number of marine compounds which are known to be bioactive and can be used in drug development. The data available on this database is based on literature and is broadly classified according to the species, compounds, targets and documents. One can simply filter the data as per requirement. Chemical structures, taxonomic profile and geographic details of the species, physicochemical and pharmacokinetic properties are available on the database for a proper

understanding. NPACT Database is a collection of plant derived chemo-protectants. It is also based on data from various findings and literature. Information like species, biological activity, structure, cell lines, molecular targets, inhibitory values etc can be found. One can search for specific cancer types or can look up for the structures directly through SMILES. Other physical properties of the compounds are also available. Natural product activity and species source database is another such database containing information for multiple natural compounds which can be used for drug development. These databases are updated regularly and have been used to preserve knowledge. We were able to collect many such NPs from these databases to help us find something which can replicate the functioning of the FDA approved drugs but also prevent their side effects. In order to derive suitable compounds for the study, one can modify the search as per the requirement of the target or the disease. Such feature is available in many databases and this helps in simplifying the research and reduces the possibilities of randomness. All these databases were used to identify natural compounds and a list of all identified compounds is given here.

Table 2 Natural Compounds derived from various databases (Lyu, 2021) (Mangal, 2013) (Hui Zhao, 2023)

PubChem ID	Compounds
NPASS	
2703	Chelerythrine
165521	5-Hydroxy-2-(4-Hydroxyphenyl) Chromen-4-One
2399	Bisindolylmaleimide IV
73293	Fascaplysin
5004	Quinalizarin
10172943	A-443654
190	Adenine
5287969	Alvocidib
10205	Plumbagin
6436247	Herbimycin
176155	Sb-203580
160355	Seliciclib
8515	Sp-600125
5169	Sb-202190
5329102	Sunitinib
123631	Gefitinib
9995236	Meridianin E
3035817	K-252A
44259	Staurosporine
CMNPD	
CHEMBL4168800	Macrophilone C
137272841	Macrophilone A
9995236	Meridianin E
CHEMBL413188	Isogranulatimide
94391	Dihydroabietic acid
71524406	Sesquibastadin
10396070	Bastadin 7
NPACT	
168115	(10)-Gingerol
588303	Cucurbitacin B
11542508	28-oxoallobetulin
150893	3,5,6,7,8,3',4'-Heptamethphoxyflavone
5317596	4-Gingerol
10664858	LMPK12140267
10453852	5-Desmethylnobiletin
152430	5-Desmethylsinensetin
10498462	(2S)-5,7,3',4'-Tetrahydroxy-6-(1,1-dimethylallyl) flavanone
10315196	6-(1,1-Dimethylallyl) naringenin
10455035	6,8-Diprenyleriodicotyl

442793	Gingerol
5281794	Shogaol
5275725	8-Gingerol
5280442	Acacetin
150068	2-acetylfuro-1,4-naphthoquinone
393601	Aglafoline
11954143	Allobetulin
5281520	Humulene
5281515	Caryophyllene
5281517	beta-Farnesene
638014	beta-Ionone
72326	Betulin
64971	Betulinic Acid
73122	Bruceoside C
2758	Eucalyptol
5282347	Alpha-Tocotrienol
10380681	Dalrubone
5282350	Delta-Tocotrienol
345501	Deoxypodophyllotoxin
5282349	Gamma-Tocotrienol
10445779	Dielsiquinone
4369270	Digitoxigenin
15478	Digoxigenin
51041991	Dinoxin B
5281613	Diosmin
2116	DL-alpha-Tocopherol
440917	Limonene
5281855	Ellagic Acid
10063979	Emorydone
99091	Epiyangambin
83489	Eriocitrin
440735	Eriodictyol
3314	Eugenol
445070	trans-Farnesol
15406	Fenchol
14525	Fenchone
1549778	Geranylacetone
5355856	Geranyl butyrate
10436583	Gericudranins A
42608135	Gericudranins B
10364206	Gericudranins C
348482	Gitoxigenin
72281	Hesperetin
10621	Hesperidin
14542255	Hiravanone

13967183	Hispidol B
441298	Hyperforin
24893995	Isodihydrocostunolide
5280863	Kaempferol
146093	Gossypetin hexamethyl ether
6549	Linalool
21672412	Lobatosides E
5352089	4-Nerolidylcatechol
259846	Lupeol
483221	Malacitanolide
10105653	Marcanine A
10265831	Marcanin B
11779478	Marcanin C
10062464	Marcanine D
1254	Menthol
6986	Menthone
7428	Methyl gallate
194774	Moscatin
31253	Myrcene
53788628	Myricetin
5352000	Myricetin 3-rhamnoside
5487413	Myricetin 3-O-glucuronide
10582	Myrtenol
92180	N(6)-(delta(2)-isopentenyl) adenine
266767	6-(gamma,gamma-Dimethylallylamino) purine riboside
932	Naringenin
442428	Naringin
442431	Narirutin
3084605	Natsudaidain
44258230	Neodiosmin
114627	Neoeriocitrin
289842	Acoschimperoside P
643820	Nerol
1549025	Neryl acetate
72344	Nobiletin
5281553	OCIMENE
205840	Odoroside H
10057	Oleandrin
10494	Oleanolic Acid
7463	P-cymene
16441	Perillaldehyde

10819	Perillyl alcohol
219100	Idronoxil
10205	Plumbagin
155626	P-mentha-2,8—dien-1-ol
442456	Poncirin
10065574	Psorothamnone A
10063027	Psorothamnone B
5280343	Quercetin
97332	Quercetin pentamethyl ether
5352005	Retusin
10503181	Remangilone A
397856	Remangilone C
331783	Rocaglamide
5280805	Rutin
145659	Sinensetin
9991528	Syriacusins A
68077	Tangeretin
439533	Taxifolin
79730	Apigenin trimethyl ether
96118	Tetramethylscutellarein
6989	Thymol
5365996	trans-Farnesol
449093	Trans-Zeatin
65724	Verbenone
2988	Deoxypodorhizone
442048	Isopimaric Acid
9978176	Isopicrodeoxypodophyllotoxin
233299	Picropodophyllotoxin acetate

10801179	2,4,4'-Trihydroxydihydrochalcone
3065428	CID 3065428
586491	2',4'-Dihydroxydihydrochalcone
5376979	2',4'-Dihydroxychalcone
10424988	4,4'-Dihydroxy-2,6-Dimethoxydihydrochalcone
5319081	Loureirin A
5281727	Pterostilbene
185609	4'-Hydroxy-7-methoxyflavan
68071	Pinocembrin
6199	Psoralen
21672700	Colubrinic Acid
151289	Isoevodiamine
5322111	Gamma-caryophyllene
14579	Guaiacylglycerol
5281628	Hispidulin
12313704	Oleanonic acid
638291	5,7,4'-trihydroxyhomoisoflavnone
5473050	Pinostilbene
15378302	14-Hydroxyhypocretenolide
24949855	Sappanene
11708657	7-Hydroxy-3-(4-hydroxybenzyl) chroman

2.8 Computational Tools: a boon for drug discovery

The entire study revolves around the use of multiple databases and tools which have been brought to use at every step. *In silico* approaches have proved to be useful and often less time consuming. All it needs is good software tools to perform the task. To identify what is suitable to use at this level of study, it is crucial to test all the available options and decide what is best. In the process of analysing what is the adverse effect caused by the drug in use, first we need to determine the most prevalent side effects,

then what causes those side effects will be studied. In the course of this study, tools for side effect prediction will be analysed. Cancer therapy often takes a toll on patient, both on physical and psychological aspects. There are multiple drugs and therapies which have been approved for general public use which have shown to cause the unwanted effects in the body. These effects appear due to unsupervised interactions of the administered molecules with various non target components. To address such issues, a different approach has to be used. Identifying such altered responses is possible through databases and various resources available online. Identifying the cause of those unanticipated effects is a challenging task. Computational approach to discover these non-target interactions include pathway- based methods and the chemical structure-based methods.

2.8.1 Pathway Based Approaches

In order to obtain data pertaining to the side effect of the drug, first understand how does it actually work. For this, thorough information about the pathogenesis of disease and mechanism of action of the drug is a prerequisite. This gives a crucial understanding of the functioning of that molecule and should be retrieved through literature study. Information about anti-cancer drugs is available on National Cancer Institute. A list of approved FDA drugs is available with observed side effects and risks. These drugs can be searched in DrugBank (David S Wishart, 2017) and PubChem where more information regarding the drugs can be obtained. All possible information regarding these therapeutic compounds is available on these databases. Next, determine the target sites. These are the sites in the entire body which have shown to interact positively with the ligand alias the drug. Databases like BindingDB (Michael K. Gilson, 2016), Therapeutic Target Database (Ying Zhou, 2024), PHAROS (Keith J Kelleher, 2023), DrugBank (David S Wishart, 2017), SwissTarget (Antoine Daina, 2019), etc provide information on what targets does a particular compound interact with and what causes off-target binding that is determining the factors possibly responsible for the adverse reaction.

2.8.2 Structure Based Approaches

Molecular docking is one of the most favored computational approaches for elucidating the interaction of two molecules. It determines how small molecules behave in the target binding site. Conformation and orientations of a ligand are determined and what is the best way possible for a strong binding can be elucidated from docking results. Such orientations are called poses and the best one is opted. The pose with a low energy is selected to be the best pose and it is used for future references. Molecular docking has been used in researches for drug designing and disease management. There are multiple tools and software programs for the

implementation of this techniques. AutoDock (Stefano Forli, 2016), AMDock (Mario S. Valdés-Tresanco, 2020), MCDock (M Liu, 1999), Glide (Kirkpatrick, 2004), GOLD (Jason Cole, 2005), FRED (McGann, 2012), CHARMM (Hugo Guterres, 2023), ACID (Fan Wang, 2019), AMBER (Gilson, 2021), SwissDock (Marine Bugnon, 2024) (Ute F. Röhrig, 2023) etc.

SIDER or Side Effect Resource (Michael Kuhn I. L., 2016), has been a very useful tool in predicting the side effects caused by each drug. One can easily determine multiple side effects and can even relate the drug labels and the possibilities of side effects. It a web- based tools based on Natural Language Processing and provide a lot of details in one click. All we have to do is provide the search engine with the drug name and it gives a table of side effects. These side effects are presented along with the likelihood of occurrence that is a percentage score is also provided along with the side effect. They can be confirmed from the FAERS (Li Y. L., 2024). It is also a database maintained by USFDA where outcome of drug use and other factors associated with it are recorded for monitoring and research purposes. Other information pertaining to the drug like the various formats of structure are also mentioned which can be used for further studies. Apart from SIDER, side effects of drugs for melanoma are also available on Medline and VigiBase. Once the side effects have been predicted and using these databases, next step is to determine possible off-target associations. This can also be determined with help of databases and to confirm these interactions, docking can be performed. Information regarding such interactions are available on DrugBank (David S Wishart, 2017), Swiss Target (Antoine Daina, 2019), STITCH (Michael Kuhn C. v., 2008), STRING (Damian Szklarczyk, 2023). STITCH and STRING help in understanding the protein- protein interactions which can be useful in determining the indirect association between drug and proteins. DrugBank and SwissTarget on the other hand help in detecting the directly interacting proteins. A list of targets along with miscellaneous information is available on both these sites. As compared to DrugBank, SwissTarget provides a larger list of potential interacting molecules which helps in identifying novel possible outcomes. From these databases, potential associating proteins can be identified which may link up to some adverse effect. These interactions can be confirmed by literature study. Along with this analysis, in silico tools can be used to analyse and confirm the involvement of the drug in use in causing the adverse effect. This can be achieved using molecular docking.

