"EXPLORING THE THERAPEUTIC POTENTIAL OF PHYTOCHEMICALS: MOLECULAR DOCKING STUDIES IN BREAST CANCER"

A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE AWARD OF THE DEGREE

OF

MASTER OF SCIENCE

IN

BIOTECHNOLOGY

Submitted by:

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2K21/MSCBIO/04

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MAY, 2023

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CANDIDATE'S DECLARATION

I Amit, Roll Number: 2K21/MSCBIO/04, student of M.Sc. Biotechnology, hereby declare that the work which is presented in the Major Project entitled — "EXPLORING THE THERAPEUTIC POTENTIAL OF PHYTOCHEMICALS: MOLECULAR DOCKING STUDIES IN BREAST CANCER" in the fulfilment of the requirement for the award of the degree of Master of Science in Biotechnology and submitted to the Department of Biotechnology, Delhi Technological University, Delhi, is an authentic record of my own carried out during the period from January- May 2023, under the supervision of Assistant Prof. Navneeta Bharadvaja

The matter presented in this report has not been submitted by me for the award for any other degree of this or any other Institute/University. The work has been accepted in IEEE Conference with the following details:

Title of the Paper: Plant Based Phytochemical Mediated Inhibition of Breast Cancer By Targeting PLAT: An In Silico Study

Author Names: Amit, Akash Rana, Navneeta Bharadvaja

Name of Conference- "Smart Technologies and System for Next Generation Computing(ICSTSN 2023)" -IEEE Conference

Conference Date and Venue: 21st and 22nd April 2023 at IFET College Of Engineering, Villupuram 605108 Tamil Nadu

Registration: Done

Status of Paper: Accepted

Date of Paper Communication: 17th March 2023

Date of Paper Acceptance: 29th March 2023

Date: Amit

CERTIFICATE

I hereby certify that the Project Dissertation "EXPLORING THE THERAPEUTIC POTENTIAL OF PHYTOCHEMICALS: MOLECULAR DOCKING STUDIES IN BREAST CANCER" Amit, Roll No. 2K21/MSCBIO/04, Department of Biotechnology, Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the degree of Master of Science is recorded for the project work carried out by the student under my supervision. To the best of my knowledge this work has not been submitted in part or full for any degree or any diploma to this university or elsewhere.

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ABSTRACT

The term "cancer" refers to a category of disorders in which some body cells begin to grow unnaturally and uncontrollably, killing millions of people globally. Metastasis is the term for the process by which tumour cells spread or infiltrate into other body parts or tissue. Breast cancer is one type of cancer that can appear in the breast tissue. Breast cancer can also affect men, although it is much less prevalent and is more often found in women. One of the most prevalent cancers in the world, breast cancer primarily affects women and very occasionally men. even though it is far less frequent. One of the most prevalent cancers in the world, breast cancer primarily affects females and occasionally males. Over the past few decades, a lot of research has been conducted to increase our understanding of the complexities of breast cancer and offer effective management strategies. This abstract provides a concise review of recent advances in the understanding and management of breast cancer, encompassing both diagnostic and therapeutic The diagnostic landscape for breast cancer has changed significantly, mostly as a result of the evolution of cutting-edge imaging equipment and biomarker-based testing. Breast abnormalities can now be detected using tomosynthesis, MRI, and digital mammography, which also helps in the early detection of malignant tumours. The identification of novel biomarkers, including HER2/neu, hormone receptors (oestrogen and progesterone), and the proliferation marker Ki-67, has also enabled a more precise classification of breast cancer subtypes. This has facilitated the creation of individualised treatment plan The paradigm for treating breast cancer has undergone a significant change, shifting towards one that is interdisciplinary and personalised. This study makes use of a number of computational tools, including Autodock Vina, Pymol, Protein Drug Bank, and PILP. PILP (Protein-Interaction Ligand Profiler). The interactions between cyclin D and plant phytochemicals are examined by means of PILP and molecular docking of the protein and ligand. Studying the interactions between proteins and ligands helps with drug discovery. The goal of this research is to determine which plant phytochemicals are most successful at preventing human cancer.

ACKNOWLEDGMENT

I would like to express my deepest gratitude to our research guide **Navneeta Bharadvaja, Department of Biotechnology, Delhi Technological University** for her unstinted inspiration, invaluable guidance, encouragement, keen interest, good wishes, and valuable suggestions throughout my entire research tenure.

I express my kind regards and gratitude to **Professor Pravir Kumar, Head of Department, Department of Biotechnology, Delhi Technological University,** and all the faculty members for helping in my project

I am thankful to **Harshita ma'am and Sidharth sir,** and all my classmates for giving me the moral boost and making my hopes alive with energy and enthusiasm to carry out the present work and helping hand at every. My sincere thanks to my parents and family members for the encouragement and moral support I received during my tenure of study.