Table 3 Side-effects predicted by SIDER

Side Effect	Data for Drug
Lymphopenia	6%-59%
Gamma-glutamyltransferase increased	2%-56%
Decreased appetite	Very common, 0%-30%
Hypophosphataemia	Common, 0%-47%

Hypoalbuminaemia	0%-53%
Hypokalaemia	2%-29%
Phosphatase alkaline increased	0%-69%
Aspartate aminotransferase increased	0%-60%
Hyperkalaemia	0%-22%
Chills	Very common, 0%- 58%
Body temperature increased	Very common, 0%-71%
Oedema peripheral	0%-31%
Alanine aminotransferase increased	0%-42%
Creatinine increased	0%-24%
Neutropenia	0%-55%
Hyperglycaemia	Common, 0%- 67%
Nausea	Very common, 0%-50.8%
Thrombocytopenia	0%-31%
Hyponatraemia	0%-55%
Pruritus	0%-31%
Bowen's disease	Common
Fatigue	Common, 0%-57%
Keratoacanthoma	Common
Actinic keratosis	Common, 0%-15%
Seborrhoeic keratosis	Common
Skin lesion	Common
Insomnia	0%-18%
Hypocalcaemia	0%-19%
Vomiting	Very common, 0%-43%
Urinary tract infection Leukopenia	0%-13%
Leukopenia	0%-62%
Haemorrhage	0%-16%
Hyperbilirubinaemia	0%-15%
Myalgia	Very common, 0%-24%
Hyperkeratosis	Very common, 0%-37%
Skin papilloma	0-24.1%

Molecular Docking has become a crucial component in drug discovery. It has now become comparatively easy to predict the possible interactions that can occur in the body using this method. Also, it has found many applications in the other areas of medicine and research. Repurposing drugs, finding better alternatives, personalized medicine et cetera are some of the major benefits. Interactions between proteins, protein- ligands, nucleic acids can be analyzed using docking. Various methods like ML, Deep Learning, NN have been used to design tools for performing this task. These tools are available on various platforms and can be used as standalone softwares or are subscription based. The main purpose behind using docking is to predict the binding affinity of the two molecules. To do this, certain scores are provided based on the bonds provided. All the data regarding structure of the molecule is derived from PDB. The

coordinates file of PDB is converted into an actual structure by the software and the binding scores are predicted. Binding energy and RMSD values are used to predict if the participating compound can interact in vivo or not. Molecular docking usually helps in filtering out the undesirable ligands in the process of drug discovery. This is used in virtual screening to reduce the number of ligands in order to screen out the ligand which are less likely to interact with the target. As many tools are available for this process, it is crucial to determine which is handy and more favorable one to use. Molecular docking is performed at the academic level as well, so it is important to know what particular tools can be used to make better predictions at a lower cost, in order to make some fruitful research. Here, we present a comparative analysis of some molecular docking tools. To use these tools, first some information is needed regarding them. Four openly available tools were used in this study and results were compared with each other. Ease of use, quality of output generated, and type of input required were the parameters analysed for every tool. The major tools for Molecular Docking are AutoDock and AutoDock Vina (Oleg Trott, 2010). They are mainly used for academic purposes. AutoDock4 is available at https://autodock.scripps.edu. It is designed to operate for protein-ligand interaction studies. It is based on Lamarckian Genetic Algorithm. A force field scoring function is used to identify the binding affinity (Stefano Forli, 2016). Ligand is optimized for different conformations and each conformation is estimated and interaction energy is predicted. This keeps on improving till a satisfactory score is achieved. AutoDock Vina is an improvement over AutoDock. It is capable of making more accurate and faster predictions as compared to AutoDock. It is based on Local Search Global Optimizer. This tool finds major application in virtual screening. SwissDock (https://www.swissdock.ch/index.php) is a web server- based tool based on Dihedral Space Sampling and EADock. CHARMM energy values are estimated based on grid scores. CB Dock2 is available online. It is a protein- ligand docking server which integrates cavity detection, docking and template fitting (Yang Liu, 2022) (Xiaocong Yang, 2022). It can perform blind docking and has mainly been used for drug discovery. It is based on AutoDock Vina for docking predictions and curvature- based cavity detection for active site prediction. The choice of tools for the entire study will be based on this study only. So, the study progresses by first identifying off-targets and then using molecular docking to establish a relationship between proteins in order to determine reason of observed side effects. Various molecular docking tools were compared in order to use a better one. AutoDock Vina is the most suitable tool of all.

Molecular Dynamics Simulation is another such tool which helps in better understanding how two molecules interact over time. It is possible to understand the effect of the ligand on the receptor molecule through simulation. Better understanding of the type of interactions is achieved through this tool. It almost effectively predicts the way proteins and other targets behave in vivo. Atomic movements of molecules are predicted and are used to generate topologies which help in identifying energy and the behaviour of the molecules. The effect of ligand on the conformation of protein is observed over the time to analyse various properties like ligand interaction, enzymatic activity, drug interactions (Durrant, 2011) (Hollingsworth, 2018). Features like

Binding energy of the complex, RMSD, RMSF, Principal Component Analysis, Radius of gyration, Pearson's cross corelation etc are analysed using this tool. There are tools like GROMACS (Mark James Abraham, 2015), AMBER (Gilson, 2021), NAMD, CHARMM which have been used over the years for predicting how efficiently the compounds can interact. It has now been possible to perform MDS on Colab using the advanced GPUs for a faster and hassle-free run. It is user friendly and takes less time for file preparation and is therefore a more suitable tool for performing simulations. Here, colab has been used to obtain the MDS results. Results for as long as 1 microsecond can be achieved using the colab notebook for MDS and it is immensely helpful particularly in terms of cost and time (Pablo R. Arantes, 2021).

CHAPTER 3

METHODOLOGY

3.1 Outline

The entire project started with literature analysis for identifying the root cause behind Melanoma, a type of skin cancer generating in melanocytes. Various FDA approved drugs and therapies were identified which have been used in treating melanoma patients. Dabrafenib is one of the drugs which is used and it targets mutated BRAF in the MAPK signalling pathway. After this, side effects of Dabrafenib were identified using databases. Databases were used to identify off targets of the drug if existed. Then, through literature analysis again, relation between this off- target binding and occurrence of adverse reactions were identified. It is found that other than BRAF, dabrafenib can also associate with AKT1. To confirm this interaction, Molecular Docking was performed which confirmed the predictions using AutoDock Vina. Later on, a list of natural compounds was generated from multiple databases for comparison with dabrafenib. Virtual Screening was performed for all these compounds using PyRx. 4 compounds were identified with comparable binding energies which was reconfirmed through Molecular Docking on AutoDock Vina. The best result was used for comparison with the dabrafenib. This was later compared by Molecular Dynamics Simulation on the Google Colab platform.

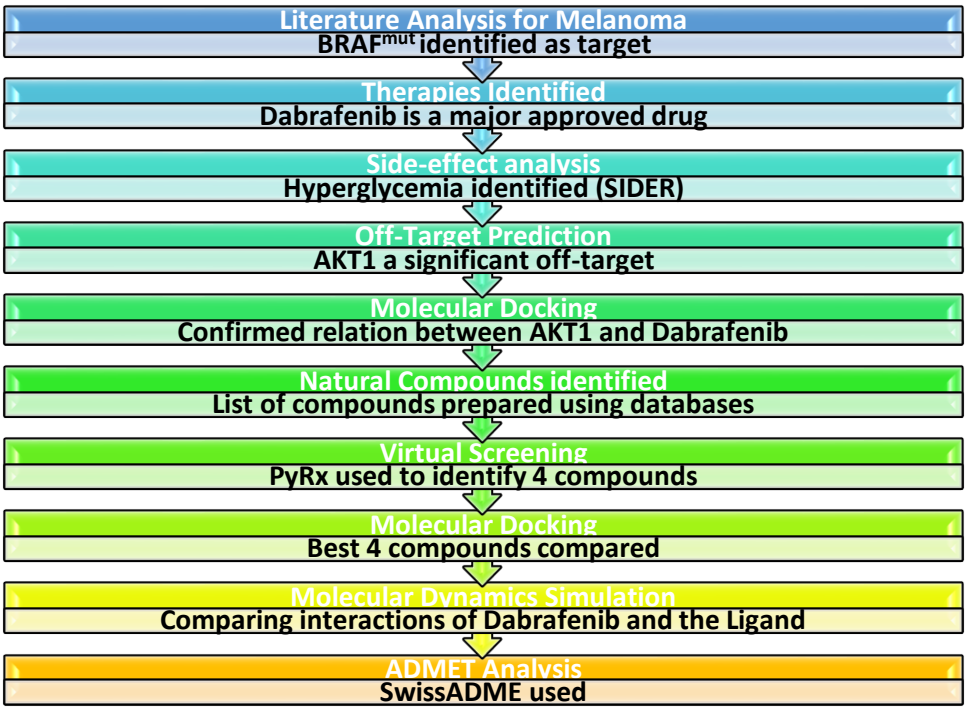

Figure 5Outline of the Study

3.2 Literature study

MAPK pathway is well explored and defined and most abundantly inflicted pathway in terms of Melanoma research. MAPK pathway is mis-regulated due to mutation in BRAF gene which leads to the uncontrolled growth of melanocytes present in any part of the body (mainly skin).

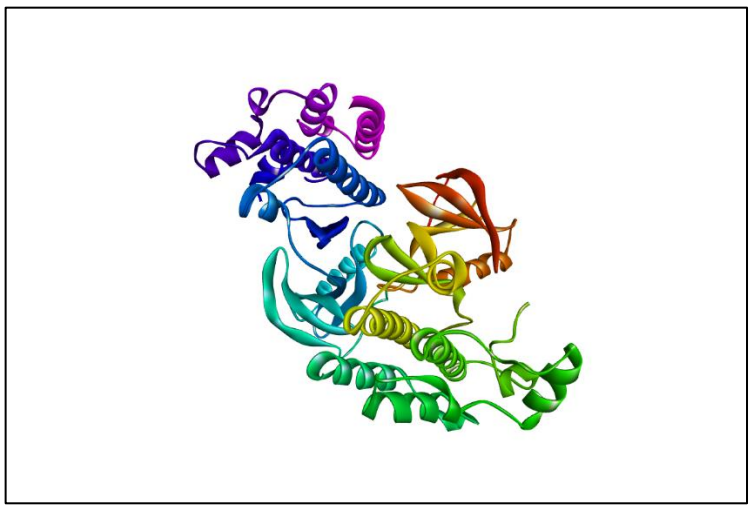

Figure 6 PDB structure of BRAF (5CSW)

3.3 Therapies identified

The National Cancer Institute (NCI) identifies major approved melanoma therapies including drugs and antibodies most of which are developed to work against $BRAF^{mut}$. Vemurafenib, Dabrafenib, Dacarbazine and Trametinib are major BRAF inhibitors used mainly for treatment of Skin and Lung Cancer.

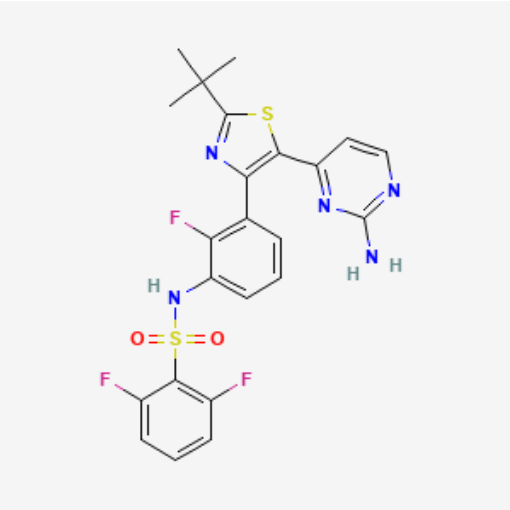

Figure 7 Dabrafenib

3.4 Side- Effect Analysis

SIDER, DrugBank and FAERS were used to search for side effects of Dabrafenib. A list of such side effects was obtained from these platforms which is given. SIDER provided a large number of adverse reactions which can be confirmed. It also associates the probability of these unwanted symptoms with the drug so it seems to be reliable and useful. Hyperglycemia was identified as one of the major side-effects as it is also observed in cancer patients under treatment, in general.

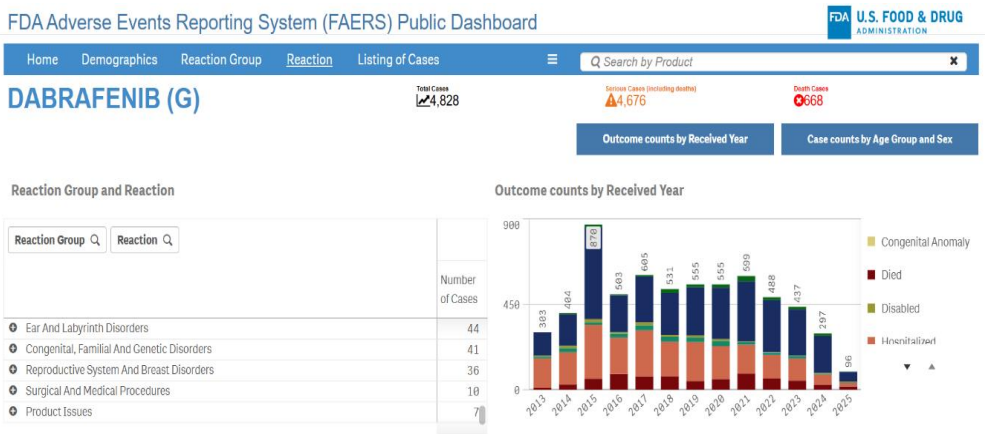

Figure 8 FAERS dashboard with predicted adverse events of Dabrafenib

3.5 Off-target Prediction

The targets other than BRAF are referred to as off-targets as the drug is not intended to associate with them. SwissTarget, Therapeutic Target Database and DrugBank were searched for such possible targets and all of the 3 databases generated tables for such receptors. Table 1 enlists all the identified off-targets. Out of many AKT1 was identified to be a significant one. Others include HGFR, LGP, MAPKinase ERK2, GAK. Though AKT1 can be successfully linked with occurrence of hyperglycemia.

3.6 Molecular Docking

To confirm the interaction of Dabrafenib with AKT1, molecular docking was performed for both the interactions i.e. BRAF-Dabrafenib and AKT1-Dabrafenib. Multiple docking tools were used for this. To do this, first PDB structures were downloaded. Dabrafenib being a ligand, wasn't available on PDB. So, SDF structure of Dabrafenib was obtained from PubChem which was later converted to PDB format using OpenBabel tool. The PDB structure of receptors (BRAF and AKT1) were prepared in BIOVIA Discovery Studio and the co-ordinates of active site were identified. Ligand was prepared in the AutoDock tools itself and then the general protocol of AutoDock Vina was performed to obtain the results. Apart from this, docking was also performed using AutoDock, SwissDock and CB-Dock2 for comparison. AutoDock Vina results are considered here.

3.7 Natural Compound identification

To obtain a list of natural compounds which may have antineoplastic properties, NPACT, NPASS and CMNPD were used. One can modify the search parameters as per requirement. For instance, the filter parameters were adjusted to "serine/threonine kinase" in NPASS to obtain such compounds which can bind to the given prompt. Similarly, NPACT was searched for such compounds which may be effective against SC. A list of compounds was identified.

3.8 Virtual Screening and Docking

PyRx is a competent software used for screening multiple compounds at once. The list generated previously was used for determining interactions with both BRAF and AKT1 for comparison. PyRx is a simple tool. It works on AutoDock Vina. The general protocol starts with uploading the receptor and converting it to pdbqt format. Later on, ligands are uploaded and after conversion to the pdbqt format, energy minimization was performed. Then Vina was initiated to start screening. The active site co-ordinates obtained previously were used and both the receptors were one by one used for VS. The best 4 compounds, Colubrinic Acid, Lupeol, Isopicrodeoxy podophyllotoxin and Gericudranins A were used to perform Molecular Docking with both the receptors on AutoDock Vina and compared to find the best suited natural compound.

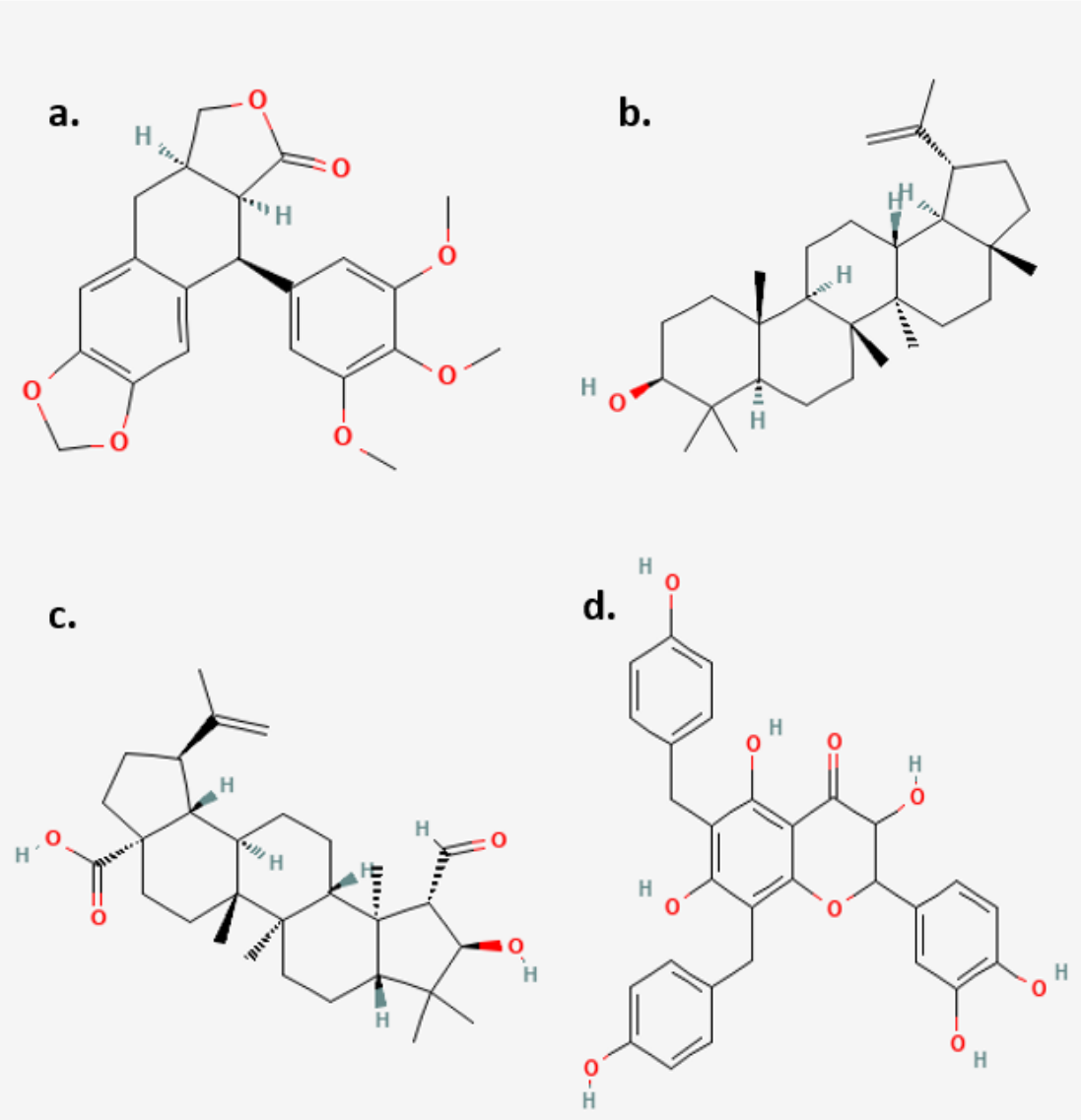

Figure 9 a. Isopicrodeoxypodophyllotoxin, b. Lupeol, c. Colubrinic Acid, d. Gericudranins A

3.9 Molecular Dynamics Simulation

MDS was performed using Google Colab's notebook to save computational time and avoid complexities. It uses google drive to generate files and the results are automatically saved in the drive. Interaction of Dabrafenib with BRAF and AKT1 and interaction of the identified natural compound, Gericudranins A with BRAF and AKT1 were detected by performing MDS and the results were compared for conclusion.

3.10 ADMET Analysis

Both the compounds were tested for ADMET properties in SwissADME. It accepts structure of compound in SMILES format. Various factors like TPSA value, Molecular weight, Drug likeliness, logP values are analysed for both the ligands.

CHAPTER 4

RESULTS

4.1 Side Effect Prediction

Databases were looked for various adverse effects. FAERS and SIDER results have been shown here.

4.2 Off- Target Prediction

Such possible sites were predicted through SwissTarget, TTD and DrugBank. AKT1 (3096), HGFR (1R0P), LGP (2QLL) and GAK (4C59) were identified to be possible sites of undirected binding.

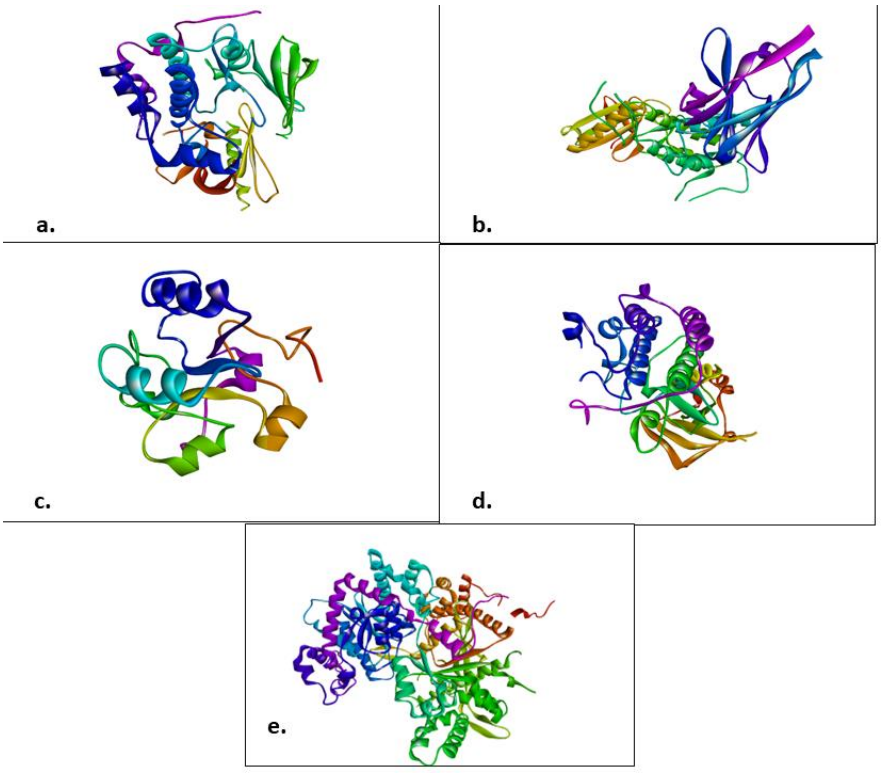

Figure 10 PDB structures of a. GAK, b.MAP Kinase/ERK2, c. HGFR, d. LGP

4.3 Molecular Docking

Docking was performed between BRAF- Dabrafenib and AKT1-Dabrafenib to compare between the two. The following result was obtained. It is clearly evident that binding between AKT-Dabrafenib (-13.7 kcal/ mol) is stronger than that between BRAF- Dabrafenib (-11.7kcal/mol).

Table 4 AutoDock results (Harshita Thakur, 2025)

Parameters → / **Protein-Ligand↓**	**Binding Energy (kcal/mol)**	**Inhibition Constant**	**Reference RMSD**	**STATISTICAL MECHANICAL ANALYSIS**			
				Q	**A (kcal/mol)**	**U (kcal/mol)**	**S (kcal/mol/K)**
BRAF-Dabrafenib	-8.26	881.15 nM	29.73	10.13	-1372.02	-7.78	4.58
AKT-Dabrafenib	-8.02	1.32µM	20.74	10.12	-1371.18	-6.94	4.58

Table 5 AutoDock Vina Results (Harshita Thakur, 2025)

Parameters→ / **Protein-Ligand↓**	**Binding Affinity (kcal/mol)**	**Distance from best mode**	
		Upper bound RMSD	**Lower bound RMSD**
BRAF-Dabrafenib	-11.7	0.000	0.000
AKT-Dabrafenib	-13.7	0.000	0.000

Table 6CB-Dock2 results (Harshita Thakur, 2025)

Parameters→ / **Protein-Ligand↓**	**FitDock score**	**Cavity volume (Å^3)**	**Pocket RMSD**
BRAF-Dabrafenib	-12.8	1931	0.0
AKT-Dabrafenib	100.4	208	3.15

Table 7 SwissDock results (Harshita Thakur, 2025)

Parameters→ **Docking↓**	**SwissParam**	**AC Score**	**RMSD**	**Polar Energy**	**Non-Polar Energy**
BRAF-Dabrafenib	-8.837	-107.373731	46.4366	24.5571	-67.1287
AKT-Dabrafenib	-9.9326	-121.673935	17.5711	17.5711	-74.4133

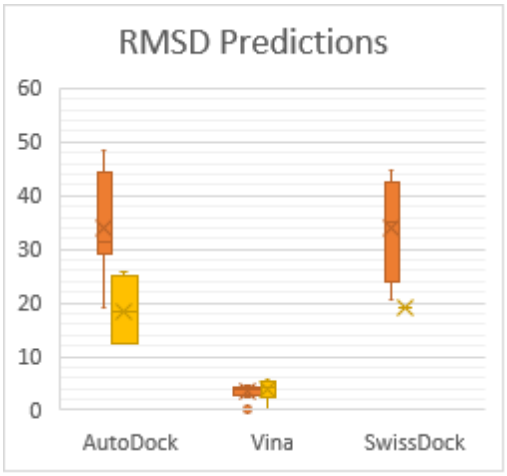

Figure 11 Comparative Analysis of Tools for RMSD predictions (Harshita Thakur, 2025)

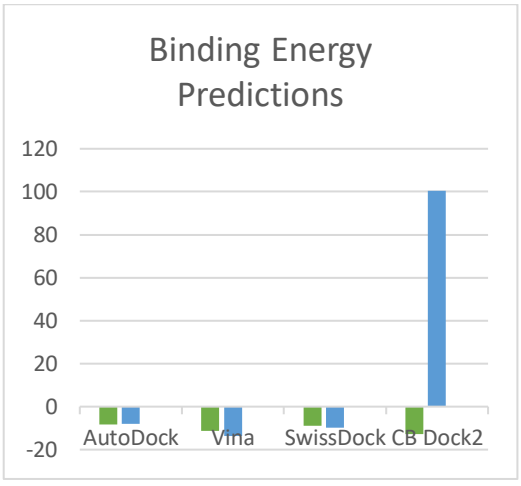

Figure 12 Comparative Analysis of tools for Binding energy (Harshita Thakur, 2025)

These are comparative graphs drawn for various tools stating that AutoDock Vina is the best tool to use. Apart from this, other targets were also analysed and here is a comparative graph for all the potential off-target binding sites which may lead to hyperglycemia.