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CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1

INTRODUCTION

One of the cancers that most frequently affects women globally is this breast cancer; although it can also affect men, it does so much less frequently. Breast cancer often starts in the milk producing glands, also known as the milk ducts or lobules. It was the root cause of about 11.7% of all new cancer cases [1]. The incidence rates can significantly vary between countries and regions, with higher rates in wealthier countries. Mammary gland cancer is expected to affect one in eight women worldwide, and only 5-10% of cases are thought to be caused by inherited issues; the remaining 90–95% are thought to be influenced by environmental and lifestyle factors. Modern medicine therefore places a great deal of emphasis on multidisciplinary research that focuses on primary prevention, risk factor modification to early disease detection, quick start of treatment (secondary prevention), as well as surveillance.The primary goal is to reduce the continuously rising morbidity, mortality, and financial costs associated with breast cancer[2]. Numerous hereditary and environmental factors, especially when they overlap, increase the risk of morbidity and the reactivation of glandular mammary cancer.Examples of environmental and lifestyle factors include ionising radiation, hormone therapy, women's reproductive conduct (preferences), alcohol , coupled with other nutritional problems, obesity, and a lack of physical activity. There are two other recognised and established risk factors: age and a family history of cancer, particularly breast cancer. This malignancy, which affects them most frequently, has been found in 80% of women over 50 who have the condition[3]. The molecular characteristics of BC must be the foundation for the therapy plans. The precise mechanisms that cause breast cancer are unknown. In wealthy countries, 60–70% of BC cases are caused by the most prevalent kind of the disease, which only affects premenopausal women Additionally, the TNBC was divided into six categories: basal-like 1 (BL-1), immunomodulatory (IM), mesenchymal stem cell-like (MSL), luminal androgen receptor (LAR), and basal-like 2 (BL-2).The precise mechanisms that cause breast cancer are unknown. In wealthy countries, 60–70% of BC cases are caused by the most prevalent kind of the disease, which only affects premenopausal women. As a result, the therapeutic approach that is used the most frequently is hormone therapy [4]. HER2 monoclonal antibodies are widely available and can be used to treat BC patients who express HER2. Patients with breast cancer who test positive for HER2 are frequently treated with chemotherapy and an anti-HER2 monoclonal antibody. TNBC treatment is more challenging than that of other BC subtypes. The recommended course of treatment for this population is chemotherapy

Mammography is a helpful screening method that uses low intensity X-rays to create high-resolution images of the breast[11].No contrast enhancing medication is required, and the entire test takes around 20 minutes More than 70% of American women (aged 50–74) have gotten mammography for screening every two years since Professor Forrest first advised against it 88.A metanalysis of 11 randomised studies found that mammography screening significantly reduced breast cancer mortality (RR=0.81) in women between the ages of 50 and 70[12]. However, there was no discernible decrease in death rates among women between the ages of 40 and 4. These results highlight the importance of mammography screening schemes. MRI has an advantage over mammography in the detection of small tumours, axillary nodal metastases, residual tumours after neoadjuvant therapy, and

undiagnosed primary breast cancer 92. Modern MRI scanners can measure tissues as small as 0.5 mm3. There is no proof, though, that MRI improves patient outcomes like the rate of ipsilateral breast tumour recurrence detection or the occurrence of contralateral breast cancer.

CHAPTER 2

LITERATURE OF REVIEW

Hesperdin is a flavonoid chemical and a part of the class of plant pigments known as flavonoids. It is most frequently found in citrus fruits, particularly in the peels and membranes of oranges and lemons. The anti-inflammatory and antioxidant properties of hesperidin make it a popular dietary supplement. Here are some crucial details about hesperidin: Due to its antioxidant characteristics, hesperidin helps the body scavenge harmful free radicals. Free radicals are unstable chemicals that can damage cells and contribute to a variety of health problems, including inflammatory conditions, chronic diseases, and ageing.

Hesperidin has anti-inflammatory properties, which have been found to have a positive impact on inflammation. It can help to lessen inflammation in the body by blocking specific enzymes from working and controlling the immune system. Hesperidin might be advantageous for keeping your cardiovascular system healthy. Research suggests that it can enhance blood vessel health, lower high blood pressure, and enhance blood flow. It might also reduce cholesterol levels. According to certain studies, hesperidin may have immunomodulatory effects, which implies it may help regulate the immune system. It might boost immune function and reduce the risk of developing specific infections. Hesperidin may have anticancer potential, according to preliminary research. Its potential to inhibit the growth of cancer cells and cause apoptosis (programmed cell death) in particular cancer types has been studied. But additional research is needed to fully understand its cancer treatment potential. Numerous other benefits of hesperidin have also been studied, such as neuroprotection, gastrointestinal health, and skin health. More research is required to determine its effectiveness and safety in these regions. Hesperidin is generally thought to be safe for the majority of people when consumed in normal food amounts, although high dosages or prolonged supplementation may have undesirable effects or interact with specific medications. Before starting any new treatment, a doctor should always be consulted.

Resveratrol, a naturally occurring compound found in many different plants, is particularly abundant in the skin of red grapes. It has recently received a great deal of interest due to its potential health benefits. The following information on resveratrol: The antioxidant properties of resveratrol are widely known for protecting cells from damage caused by harmful substances known as free radicals. It is believed that antioxidants can help reduce the chance of developing a variety of diseases, such as heart disease and several cancers. Research on resveratrol's potential benefits for cardiovascular health is extensive. It is thought to improve blood flow, reduce inflammation, and prevent the oxidation of low-density lipoprotein (LDL), also known as "bad" cholesterol. These results might reduce the risk.