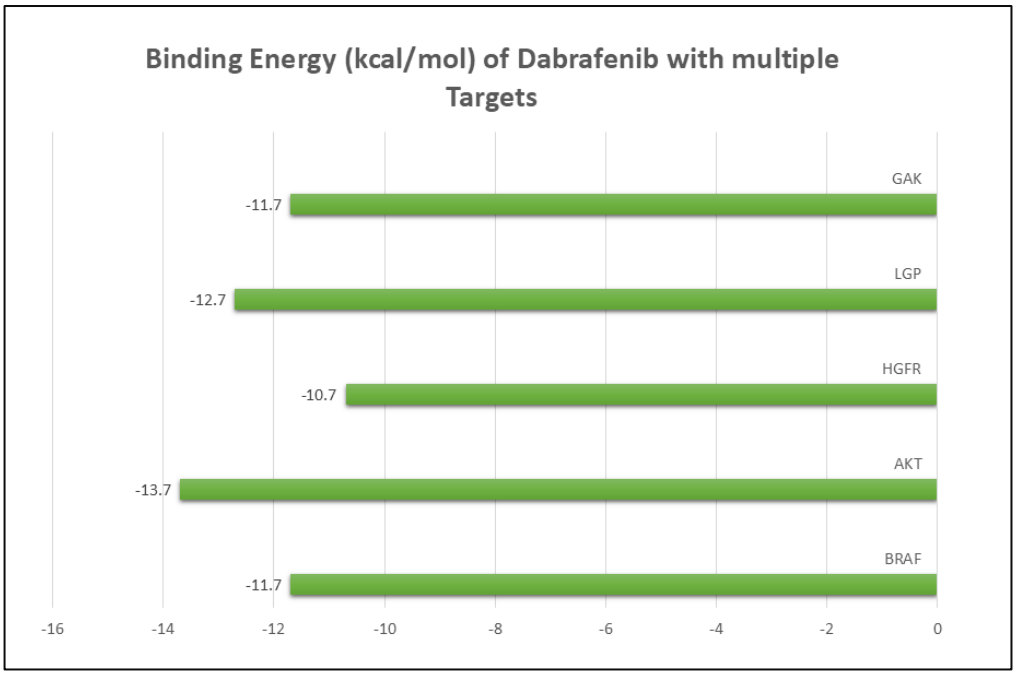

Figure 13 Comparison of Binding Energy between Dabrafenib and various targets

As it is evident that Dabrafenib can associate with multiple targets and all of these, in one way or the other, contribute to the glucose metabolism in the human body. This, in a way highlights how Dabrafenib is responsible for occurrence of Hyperglycemia.

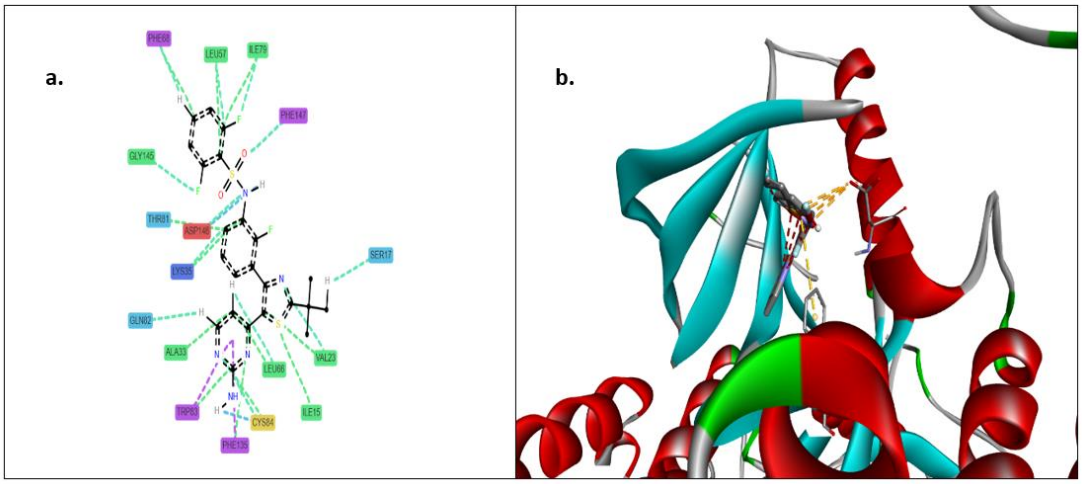

Figure 14 a. 2D interaction plot between BRAF-Dabrafenib, b. Bond formations between the two

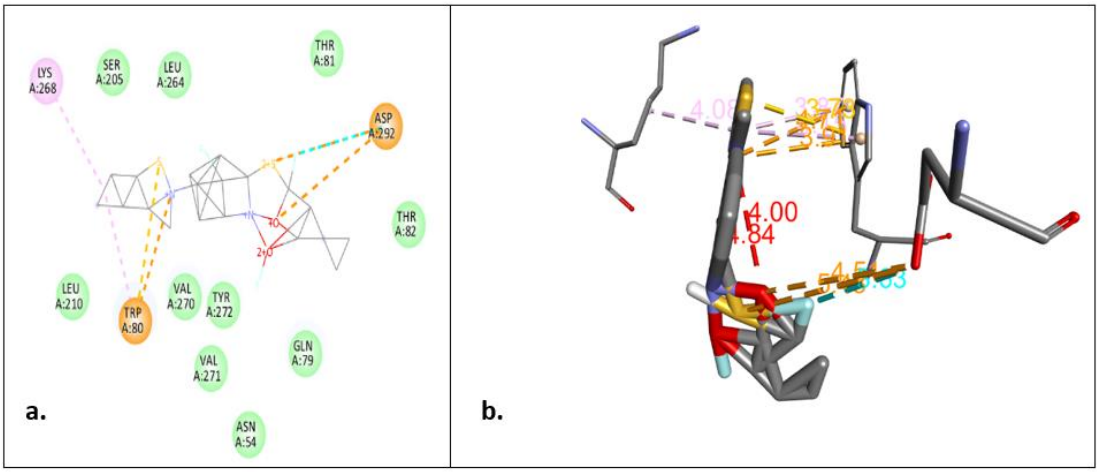

Figure 15 a. 2D interaction plot between AKT-Dabrafenib, b. bond lengths between the two

Comparative analysis of multiple tools showed that Dabrafenib has better affinity for AKT1 which is an off target than the actual target (BRAF). This confirms the binding between the two and provides a substantial reason for the occurrence of hyperglycemia.

4.4 Natural Compound Identification

Through Virtual screening on PyRx, all the compounds listed in table were analysed and some specific compounds were selected for further analysis. This table enlists binding energies of these compounds with BRAF, AKT and LGP. Out of these four compounds, it is evident that Gericudranin A is the most suitable compound to be a drug which can replace dabrafenib and be used as its substitute.

Table 8 Virtual Screening Results derived from PyRx

Macromolecule→		**Binding Energy (Kcal/mol)↓**		
Ligand and PubChem ID↓		**BRAF (target)**	**AKT (off-target)**	**LGP (off-target)**
Dabrafenib (FDA drug)	**44462760**	**-11.7**	**-13.7**	**-12.7**
Colubrinic Acid	21672700	-9.3	-9.8	-8.7
Lupeol	2598176	-9.3	-9.9	-8.7

Isopicrodeoxypodophyllotoxin	9978176	-8.8	-9.4	-7.9
Gericudranins A	10436583	-10.8	-9.8	-10.2
(2S)-1-(1H-Indol-3-YL)-3-{[5-(3-methyl-1H-indazol-5-YL)pyridin-3-YL]oxy}propan-2-amine	10172943	-10.3	-11.3	-9.8
SB 203580	176155	-9.7	-10.5	-9.1
Bisindolylmaleimide IV	2399	-9.5	-10.1	-8.8
Chelerythrine	2703	-9	-11.4	-7.9
Sunitinib	5329102	-9.6	-9.6	-8.5
Alvocidib	5287969	-9.6	-11.2	-8.9
Dehydroabietic Acid	94391	-9.5	-10.4	-8.8
Isogranulatimide	135418335	-9.4	-10.7	-9.2
(2S)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-6,8-bis[(E)-3-methylbut-1-enyl]-2,3-dihydrochromen-4-one	10455035	-9.8	-10.7	-8.9
(2S)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-6-(2-hydroxy-3-methylbut-3-enyl)-8-[(E)-3-methylbut-1-enyl]-2,3-dihydrochromen-4-one	10575105	-9.5	-10.3	-9
Eriocitrin	83489	-9.7	-12	-10.6
Diosmin	5281613	-9.7	-11.6	-10.5
Alpha-Tocotrienol	5282347	-9.9	-9.5	-9.2
Hesperidin	10621	-9.9	-10.9	-10.9
Neoeriocitrin	114627	-9.9	-11.7	-11.1
Naringin	442428	-9.6	-11.7	-10.9
Narirutin	442431	-9.6	-11.7	-10.6
Neodiosmin	44258230	-10.2	-10.3	-11.4
Remangilone C	397856	-9.5	-10.5	-9
Poncirin	442456	-9.6	-12.3	-10.5
Rutin	5280805	-9.4	-11.6	-10.5
Gericudranins C	10364206	-9.5	-10.2	-9.8
cis-3-O-p-hydroxycinnamoyl ursolic acid	24203732	-9.5	-13.3	-10.7
Gericudranins B	42608135	-9.9	-10.4	-9.3
Alpha-Naphthoflavone	11790	-9.9	-11.5	-9.5

This table enlists some of the most suitable results obtained from Virtual Screening. Top four items were picked for selective comparison and further analysis. On comparison between these compounds through Molecular Docking on AutoDock, it was found that Gericudranin A has a comparative binding affinity to BRAF (-10.8 Kcal/mol). It is the closest to that of BRAF-Dabrafenib (-11.7 kcal/mol). This means that both these compounds can associate with the target BRAF in a comparative

manner. Our goal is to identify such a compound which can effectively bind to BRAF but doesn't associate with AKT1 the way dabrafenib does. Gericudranin A matches the same parameter in this case as well. The binding affinity between AKT1 and Dabrafenib is -13.7 kcal/mol whereas that between AKT1 and Gericudranin A is -9.8kcal/mol which is significantly less than the other. This makes it a suitable drug candidate.

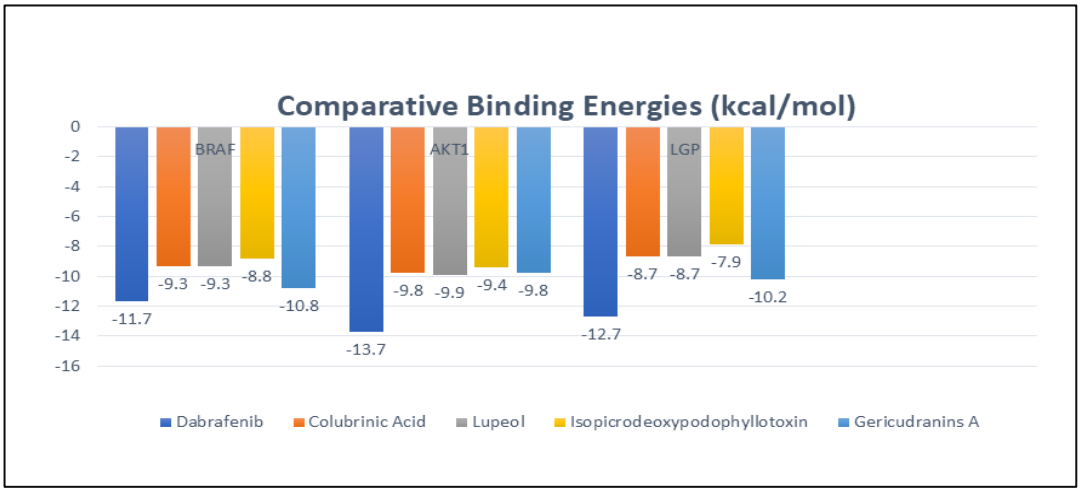

Figure 16 Comparing binding energies for association between BRAF, AKT, LGP and shortlisted Natural Compounds

The docked compounds were visualized in BIOVIA Discovery Studio and here are the interaction diagrams for the same. They represent the 2D interaction diagrams, bond length and type of bonds.

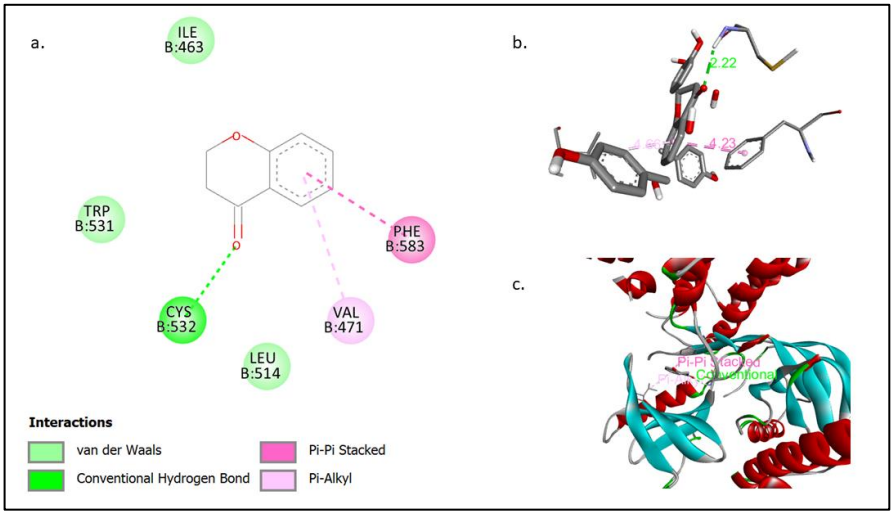

Figure 17a. 2D interaction plot, b. bond lengths, c. types of bonds for interaction between BRAF and Gericudranins A

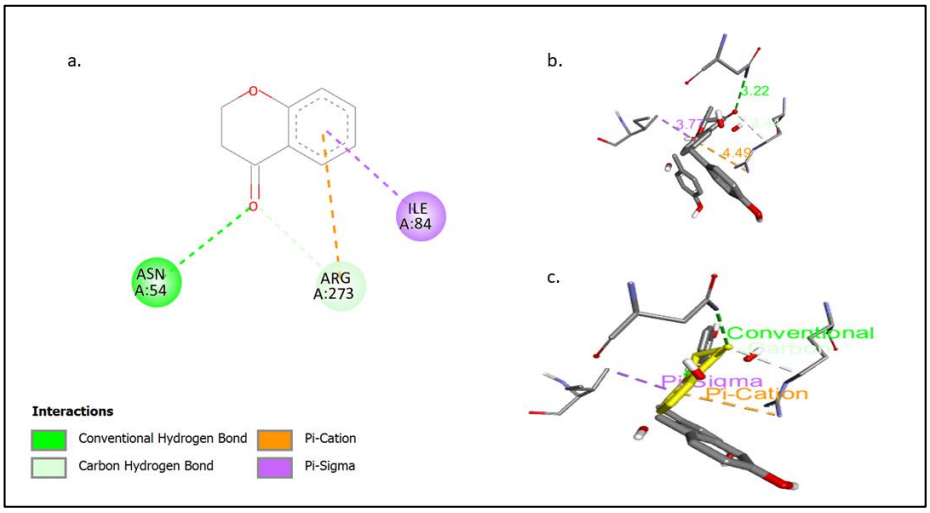

Figure 18a. 2D interaction plot, b. bond lengths, c. types of bonds for interaction between AKT and Gericudranins A

4.5 Molecular Dynamics Simulation

MDS for 4 sets, BRAF-Dabrafenib, BRAF- Gericudranin A, AKT1-Dabrafenib and AKT1-Gericudranin A was performed on Google Colab for 20 nanoseconds each. The RMSD comparison of all four sets suggest that Dabrafenib stably binds to AKT. The RMSD plots also reflect how Gericudranins A can replicate the role of Dabrafenib in associating with BRAF. Higher RMSD values for AKT interacting with Gericudranins A explain how it doesn't interact as efficiently as Dabrafenib does.

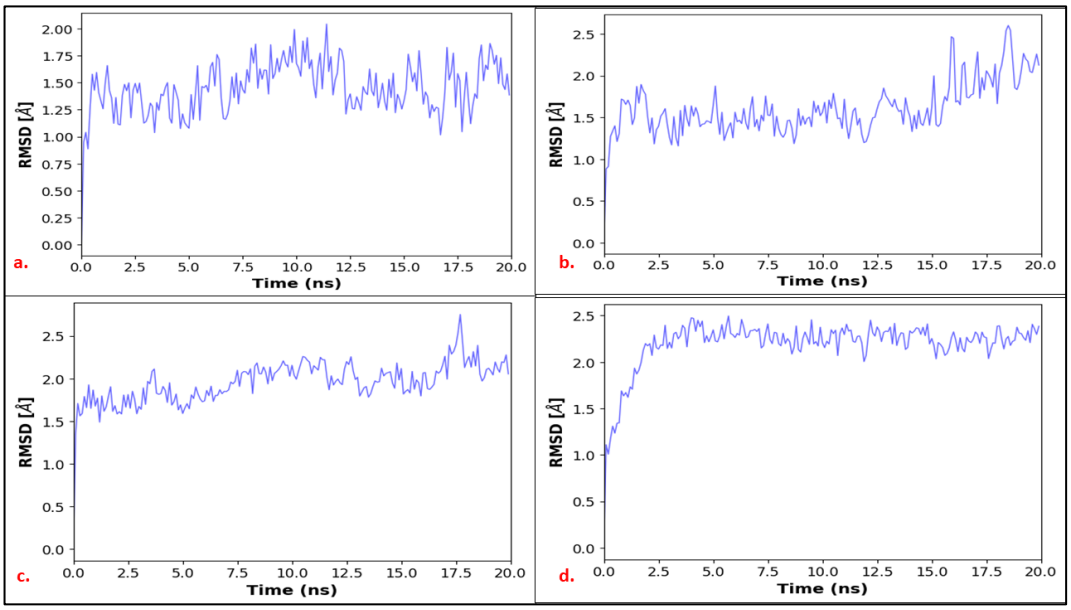

Figure 19 RMSD Plot for interaction between a. BRAF-Dabrafenib, b.BRAF- Gericudranins A, c. AKT-Dabrafenib, d. AKT- Gericudranins A

The given 2D RMSD plot further help in explaining the sort of relationship these proteins have with ligands. A clear purple line in the first plot suggests an overall dynamic system. There are a few specific conformations which exist which are represented with light purple squares along the diagonal. The appearance of prominent purple squares shows lower RMSD values which means presence of stronger and stable interactions. AKT and Dabrafenib RMSD plot displays such purple squares which possibly indicate the stronger binding. Gericudranins A again shows stable interaction with BRAF but lacks this stability with AKT.

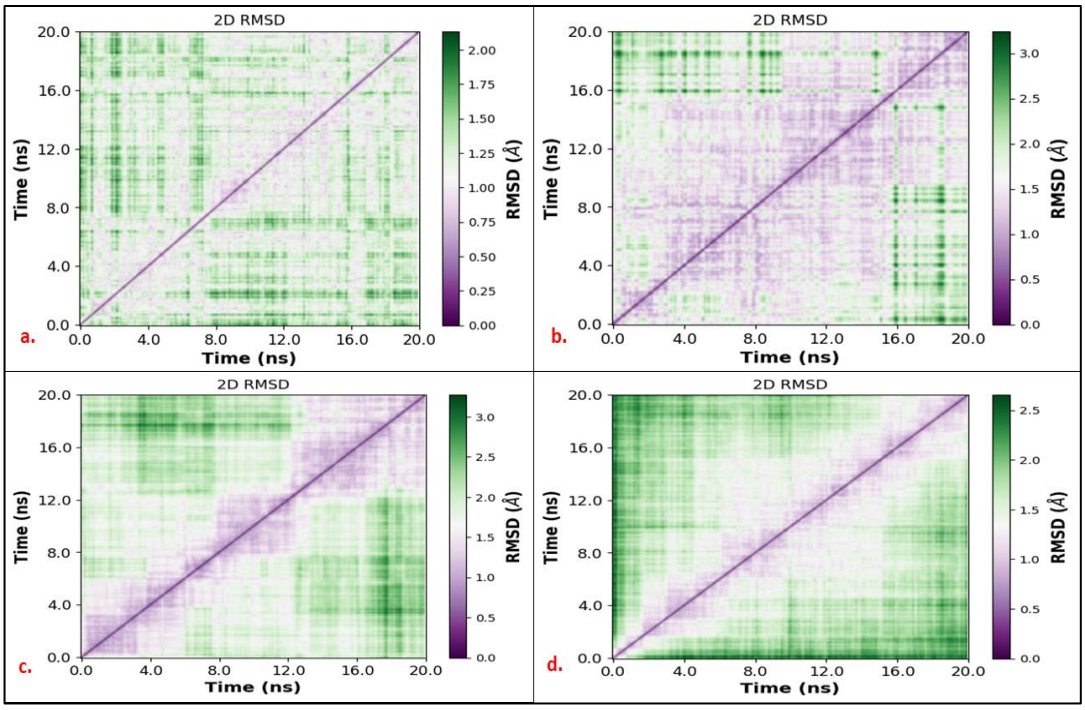

Figure 20 2D RMSD Plot for interaction between a. BRAF-Dabrafenib, b.BRAF- Gericudranins A, c. AKT-Dabrafenib, d. AKT- Gericudranins A

RMSF studies help in analysing the residue in the protein structure which might be interacting with the ligand. They help in identifying the regions or domains where protein might have been stable and regions where flexibility would have existed. Stable regions indicate non-activity residues and the ones with higher RMSF indicate the residues which are interacting. It is difficult to compare proteins in terms of RMSF as they are different in structure and hence may behave differently.