Effects on Inflammation: Studies have shown that resveratrol has anti-inflammatory properties, which may assist to reduce inflammation in the body. Among the diseases associated with chronic inflammation are heart disease, diabetes, and a number of malignancies. Potential Cancer-Preventive Effects: According to research, resveratrol may have the ability to prevent cancer. It has been shown in laboratory studies to trigger apoptosis (cell death) and to stop the growth of cancer cells. More research is required to completely understand its effects on the various cancer types in humans. There has been research on the possible benefits of resveratrol for brain health and neurodegenerative diseases . It may provide some protection against age-related cognitive decline and neurodegenerative disorders like Alzheimer's, according to some research. But more research is required. Along with other potential benefits, resveratrol has also been studied for its potential effect on diabetes, obesity, and longevity. There are limited and inconsistent human studies in these areas, despite some encouraging animal trials. Although there are several areas where resveratrol shows promise, it's crucial to remember that the majority of the research has been conducted on cell cultures and animal models. To determine the drug's effectiveness and the best dosage for different medical conditions, human clinical trials are still necessary.

Due to its potential health benefits, notably its role in the treatment and prevention of cancer, it has generated interest. Because there is currently little data addressing resveratrol's effects directly on breast cancer, more research is necessary to fully understand its potential. It has been found to halt the growth of breast cancer cells in test tubes and animal models. Additionally, it has shown anti-inflammatory and antioxidant qualities, which may also play a role in its potential anti-cancer effect. There isn't much information accessible, and studies on humans are still being undertaken. Some studies suggest that resveratrol use may reduce the risk of breast cancer. These studies, however, lack a definite cause-and-effect relationship because they are observational in nature. Remember that resveratrol has a low bioavailability, which can make it difficult for the body to properly absorb and utilise it.This has raised questions about its efficacy and if higher doses or alternative delivery methods are needed to produce discernible results. Despite some promising data from laboratory studies and observational research, more well designed clinical trials are needed to determine the potential importance of resveratrol in the prevention and treatment of breast cancer. 2.3. Because of its potential health benefits, particularly its anticancer properties, it has generated interest. Some preliminary research suggests that berberine may have beneficial effects in the treatment of breast cancer in particular, but more studies are needed to prove its usefulness and safety In laboratory research using breast cancer cells, berberine may have anticancer properties.It has been shown to inhibit the growth and proliferation of cancer cells, to stop the cell cycle, to promote apoptosis (programmed cell death), and to stop the spread of tumours.

It has also been reported that berberine modifies a variety of signalling pathways linked to the development and progression of cancer, including those involved in angiogenesis and inflammation. There has been a limited amount of study utilising animal models of breast cancer, but the findings are promising. For instance, berberine has been shown to inhibit tumour growth and decrease tumour volume in mice with breast cancer. It is important to keep in mind that these findings from laboratory and animal studies may not necessarily translate to therapeutic outcomes for people. There aren't many clinical trials now looking at berberine's effects on breast cancer. According to certain studies, berberine may be beneficial when used in conjunction with other anticancer drugs or as an adjuvant therapy. To provide more concrete evidence of the efficacy and safety of berberine especially for the treatment of breast cancer, larger, well designed clinical trials are needed. When utilising berberine or any other natural supplement for breast cancer, it's imperative to act with caution. Consultation with a

medical expert, such as an oncologist, is required before thinking about using berberine or any other complementary therapy. They can provide customised advice and consider any combinations with additional treatments or medications

Silymarin, a collection of flavonolignans, is derived from the milk thistle plant (Silybum marianum).It has been researched for potential health benefits, such as its use as an all-natural liver problem treatment and its anticancer properties. The research on silymarin for breast cancer is still in its infancy, and there is little clinical proof to support it. Nevertheless, a number of preclinical studies and lab testing regarding silymarin's potential impact on breast cancer cells have produced favourable outcomes. Numerous anticancer effects of silymarin have been identified, including those that restrict cell growth, lessen inflammation, halt angiogenesis, and encourage programmed cell death. These properties suggest that silymarin may be able to prevent the growth and spread of breast cancer cells.A According to some research, silymarin may help slow the spread of breast cancer by having a chemopreventive impact. It has been said to possess antioxidant properties that can assist in protecting cells from DNA damage brought on by oxidative stress.

Additionally, silymarin has been shown to inhibit particular enzymes necessary for the metabolism of carcinogens, potentially reducing the risk of cancer development. Additionally, silymarin has been investigated in conjunction with established cancer treatments including chemotherapy and radiation. According to some studies, silymarin may increase the efficiency of certain medications and minimise their side effects. More study is required to determine the appropriate dosage and combination approaches. It's important to remember that laboratory experiments and animal models are the mainstays of the majority of the existing research on silymarin and breast cancer. Clinical trials are necessary to evaluate a treatment's efficacy, safety, and potential interactions with other therapies.

Mitomycin c a chemotherapy drug, has been used to treat malignancies other than breast cancer. It is a member of the class of medications known as alkylating agents, which work by interfering with cancer cells' DNA, preventing their ability to reproduce, and ultimately leading to cell death Mitomycin Most studies on mitomycin have focused on its use in chemotherapy regimens involving many drugs for the treatment of breast cancer. Variables like the stage and characteristics of the breast cancer as well as particular patient concerns may have an impact on how it is applied. Important considerations regarding the use of mitomycin in breast cancer combination therapy include the following: Mitomycin is frequently administered in a regimen together with other chemotherapy drugs like fluorouracil (5-FU). These concoctions, which are frequently administered intravenously, are made to enhance the therapeutic effect. Metastatic breast cancer refers to breast cancer that has spread to other bodily locations.It has being investigated whether mitomycin might be used to treat this disorder. Clinical trials have examined its effectiveness when used in conjunction with other drugs to determine the most effective course of treatment. Additionally, studies on the use of mitomycin as an adjuvant therapy for early-stage breast cancer have been conducted.