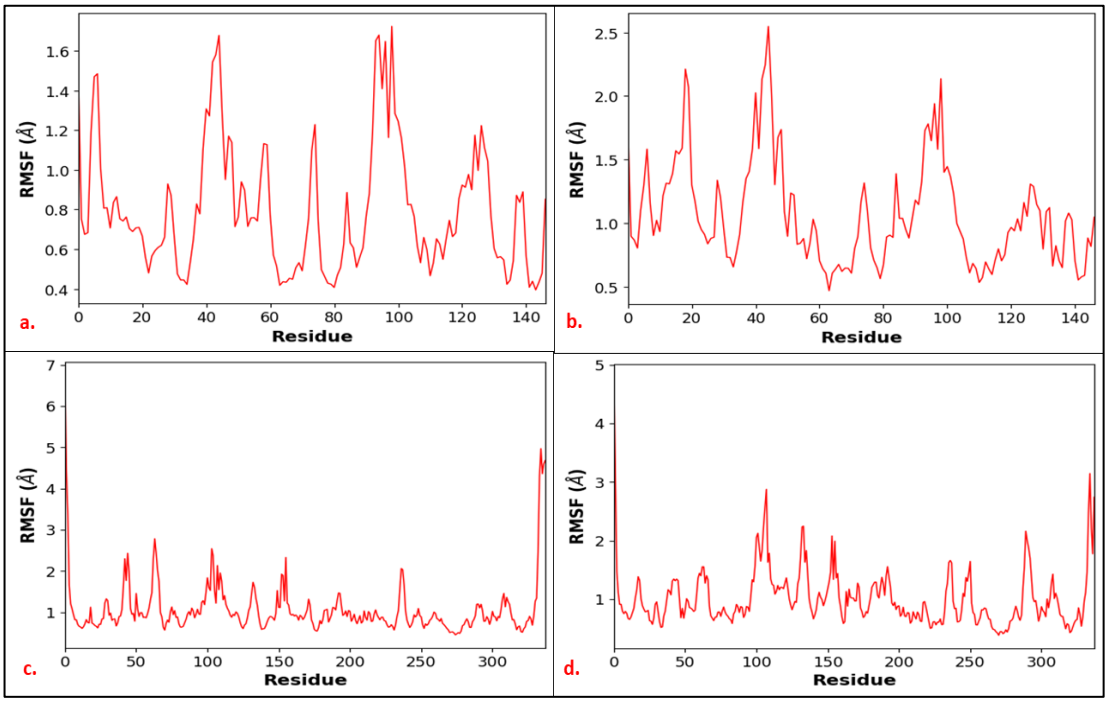

Figure 21 RMSF Plot for interaction between a. BRAF-Dabrafenib, b.BRAF- Gericudranins A, c. AKT-Dabrafenib, d. AKT- Gericudranins A

Radius of gyration analysis helps is identifying how does the structure of protein move and how conformational changes may occur due to a ligand interaction over time. This focuses on stability of the system as well as indicate the way two components of system interact with each other. As we can see here that, on comparing interaction of dabrafenib, system is expanding which implies the protein is interacting better. Even in case of BRAF, the system seems to be expanding in case of Gericudranins A suggesting similar interactions. Comparing interaction of AKT, it can be seen that it expands when binding to Dabrafenib, whereas is contracting in case of Gericudranins A.

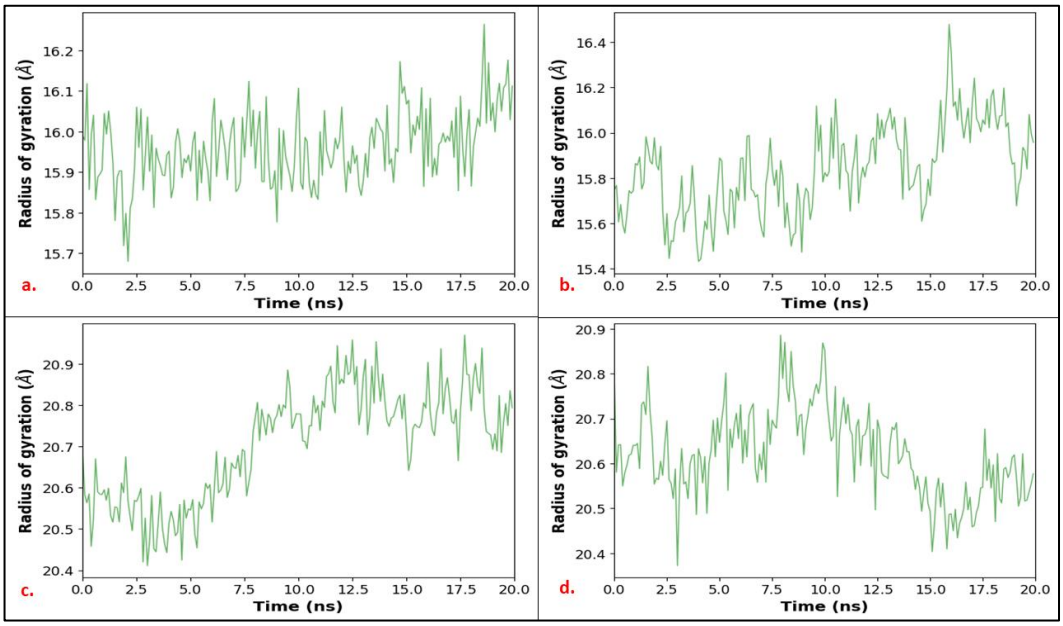

Figure 22 Radius of Gyration Plot for interaction between a. BRAF-Dabrafenib, b.BRAF- Gericudranins A, c. AKT-Dabrafenib, d. AKT- Gericudranins A

This is a comparison between the Principal Components of the four systems showing change in protein conformation over time. As in first two cases, there's not significant clustering, we can say that there is a drastic shift in stability over the time and multiple binding forces are active together. There is no clear distinction between the "open" and "close" stages of the protein. AKT on the other hand, shows significant changes in conformation over time. It moves from a closed conformation to an open conformation over period of 20ns when associating with Dabrafenib, suggesting it is accommodating the drug. Whereas, when interacting with Gericudranins A, it moves from a stable conformation to a close conformation, indicating it may not be associating with the ligand effectively.

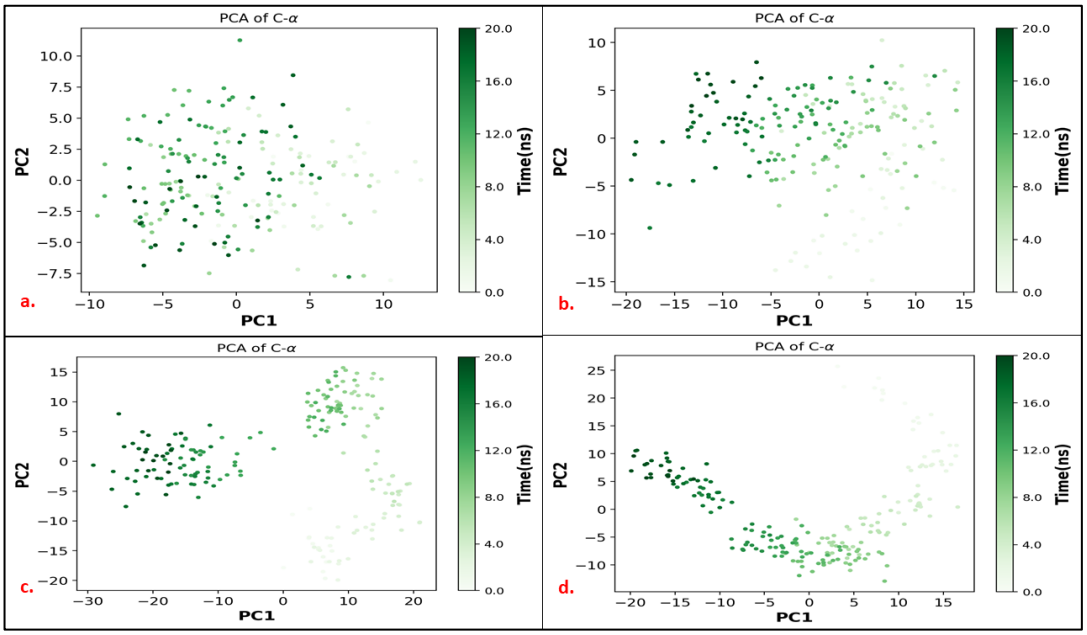

Figure 23 Principal Component Analysis Plot for interaction between a. BRAF-Dabrafenib, b.BRAF- Gericudranins A, c. AKT-Dabrafenib, d. AKT- Gericudranins A

This is Pearson's Cross Corelation Plot for the four sets of interactions. It helps in analysing the corelated motion of residues throughout the time. Positive aur purple C_{ij} values represent corelated motion, i.e both the atoms move in the same direction reflecting that the residues in the regions 20-40, 50 and 90-110 move together and may be are involved in ligand recognition. The similarity in both these plots suggests protein behaves in same way towards the ligands.

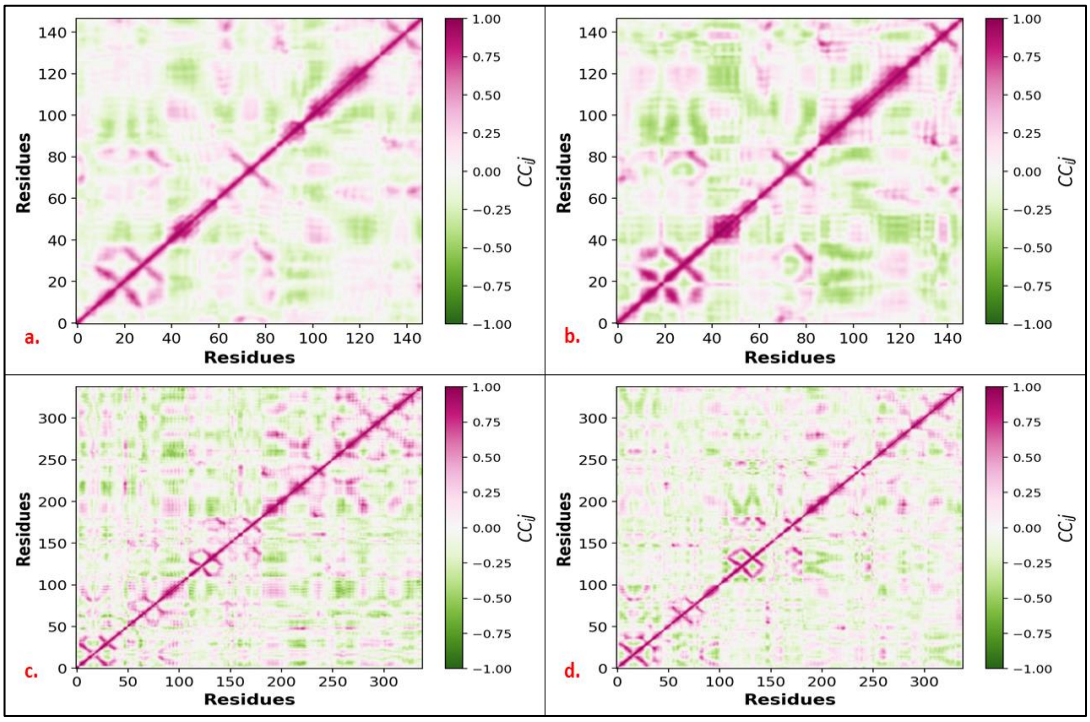

Figure 24 Pearsons's Cross Corelation Plot for interaction between a. BRAF-Dabrafenib, b.BRAF- Gericudranins A, c. AKT-Dabrafenib, d. AKT- Gericudranins A

All these plots helped in understanding the way both proteins behave with both the ligands over the duration of 20ns and we were able to prove the Docking results which suggest better interaction of Dabrafenib to AKT. Also, it is now clear that Gericudranins A mimics Dabrafenib in binding to BRAF whereas doesn't effectively associate with AKT, making it an appropriate candidate for Melanoma curing drug which doesn't cause Hyperglycemia.

4.6 ADMET Properties

The following represents results for ADMET analysis. Both the compounds have comparable molecular weight and other properties like TPSA and drug metabolism also is similar. On some editing and modulation, it is possible to make Gericudranins A, a drug like molecule. In this way, it will become more bioavailable and can be used as a drug. A higher TPSA value of Gericudranin A implies its low absorption in the GI tract whereas permissible ilogP value indicates oral bioavailability. The raw compound definitely leads modulation in order to decrease the Topological Polar Surface Area (TPSA) for better bioavailability in GI tract and increase its drug-likeness.