Adjuvant therapy refers to treatment provided after surgery or other main treatments to reduce the likelihood of cancer recurrence. However, other chemotherapy drugs like mitomycin are used in this condition more frequently. It's important to remember that each patient's circumstances may affect the use of mitomycin and specific treatment plans, therefore decisions on treatment should always be made in consultation with an oncologist or other healthcare provider.They can provide specific guidance based on factors like the stage of the malignancy, overall health, and potential adverse effects. Similar to other chemotherapy drugs, mitomycin can have side effects such as nausea, vomiting, bone marrow suppression (reduced synthesis of blood cells), and increased susceptibility to infections. Throughout

therapy, careful observation and supportive care are typically provided to help manage any potential side effects.

Andrographis paniculata, sometimes known as the "King of Bitters," is a plant from which an organic compound called andrographolide is extracted.It has long been used in Ayurvedic and traditional Chinese medicine because of its medicinal properties. The possible anticancer effects of andrographolide, particularly its application in the treatment of breast cancer, have recently attracted attention. To assess andrographolide's efficacy and safety, more research is needed as this area of the study is still in its infancy. Here is a list of what is currently known: alterations to cell proliferation Andrographolide had anti-proliferative effects on breast cancer cells in laboratory studies. It could be able to stop the spread of cancer cells by preventing their division and proliferation. Apoptosis induction is crucial for controlling cell proliferation and preventing cancer. A controlled kind of cell death is called apoptosis.

The possible anticancer qualities of andrographolide may be explained by the fact that it has been demonstrated to cause breast cancer cells to undergo apoptosis. preventing metastasis One of the main problems with breast cancer is metastasis, which is the spread of cancer cells to different sections of the body.In preclinical experiments, andrographolide reduced the invasion, metastasis, and migration of cancer cells. According to these results, andrographolide may aid in halting the spread of breast cancer cells. It has been discovered that andrographolide affects a variety of signalling pathways that are essential for the survival and growth of cancer cells. Andrographolide may be able to prevent cancer cells from multiplying and surviving by focusing on these pathways. Several studies have examined the potential for combining andrographolide with additional anticancer medications, including as chemotherapy or targeted therapies. In the management of breast cancer, the combination method seeks to improve therapeutic outcomes and decrease medication resistance. To discover the proper combinations and treatment schemes, more research is necessary. Although early research on andrographolide's anticancer potential is encouraging, it's important to keep in mind that the majority of these studies have used animal models or lab settings. Human clinical trials must be conducted to assess the efficiency, safety, and dose of andrographolide in the treatment of breast cancer.

Cottonseed meal, cottonseed oil, and other components of the cotton plant all include the naturally occurring substance known as gossypol. Its possible anticancer characteristics have sparked interest in research on cancer, particularly breast cancer. According to studies, gossypol can inhibit the growth of other cancer types and cause apoptosis, or programmed cell death, in breast cancer cells. It has been found to inhibit a number of cellular processes crucial to the growth and spread of cancer.Gossypol has demonstrated promising outcomes in preclinical research and early clinical trials for the treatment of breast cancer.In both lab and animal models,

It has been seen to stop the growth of breast cancer cells. Gossypol has also shown that it can make breast cancer cells more vulnerable to chemotherapy and radiation therapy, potentially improving the efficacy of these treatments.

Gossypol has demonstrated potential as a cancer treatment, but more studies are required to completely understand its efficacy and safety in the treatment of breast cancer.Clinical trials are still being conducted to assess its efficacy, the optimal dosage, and any potential negative effects in patients with breast cancer. When managing breast cancer, it is essential to adhere to evidence-based recommendations and seek the counsel of medical professionals, just like with any other treatment.They might offer the most latest details on treatments that are available, such as any gossypol or other innovative therapy advancements.

Indirubin, a naturally occurring chemical obtained from indigo plants, is frequently used in traditional Chinese medicine. It has sparked attention in cancer research because of its alleged anti-cancer properties. Indirubin's effects on breast cancer cells and tumours have been examined in a number of studies, while research on this subject is still in its early phases. In vitro tests, which were performed in a lab environment using cells, have shown that indirubin can decrease the proliferation (growth) of breast cancer cells. Since indorubin or its derivatives have just lately been the focus of clinical study, it is unknown if they are safe, effective, or should be used in what dosages to treat breast cancer.

Vicenin-2, a key bioactive component of Ocimum sanctum Linn, often known as tulsi, exhibits a variety of pharmacologic actions. The primary substance obtained from Moringa oleifera, Peperomia blanda, and Ocimum sanctum Linn is vicenin 2. It is also known as 8-di-C-glucoside apigenin-6. Hepatoprotection, anti-oxidant, anti-inflammatory, anti-glycation, and anti-nociceptive activities are just a few of its pharmacological advantages. In the colitis model of inflammatory bowel disease (IBD), vicenin-2-enriched herbal medications actively elicited anti-inflammatory responses, according to multiple research. By suppressing nuclear factor-B (NF-B), the main vicenin-2 component present in U. circularis is used to stop the formation of inflammatory mediators such tumour necrosis factor (TNF-) and nitric oxide (NO).

This proved that carrageenan-induced edoema in rats has an anti-inflammatory effect [16]. Additionally, the apical herb Ocimum sanctum in combination with vicenin-2, a common therapeutic ingredient, caused anti-angiogenic and anti-proliferative actions in prostate cancer cell carcinoma. When coupled with docetaxel, a typical drug for reducing androgen levels in prostate cancer, vicenin-2 decreased the growth of prostate cancer in vivo [17]. The anticancer properties of vicenin-2 have also been demonstrated against human hepatocellular carcinoma.

The chemical irofulven belongs to the group of drugs called DNA-alkylating agents. It is being studied for its potential use in the treatment of malignancies, including breast cancer[18]. In preclinical studies, irofulven was discovered to exhibit activity against breast cancer cells. It works by binding to the cancer cells' DNA and damaging it, which kills the cancer cells. Another function of irofulven has been found to be the prevention of angiogenesis, the growth of new blood vessels that feed tumours. Irofulven's clinical development for breast cancer has run into problems, despite positive preclinical results. Early-phase clinical trials conducted in the late 1990s and early 2000s showed minimal efficacy and significant toxicity. liver damage, gastrointestinal issues, and hematologic abnormalities were some of these toxicities. [19]These concerns have limited the further development of irofulven in breast cancer.As of my knowledge's expiration date in September 2021, there are no recent clinical trials or approvals specifically focusing on irofulven for the treatment of breast cancer. A healthcare professional or recent medical literature should be consulted for the most recent information regarding irofulven and its potential as advancements in cancer research and therapy may have taken place since then. Irofulven is a chemical compound created from a poison found naturally in mushrooms of the Irofulven species.It belongs to the class of drugs called DNA-alkylating agents, and scientists have investigated its possible anticancer capabilities.

Irofulven works by creating a covalent link with the DNA of the cancer cells, which damages the DNA and obstructs the transcription and replication processes. Finally, this results in cell cycle arrest and triggers apoptosis (programmed cell death) in cancer cells. The chemical has demonstrated activity against cancer cells originating from breast, ovarian, prostate, lung, and pancreatic malignancies in preclinical studies. Both haematological and solid tumours have been studied in relation to it. The chemical has demonstrated activity against cancer cells originating from breast, ovarian, prostate, lung,

and pancreatic malignancies in preclinical studies.Both haematological and solid tumours have been studied in relation to it. Irofulven has undergone extensive testing in clinical trials, both as a single agent and in combination with other chemotherapy drugs. Its development has been hampered by significant toxicities discovered in early experiments, including as bone marrow suppression, liver toxicity, gastrointestinal side effects, and cardiovascular events. These toxicities have hampered its continued clinical development [20].

Cyclin D the control of the cell cycle depends on a protein known as cyclin D1.It helps control cell division and the passage through the various cell cycle phases. It is well known that Cyclin D1 contributes to the development and progression of breast cancer as a result of extensive research on the subject. Numerous instances of breast cancer have been discovered to overexpress cyclin D1. This suggests that the cyclin D1 protein is present in cancer cells at overly high amounts. Some breast cancer subtypes, such oestrogen receptor-positive (ER+) breast cancer, are frequently associated with cyclin D1 overexpression. Specific clinical characteristics and prognoses have been associated with breast tumours that overexpress the cyclin D1 protein.It has been linked in multiple studies to a worse prognosis, lymph node involvement, larger tumours, and a higher tumour grade. However, the usefulness of cyclin D1 as a prognostic marker may vary based on the specific subtype of breast cancer and other pertinent biological factors. Our expanding awareness of the role of cyclin D1 in breast cancer has led to the investigation of treatment strategies that target this protein. Researchers have studied drugs that can inhibit the expression of cyclin D1 or its interaction with CDKs in an effort to block the unregulated cell division and proliferation of breast cancer cells. Finally, it has been discovered that cyclin D1, a protein that regulates the cell cycle, is overexpressed in a tiny proportion of breast cancer cases.It encourages unregulated cell division and proliferation in breast cancer cells. Having a better understanding of cyclin D1's role in breast cancer may aid in developing specialised treatments for different subtypes of the diseases[21].

Ki-67, also known as the Ki-67 antigen or the Ki-67 protein, is a biological marker that is routinely used to measure the proliferation of breast cancer cells. It is named after Kiel, a city in Germany, where it was first discovered. The major technique used to assess Ki-67 in breast cancer is immunohistochemistry (IHC) testing on tumour tissue samples taken from a biopsy or surgical resection.IHC labelling is used to determine whether the Ki-67 protein is present in the nucleus of cancer cells. The percentage of cancer cells that have positive Ki-67 staining is represented by the Ki-67 labelling index, also known as the Ki-67 proliferation index. It serves as a gauge of the amount of cancer cells that are actively growing and is widely used to assess the aggressiveness or growth potential of tumours[22]. Higher Ki-67 labelling indices are associated with worse prognosis and more aggressive behaviour in breast cancer cases.There is typically a stronger tendency for rapid growth and dissemination in these malignancies. The prognosis is often better for breast cancer cases with a lower Ki-67 labelling score, which tend to act more quietly. The Ki-67 index is widely used as part of a full evaluation of breast cancer, along with other factors such tumour size, grade, hormone receptor status (oestrogen receptor and progesterone receptor), and human epidermal growth factor receptor 2 (HER2) status.These elements have a role in determining the optimum treatment plan and patient management strategy.[23]

CHAPTER 3

MATERIALS AND METHODS

Based on bioinformatics tools like InstaDock, Discovery Studio Visualizer, GROMACS, and PyMOL, a methodical approach to drug design and discovery was established.