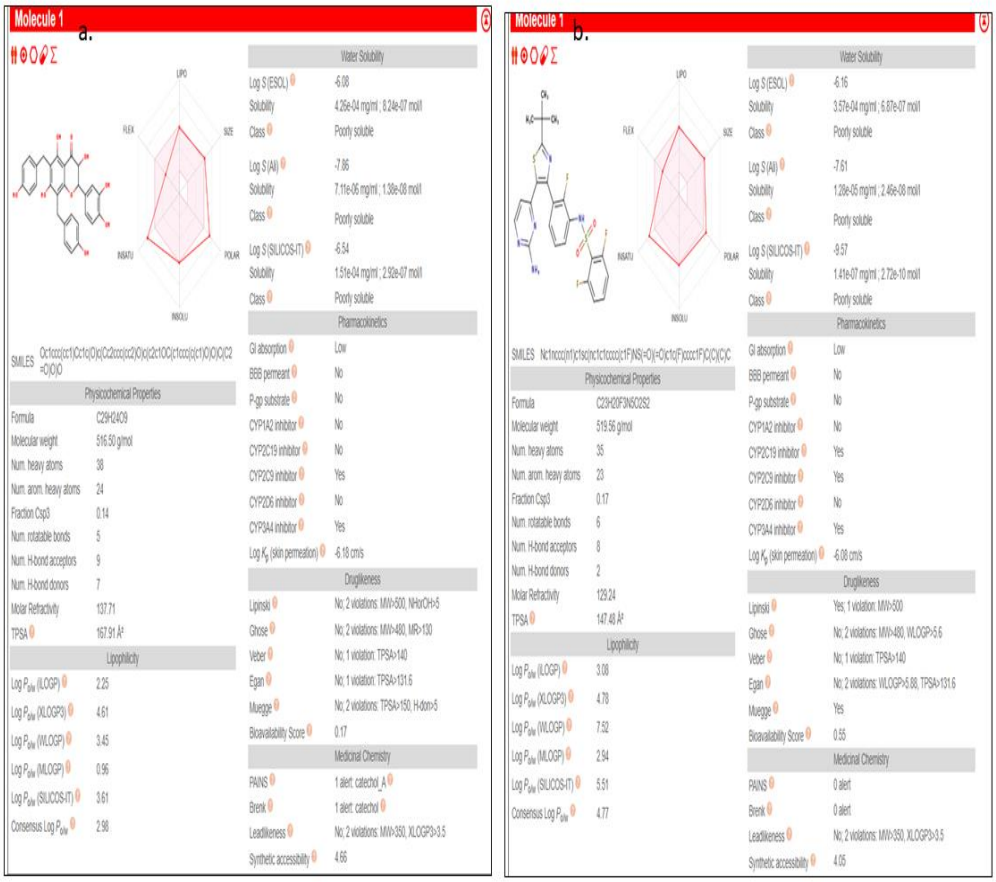

Figure 25 Comparison between ADMET properties of a. Gericudranins A, b. Dabrafenib

CHAPTER 5

DISCUSSION

Melanocytes are the main cells accountable for the pigmentation in skin (production of melanin) and UV protection. Skin color plays a major role in cancer susceptibility. This is due to difference in melanin production. Melanocytes are dendritic cells which migrate from neural crest to the epidermis and the hair follicles. Melanocyte stem cells reside in the hair follicles. Melanocytes are associated with multiple keratinocytes and transport melanin to those keratinocytes in form of small vesicles called melanosomes. These melanosomes move to the sun exposed face of the nucleus of keratinocytes. They synthesize eumelanin (the dark pigment) and phaeomelanin (red-yellow pigment) from tyrosine. UV Radiation causes tanning by stimulating the melanin. It oxidizes the melanin and increases production of melanin. Tanning is a protective mechanism which involves melanin oxidation, production of more melanin and modification in melanosome distribution (Zamudio Díaz, 2024). Mutations cause melanocytes to behave differently and replicate in an uncontrolled fashion leading to melanoma. Various forms of melanoma appear. Most of the time the patients aren't able to identify what is melanoma and how it is impacting them. Various drugs and therapies have been approved by the FDA but they have met some challenges. Vemurafenib which was the first and the most common drug is now showing resistance in patients as other mutations have given rise to melanoma and most of the drugs designed are yet under trials which target other proteins other than BRAF. Dabrafenib administration has certain side effects. In general use of these drugs causes one or the other adverse effect. Hyperglycemia is one of them (Jonathan W. Goldman, 2016). So, it is crucial to find a substitute for such drug. Use of natural compounds has been a part of tradition for many ethnicities and they have practiced it for ages.

There are many phytochemicals which have proved their value in cancer medicine as well. Turmeric has been researched upon to determine the anti- cancer properties and many more plants and natural compounds are under monitor for deciphering something useful and safer. In treating skin cancer as well, *Saraca indica* has been found to have chemo-preventive effects. Other plants identified as useful are *Taxus buccata* and *Emblica officinalis*. It is crucial to identify important metabolites and phytochemicals of anti-cancer properties. This will not only help in making better medicinal compounds but also will promote research in such fields and help in taking the medical biology to every doorstep. Other drugs like Dabrafenib, Trametinib are

used for treating melanoma and are used widely. They too show certain side effects which are nothing but undesirable interactions which give rise to such conditions which instead of curing a person make him sick, that too with some other disease. To analyze Dabrafenib for its side effects (Ng TSC, 2022), docking has to be performed and for that it is crucial to know which tool will be best suited for this process. For this, Autodock, AutoDock Vina, SwissDock, CB-Dock2 were used to compare and determine the best tool for academic use.

Gericudranins A is a potential antineoplastic compound which can be used to treat Melanoma patients. It is a flavonoid obtained from the stems and bark of melon berry (*Cudrania tricuspidata*). Earlier, the extracts of the plant have been used to detect anti-cancer activity in five cancer cell lines for skin, colon, kidney and lymphoid tissue (CRL-1579, UO-31, LOX-IMVI, Molt-4F) (In-Kyoung Lee, 1995). Gericudranins A has shown significant interaction with BRAF, the actual mutated site causing Melanoma. On contrary, it doesn't associate with AKT as efficiently as dabrafenib does, thus avoiding occurrence of side effects. This is a desired asect of the drug. Our study highlighted not only how the hyperglycemia can occur but also light was shed on how dabrafenib can engage with multiple targets which can possibly cause the adverse reaction. It can be said that Gericudranins A can be used as a substitute for Dabrafenib. Though there can be some discrepancies in terms of the ADMET properties of the compound, it still is comparable to the approved drug and can be resolved with minor changes in the structure.

CHAPTER 6

CONCLUSION

There are multiple treatments available for Melanoma which is caused due to mutations in BRAF gene. Prominent drugs administered to such patients include Vemurafenib, Dabrafenib, Trametinib. These all are beneficial against specific BRAF mutations. Over the years, multiple studies have highlighted how other underlying mutations in the major signalling pathways can also been a sole reason behind Melanoma. This explains why multiple patients have developed a resistance for the classical treatment options. Reason behind this resistance is not that the drug is being rejected. But it simply means it is ineffective as something else is causing cancer. Unfortunately, there is no approved drug or treatment available at present which is effective on other mutated targets. Natural compounds offer a great helping hand in eradicating invasive cancers like Melanoma because of the long- term therapeutic benefits they offer. As this study highlights, they can be used to develop better alternatives for the drugs present. We saw that the unwanted interactions of Dabrafenib can cause hyperglycemia in patients and it is even not possible to treat such kind of imbalance with some medication. It becomes necessary to explore the world and find simpler and natural solutions. Gericudranins A, in this case proved to be the one alternative which can help in eradicating Melanoma with less adverse effects. It is at times not possible to completely replace the drug with some new compound but dose alterations and combination therapies can be of great use. This is why clinical trials are conducted and only after approval through such trials, a compound can be called drug. This study not only opened the scope for discovery of more such compounds which can help eradicated Melanoma but also highlighted the need to find more drugs which target other signalling pathways as well.

REFERENCES

1. Abdullah A. Al-Badr, M. M. (2016). Dacarbazine. In M. M. Abdullah A. Al-Badr, *Profiles of Drug Substances, Excipients and Related Methodology,* (pp. 323-377). Academic Press.
2. Alqathama, A. (2020). BRAF in malignant melanoma progression and metastasis: potentials and challenges. *American journal of cancer research*, 1103-1114.
3. Antoine Daina, O. M. (2019). SwissTargetPrediction: updated data and new features for efficient prediction of protein targets of small molecules. *Nucleic Acids Research, 47*(W1), W357.
4. Bengoa-Vergniory, N. &. (2015). Canonical and noncanonical Wnt signaling in neural stem/progenitor cells. *Cellular and Molecular Life Science*.
5. Bingxian Xie, Q. C. (2016). The Inactivation of RabGAP Function of AS160 Promotes Lysosomal Degradation of GLUT4 and Causes Postprandial Hyperglycemia and Hyperinsulinemia. *Diabetes*, 3327–3340.
6. Bollag, G. T. (2012). Vemurafenib: the first drug approved for BRAF-mutant cancer. *Nature Reviews Drug Discovery*, 873-886.
7. Burge, S. a. (2010). *Oxford Handbook of Medical Dermatology.* Oxford University Press.
8. Burge, S. R. (2016). *Oxford Handbook of Medical Dermatology.* Oxford: Oxford Medical Handbooks.
9. Burotto, M. C.-M. (2014). The MAPK pathway across different malignancies: A new perspective. *Cancer*, 3446-3456.
10. Cai Jiaying, W. J. (2025). Perspectives on the α5 nicotinic acetylcholine receptor in lung cancer progression. *Frontiers in Cell and Developmental Biology*.
11. Carrà, G. L. (2020). P53 vs NF-κB: the role of nuclear factor-kappa B in the regulation of p53 activity and vice versa. *Cellular and Molecular Life Sciences*, 4449–4458.
12. Chauhan, J. S.-P. (2022). The MITF regulatory network in melanoma. *Pigment Cell & Melanoma Research*, 517-533.
13. Daina, A. a. (2024). Testing the predictive power of reverse screening to infer drug targets, with the help of machine learning. *Comms. Chem*.

14. Daina, A. M. (2019). SwissTargetPrediction: updated data and new features for efficient prediction of protein targets of small molecules. *Nucl. Acids Res*, W357-W364.

15. Damian Szklarczyk, R. K. (2023). he STRING database in 2023: protein–protein association networks and functional enrichment analyses for any sequenced genome of interest. *Nucleic Acids Research*, D638–D646.

16. David S Wishart, Y. D. (2017). DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic Acids Research, 46*(D1), D1074-D1082.

17. Davis, E. J. (2018). Melanoma: What do all the mutations mean? *Cancer*, 3490-3499.

18. DeVita, V. T. (2023). *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology.* Lippincott Williams & Wilkins, a Wolters Kluwer business.

19. Durrant, J. M. (2011). Molecular dynamics simulations and drug discovery. *BMC Biology*, 71.

20. Fan Wang, F.-X. W.-Z.-Y.-W.-F.-F. (2019). ACID: a free tool for drug repurposing using consensus inverse docking strategy. *Journal of Cheminformatics, 11*(1), 73.

21. G., F. (2020). Actinomycin D: a new opening for an old drug. *Neuro-oncology*, 1235–1236.

22. Gajos-Michniewicz, A. &. (2020). WNT Signaling in Melanoma. *International journal of molecular sciences*.

23. Garzón-Orjuela N, P.-P. L. (2020). Efficacy and safety of dabrafenib–trametinib in the treatment of unresectable advanced/metastatic melanoma with BRAF-V600 mutation: A systematic review and network meta-analysis. *Dermatologic Therapy, 33*(2), e13145.

24. Gauci, M. B. (2018). Occurrence of type 1 and type 2 diabetes in patients treated with immunotherapy (anti-PD-1 and/or anti-CTLA-4) for metastatic melanoma: a retrospective study. *Cancer Immunol Immunotherapy*.

25. Gençler, B. G. (2016). Cutaneous Side Effects of BRAF Inhibitors in Advanced Melanoma: Review of the Literature. *Dermatology Research and Practice*.

26. Gilson, G. H. (2021). Automation of absolute protein-ligand binding free energy calculations for docking refinement and compound evaluation. *Scientific Reports, 11*(1), 1116.

27. Guo, W. (2021). Signal pathways of melanoma and targeted therapy. *Signal Transduction and Targeted Therapy*, 424.

28. Han, N. L. (2022). Natural Marine Products: Anti-Colorectal Cancer In Vitro and In Vivo. *Marine Drugs*.

29. Harshita Thakur, A. D. (2025). Comparative Analysis of in Silico Tools for Drug Side Effect Prediction. *International Conference on Intelligent Control, Computing and Communications (IC3)* (pp. 295-298). Mathura: IEEE.

30. Hollingsworth, S. A. (2018). Molecular Dynamics Simulation for All. *Elsevier*, 1129-1143.

31. Hugo Guterres, W. I. (2023). CHARMM-GUI-Based Induced Fit Docking Workflow to Generate Reliable Protein–Ligand Binding Modes. *Journal of Chemical Information and Modeling, 63*(15), 4772-4779.

32. Hui Zhao, Y. Y.-Y. (2023). NPASS database update 2023: quantitative natural product activity and species source database for biomedical research. *Nucleic Acids Research*, D621–D628.