Utilising molecular docking, it is possible to foretell the ideal orientation and binding affinity of tiny molecules for a receptor, usually a protein. To determine the optimal structural pose and binding affinity of chosen drugs towards CYCLIN D, a virtual screening technique utilising the molecular docking approach was performed. A blind search area in InstaDock with a 70-square-inch grid For the X, Y, and Z coordinates, respectively, A, 80 A, and 80 A were employed. For protein-ligand docking in this investigation. The X, Y, and Z axes were arranged to be in the grid's centre.The grid spacing was set to 1 A, while the other docking parameters were kept at their default values. Analyse the docking characteristics and various binding affinities of the phytochemicals to CYCLIN D using the InstaDock programme. Depending on the ligand efficiency and energy values, different docking outcomes were obtained. For the purpose of studying interactions, docking poses for each phytocompound were developed using the Discovery Studio Visualizer and pymol.

After discovering the high-affinity CYCLIN D binding partners using the molecular docking approach, the ADMET parameters of the changed compounds were calculated using SwissADME and other tools. PkCSM server servers. Second, avoid compounds that have a higher ability to generate a lot of connections, such as Patterns. 50 buildings exhibiting blooming ADMET and Drug-like features free of hazardous patterns were selected as the targets for our PAINS (pan-assay interference detecting substances) filter a more thorough analysis.

Predicting a compound's biological activity is one of the crucial steps in the creation of novel medications. Using the PASS webserver51, the biological properties of the chosen compounds were predicted. Please, the ADMET lter. Based on the chemical connection's structure-activity relationship, the web server PASS predicts biological characteristics. A brief summary of potential biological traits

that could result from *Pi* and *Pa* (probability of being active) is provided. By comparing the investigation with the ratio of (probability of being inactive),a system containing a database of well-known chemicals within several biological traits. It demonstrates that the higher the *Pa* the more significant the value, the more likely it is that a biological characteristic of the investigated drug. The findings of docked Chemicals were generated for the potential causes—Modifications of the changed substances, and their analysis with PyMOL and the Discovery Studio Visualizer followed. Polar interactions, as described in 3.5 A, were seen in PyMOL's closed model interactions between the drugs and CYCLIN D. Utilising the Discovery Studio Visualizer, a thorough investigation of interactions between drugs that have a CYCLIN D binding pocket was conducted. The only substances chosen were those that were known to interact with the key residues in the CYCLIN D binding pocket. Additionally, the compounds that showed a close bond with the CYCLIN D binding site residues were chosen for additional investigation.

The results of the docking between CYCLIN D and the selected silmayrin and hesperdin were verified as being compounds orated through research employing MD simulation. Structure of CYCLIN D, interacts with silmayrin and hesperdin were analysed using GROMACS v5.5.1. The entryway is wide open. a well-liked MD simulation programme for the pharmaceutical Discovery. Topologies were created for the receptor-ligand complexes using the PRODRG server to change the parameters for the compounds. You can construct topologies with assurance using the PRODRG server. coordination of molecules at small scales. Each was given its own systemthe boundaries of the cubic box are separated from its centre by a solvation distance of 10 A. Simple point charge (SPC) 216 is represented as a water model.

The simulated systems were additionally neutralised by properly adsorbing counterions (Na+ and Cl).The solvated system's decreased energy decreased any potential steric barriers between the atoms. 1500 drop that is the steepest, followed by gradient conjugation techniques. from 0 to 300 degrees Fahrenheit, continuous volume, The two-step equilibria exist at K) temperature and 1 atm pressure.

A 100-ps experiment was conducted with the periodic boundary setup. It took 100 ns for each system to simulate. By analysing the resulting information, protein-ligand stability is demonstrated. We used the GROMACS tools in great depth for our analysis.

It is important to identify principal components (PCs), which measure the direction of maximum data variation, in order to achieve this reduction. Each is represented by just a few elements. Consider utilising a sample of a few numbers instead of values for many variables. After that, the sample can be plotted to produce vivid comparisons of differences and similarities between Analyse the sample's capacity to be grouped with other samples.

PCA also demonstrates the high amplitude motion in MD.Trajectories.61 We looked into the MD trajectories of CYCLIN D.CYCLIN D-hesperdin and CYCLIN D-silmayrin complexes for conformational sampling, stability, and atomic motion. Using PCA and analysis of the free energy landscape (FEL)

CHAPTER 4

RESULTS

Table 1. Binding energy of phytochemicals of respective ligands

Index	Phytochemicals (Ligand)	Protein (Receptor)	Residue	AA	Distance	Affinity (kcal/mol)	Mode
1	Resveratrol	Ki-67	24C	PRO	3.72	-7.6	1
2	Mitomycin C	Ki-67	406D	GLU	3.89	-7.3	1
3	Epothilone D	Ki-67	24C	PRO	3.70	-8.3	1
4	Irofulven	Ki-67	68C	GLN	3.51	-7.7	1
5	Standard Inhibitor	Ki-67	191	ARG	3.99	-5.7	1

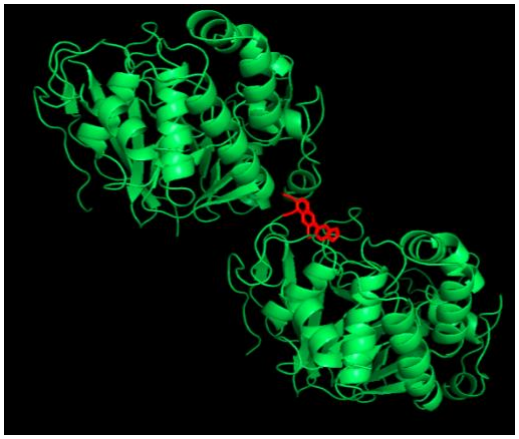

Figure 1. INTERACTION BETWEEN HESPERIDIN AND KI-67 PROTEIN IN PYMOL

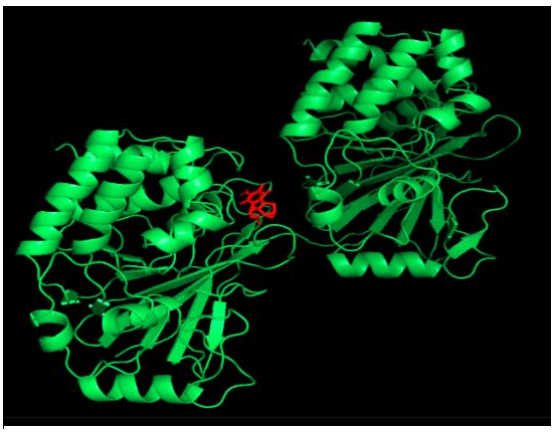

FIGURE 2: INTERACTION BETWEEN HESPERIDIN AND KI-67 PROTEIN IN PYMOL

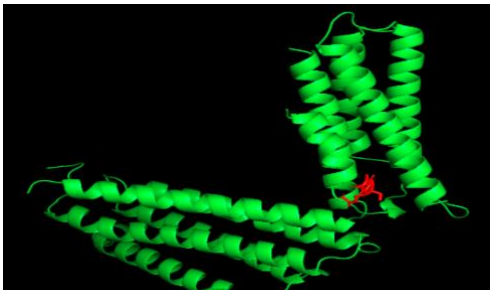

Figure 3. .INTERACTION BETWEEN VICENIN AND KI-67 PROTEIN IN PYMOL

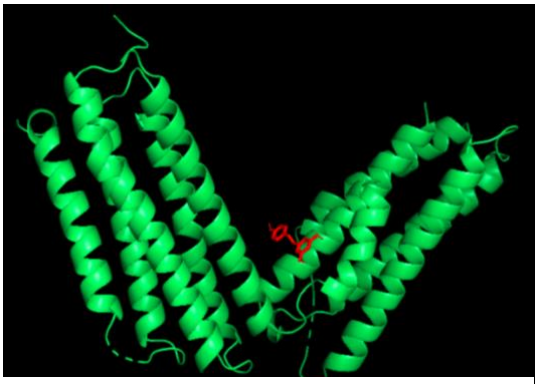

Figure 4. INTERACTION BETWEEN MITOMYCIN C AND KI-67 PROTEIN IN PYMOL

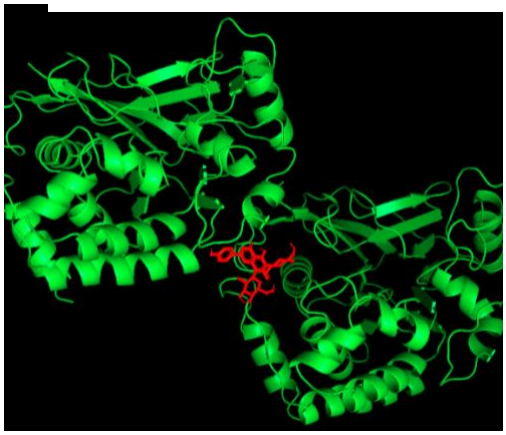

Figure 5. . INTERACTION BETWEEN SILYMARIN AND KI-67 PROTEIN IN PYMOL

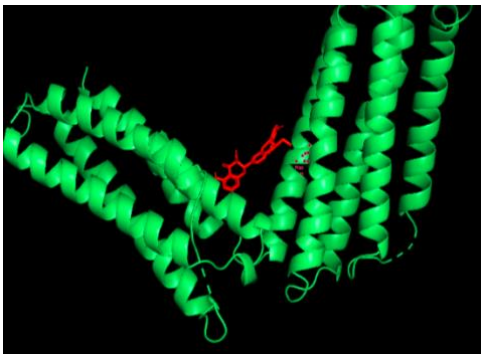

Figure 6 INTERACTION BETWEEN BERBERINE AND KI-67 PROTEIN IN PYMOL

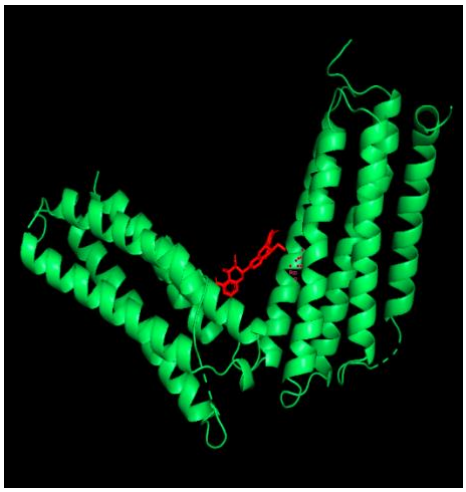

Figure 7. INTERACTION BETWEEN SILYMARIN AND CYCLIN D-1 PROTEIN IN PYMOL

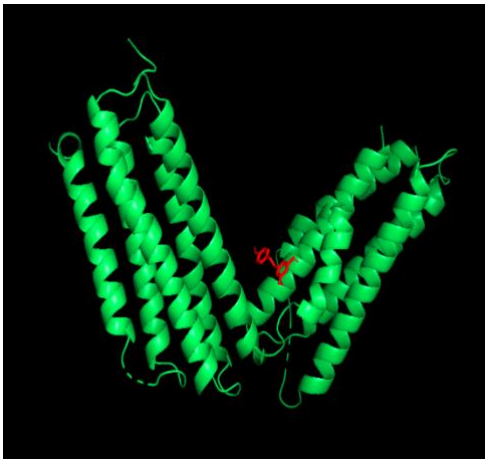

Figure 8. INTERACTION BETWEEN BERBERINE AND CYCLIN D-1 PROTEIN IN PYMOL

Table 2. Binding energy of phytochemicals of respective ligands

Index	Phytochemicals (Ligand)	Protein (Receptor)	Residue	AA	Distance	Affinity (kcal/mol)	Mode
1	**Andrographolide**	**Cyclin D-1**	117A	LEU	3.34	**-5.9**	**1**
2	**Mitomycin C**	**PLAT**	190A	ALA	3.80	**-6.6**	**1**

3	**Irofulven**	**PLAT**	190A	ALA	3.80	**-6.8**	**1**
4	**Epothilone D**	**PLAT**	190A	ALA	3.80	**-6.8**	**1**
5	**Mitomycin C**	**Cyclin D-1**	163	**PRO**	**3.81**	**-5.7**	**1**
6	**Irofulven**	**Cyclin D-1**	257A	LYS	3.84	**-5.3**	**1**
7	**Standard Inhibitor**	**Cyclin D-1**	117A	LEU	3.34	**-5.1**	**1**
8	**Standard Inhibitor**	**PLAT**	190A	ALA	3.80	**-5.0**	**1**

CHAPTER 5

OBSEVATION

Molecular docking between a phytochemical (a naturally occurring plant compound with potential therapeutic properties) and a protein (Cyclin D and) can be used to explore their interaction and investigate potential binding modes. This can provide insights into the molecular mechanisms underlying the bioactivity of the phytochemical and aid in drug discovery or developments.

The molecules with the highest binding energies are chosen. The compound with maximum negative binding energy is Epothilone D (-8.3 in kcal/mol) against KI-67 protein which makes this compound for the creation of medications that block the Cyclin D