33. Hung, C. N. (2025). Recent Developments in Targeting the Cell Cycle in Melanoma. *Cancers*.

34. Hyeraci, M. P. (2023). Systemic Photoprotection in Melanoma and Non-Melanoma Skin Cancer. *Biomolecules*.

35. Improgo, M. R. (2010). From smoking to lung cancer: the CHRNA5/A3/B4 connection. *Oncogene*, 4874-4884.

36. In-Kyoung Lee, C.-J. K.-S.-M.-D. (1995). Cytotoxic benzyl dihydroflavonols from Cudrania tricuspidata. *Phytochemistry*, 213-216.

37. Isberner, N. G.-T.-C. (2022). Monitoring of Dabrafenib and Trametinib in Serum and Self-Sampled Capillary Blood in Patients with BRAFV600-Mutant Melanoma. *Cancers*.

38. Jalal, A. G. (2025). Endocrine effects of MEK and BRAF inhibitor therapy in paediatric patients: a tertiary centre experience. *Journal of Neuro-Oncology*, 257-263.

39. Jason Cole, J. N. (2005). Protein-Ligand Docking and Virtual Screening with GOLD. In *Virtual Screening in Drug Discovery.* Taylor & Francis CRC Press.

40. Jonathan W. Goldman, M. A. (2016). Hyperglycemia Associated With Targeted Oncologic Treatment: Mechanisms and Management. *The Oncologist*, 1326–1336.

41. Keith J Kelleher, T. K.-T. (2023). Pharos 2023: an integrated resource for the understudied human proteome. *Nucleic Acids Research, 51*(D1), D1405.

42. Kirkpatrick, P. (2004). Gliding to success. *Nature Reviews Drug Discovery, 3*(4), 299.

43. Kovacs, D. M. (2016). The role of Wnt/β-catenin signaling pathway in melanoma epithelial-to-mesenchymal-like switching: evidences from patients-derived cell lines. *Oncotarget*.

44. LA, W. (2021). Management of Diabetes in the Patient With Cancer. *Journal of the advanced practitioner in oncology*, 258–260.

45. Li, W. S. (2006). The role of cell cycle regulatory proteins in the pathogenesis of melanoma. *Pathology*, 287–301.

46. Li, Y. L. (2024). Alpelisib-related adverse events: The FDA Adverse Event Reporting System Database (FAERS) pharmacovigilance study. *Heliyon*.

47. Liu Y, Y. S. (2020). Cellular senescence and cancer: Focusing on traditional Chinese medicine and natural products. *Cell Proliferation*.

48. Lyu, C. C. (2021). CMNPD: a comprehensive marine natural products database towards facilitating drug discovery from the ocean. *Nucleic acids research*, D509–D515.

49. M Liu, S. W. (1999). MCDOCK: A Monte Carlo simulation approach to the molecular docking problem. *Journal of Computer-Aided Molecular Design, 13*(5), 435-451.

50. Macdonald, J. B. (2015). Cutaneous adverse effects of targeted therapies: Part II: Inhibitors of intracellular molecular signaling pathways. *Journal of the American Academy of Dermatology*, 221-236.

51. Mali, S. B. (2023). Cancer treatment: Role of natural products. Time to have a serious rethink. *Oral Oncology Reports*.

52. Mangal, M. S. (2013). NPACT: Naturally Occurring Plant-based Anti-cancer Compound-Activity-Target database. *Nucleic acids research*, D1124–D1129.

53. Marine Bugnon, U. F. (2024). SwissDock 2024: major enhancements for small-molecule docking with Attracting Cavities and AutoDock Vina. *Nucleic Acids Research, 52*(W1), W324-W332.

54. Mario S. Valdés-Tresanco, M. E.-T. (2020). AMDock: a versatile graphical tool for assisting molecular docking with Autodock Vina and Autodock4. *Biology Direct, 15*(1), 12.

55. Mark James Abraham, T. M. (2015). GROMACS: High performance molecular simulations through multi-level parallelism from laptops to supercomputers. *SoftwareX*, 19-25.

56. Martinez-Marin, D. S. (2025). Frizzled receptors: gatekeepers of Wnt signaling in development and disease. *Frontiers in cell and developmental biology*.

57. McGann, M. (2012). FRED and HYBRID docking performance on standardized datasets. *Journal of Computer-Aided Molecular Design, 26*(8), 897-906.

58. Menzies, A. M. (2014). Dabrafenib and Trametinib, Alone and in Combination for BRAF-Mutant Metastatic Melanoma. *Clinical Cancer Research*, 2035-2043.

59. Michael K. Gilson, T. L. (2016). BindingDB in 2015: A public database for medicinal chemistry, computational chemistry and systems pharmacology. *Nucleic Acids Research, 44*(D1), D1045-D1053.

60. Michael Kuhn, C. v. (2008). STITCH: interaction networks of chemicals and proteins. *Nucleic Acids Research,* , D684–D688.

61. Michael Kuhn, I. L. (2016). The SIDER database of drugs and side effects. *Nucleic Acids Research*, D1075–D1079.

62. Mîinea, C. P. (2005). AS160, the Akt substrate regulating GLUT4 translocation, has a functional Rab GTPase-activating protein domain. *he Biochemical journal*, 87–93.

63. Mikheil, D. P. (2023). Notch Signaling Suppresses Melanoma Tumor Development in BRAF/Pten Mice. *Cancers*.

64. Naeem, A. H. (2022). Natural Products as Anticancer Agents: Current Status and Future Perspectives. *Molecules*.

65. National Cancer Institute. (2024, November 25). Retrieved from cancer.gov: https://www.cancer.gov/about-cancer/treatment/drugs/melanoma

66. Ng TSC, H. H.-H. (2022). Overcoming differential tumor penetration of BRAF inhibitors using computationally guided combination therapy. *Science Advances, 8*(17), eabl6339.

67. Nguyen, N. T. (2019). MITF and UV responses in skin: From pigmentation to addiction. *Pigment Cell and Melanoma Research*, 224–236.

68. Oleg Trott, A. J. (2010). AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal og Computational Chemistry, 31*(2), 455-461.

69. Pablo R. Arantes, M. D.-B. (2021). Making it Rain: Cloud-Based Molecular Simulations for Everyone. *Journal of Chemical Information and Modeling*.

70. Reinhard Dummer, A. H. (2020). Five-Year Analysis of Adjuvant Dabrafenib plus Trametinib in Stage III Melanoma. *New England Journal of Medicine*, 1139-1148.

71. Sample A, H. Y. (2018). Mechanisms and prevention of UV-induced melanoma. *Photodermatology, Photoimmunology & Photomedicine*, 13-24.

72. Shaik, B. B. (2022). Role of Natural Products in Developing Novel Anticancer Agents: A Perspective. *Chemistry & Biodiversity*.

73. Sheema Hashem, T. A.-M. (2022). Targeting cancer signaling pathways by natural products: Exploring promising anti-cancer agents. *Biomedicine & Pharmacotherapy*.

74. Sloot, S. F. (2014). Long-term effects of BRAF inhibitors in melanoma treatment: friend or foe? *Expert Opinion on Pharmacotherapy*, 589–592.

75. Stefano Forli, R. H. (2016). Computational protein–ligand docking and virtual drug screening with the AutoDock suite. *Nature Protocols, 11*(5), 905-919.

76. Ute F. Röhrig, M. G. (2023). Attracting Cavities 2.0: Improving the Flexibility and Robustness for Small-Molecule Docking. *Journal of Chemical Information and Modeling, 63*(12), 3925-3940.

77. Vergès, B. C. (2015). mTOR inhibitors and diabetes. *Diabetes Research and Clinical Practice*, 101-108.

78. Watson, I. R.-H. (2014). The RAC1 P29S hotspot mutation in melanoma confers resistance to pharmacological inhibition of RAF. *Cancer Research*, 4845–4852.

79. Xiaocong Yang, Y. L.-X. (2022). FitDock: protein–ligand docking by template fitting. *Briefings in Bioinformatics, 23*(3), bbac087.

80. Yajima, I. K. (2012). RAS/RAF/MEK/ERK and PI3K/PTEN/AKT Signaling in Malignant Melanoma Progression and Therapy. *Dermatology Research and Practice*, 354191.

81. Yang Liu, X. Y.-X. (2022). CB-Dock2: improved protein–ligand blind docking by integrating cavity detection, docking and homologous template fitting. *Nucleic Acids Research, 50*(W1), W159-W164.

82. Yardman-Frank, J. a. (2021). Skin pigmentation and its control: From ultraviolet radiation to stem cells. *Experimental Dermatology*, 560-571.

83. Ying Zhou, Y. Z. (2024). TTD: Therapeutic Target Database describing target druggability information. *Nucleic Acids Research, 52*(D1), D1465-D1477.

84. Yongfeng Chen, Z. C. (2021). The involvement of noncanonical Wnt signaling in cancers. *Biomedicine & Pharmacotherapy*.

85. Zamudio Díaz, D. B. (2024). Significance of melanin distribution in the epidermis for the protective effect against UV light. *Scientific Reports*, 3488.

86. Zeiser R, A. H. (2018). Trametinib. *Recent Results Cancer Research*, 91–100.

87. Zhou, B. L. (2022). Notch signaling pathway: architecture, disease, and therapeutics. *Signal Transduction and Targeted Therapy*, 95.

PUBLICATIONS

- H. Thakur and A. Das, "Comparative Analysis of in Silico Tools for Drug Side Effect Prediction," 2025 International Conference on Intelligent Control, Computing and Communications (IC3), Mathura, India, 2025, pp. 295-298, doi: 10.1109/IC363308.2025.10956741. keywords: {Drugs;Machine learning algorithms;Reviews;Melanoma;Machine learning;Prediction algorithms;Biology;Compounds;Intelligent control;Cancer;molecular docking;autoDock;swissDock;autoDock vina},

IEEE
UP SECTION (INDIA)

GL BAJAJ
Group of Institutions
Mathura
FIND YOUR SPARK
Approved by AICTE & Affiliated to AKTU

GL BAJAJ GROUP OF INSTITUTIONS

Mathura, Uttar Pradesh, India

CERTIFICATE OF ACKNOWLEDGEMENT

Presented to

Harshita Thakur

M.Tech Bioinformatics

In recognition and appreciation of valuable contribution of paper entitled

Comparative analysis of in silico tools for drug side effect prediction

as

Presenter

in International Conference on

Intelligent Control, Computing and Communications (IC3-2025)

at GL Bajaj Group of Institutions, Mathura on February 13-14, 2025

GLBM/IC3-2025/63308/ 92

Dr. Ram Veer Singh Sengar
Conference Convener (IC3-2025)

Prof. (Dr.) V. K. Singh
Conference Chair (IC3-2025)

Prof. Neeta Awasthy
General Chair (IC3-2025)

Harshita Thakur.docx

Delhi Technological University

Document Details

Submission ID
trn:oid:::27535:97768441

Submission Date
May 26, 2025, 11:55 AM GMT+5:30

Download Date
May 26, 2025, 11:58 AM GMT+5:30

File Name
Harshita Thakur.docx

File Size
6.5 MB

55 Pages

14,841 Words

84,585 Characters

turnitin Page 1 of 62 - Cover Page Submission ID trn:oid:::27535:97768441

8% Overall Similarity

The combined total of all matches, including overlapping sources, for each database.

Filtered from the Report

- Bibliography

Match Groups

- **86** Not Cited or Quoted 6%
  Matches with neither in-text citation nor quotation marks
- **15** Missing Quotations 1%
  Matches that are still very similar to source material
- **0** Missing Citation 0%
  Matches that have quotation marks, but no in-text citation
- **0** Cited and Quoted 0%
  Matches with in-text citation present, but no quotation marks

Top Sources

6% Internet sources
3% Publications
3% Submitted works (Student Papers)

Integrity Flags

0 Integrity Flags for Review

No suspicious text manipulations found.

Our system's algorithms look deeply at a document for any inconsistencies that would set it apart from a normal submission. If we notice something strange, we flag it for you to review.

A Flag is not necessarily an indicator of a problem. However, we'd recommend you focus your attention there for further review.

DELHI TECHNOLOGICAL UNIVERSITY

(Formerly Delhi College of Engineering)

Shahbad Daulatpur, Main Bawana Road, Delhi-42

PLAGIARISM VERIFICATION

Title of the Thesis

_____

Total Pages _____. Name of the Scholar_____

Supervisor (s)

(1)_____

(2)_____

(3)_____

Department _____

This is to report that the above thesis was scanned for similarity detection. Process and outcome is given below:

Software used: _____ Similarity Index: _____, Total Word Count: _____

Date: _____

Candidate's Signature **Signature of Supervisor**