protein in breast cancer and serve as therapeutic agents for the condition. Maximum binding energy for Cyclin D-1 and PLAT is Mitomycin D (-5.7) and Irofulven and Epothilone D(-6.8) respectively.

CONCLUSION

Potential cancer treatments include the pharmacologic suppression of cyclin-D, which has anticancer and antiviral effectiveness. This research intends to support the therapeutic management of cancer by employing natural compounds that target Cyclin D, such as Hesperidin and Silmayrin. We have performed an in silico investigation utilising cutting-edge computational methodologies using Cyclin D as an appealing target for creating anticancer treatments. By evaluating their physicochemical, drug-like, and stable binding to Ki-67 qualities, two phytoconstituents, Hesperidin and Silmayrin, were discovered. We suggest future research into Hesperdin and Silmayrin in in vitro and in vivo conditions to create anticancer medicines. To further investigate this, we conducted an in-silico analysis using state-of-the-art computational techniques. Our investigation concentrated on hesperidin and silmayrin, two distinct natural compounds with the potential to target cyclin D. In-silico research simulates employing computer simulations and algorithms to examine interactions between molecules, providing crucial insights into their behaviour and potential effects. During our investigation, we assessed the physicochemical properties and drug-like qualities of hesperidin and silmayrin. Additionally, we assessed their ability to persistently bind to the cancer-related protein Ki-67. These evaluations provided crucial information regarding the potential efficacy and safety of these compounds as anticancer medications. Our investigation revealed that Hesperidin and Silmayrin both demonstrated favourable characteristics that suggest their potential as therapeutic candidates for cancer treatments. However, it is essential to further investigate these compounds under in vitro and in vivo conditions, i.e., studies conducted on animals and in lab settings, respectively. Through more research, we will be

able to assess the effectiveness of Hesperidin and Silmayrin in real biological systems and gain a clearer understanding of the mechanisms behind their interactions with Cyclin D. This information is crucial for the development of novel anticancer medications that enhance the potency of these chemical compounds.Our in-silico research consequently identified Hesperidin and Silmayrin as potential candidates for Cyclin D targeting in the treatment of cancer. Additional laboratory and animal model research will be extremely beneficial for the creation of future anticancer medications.

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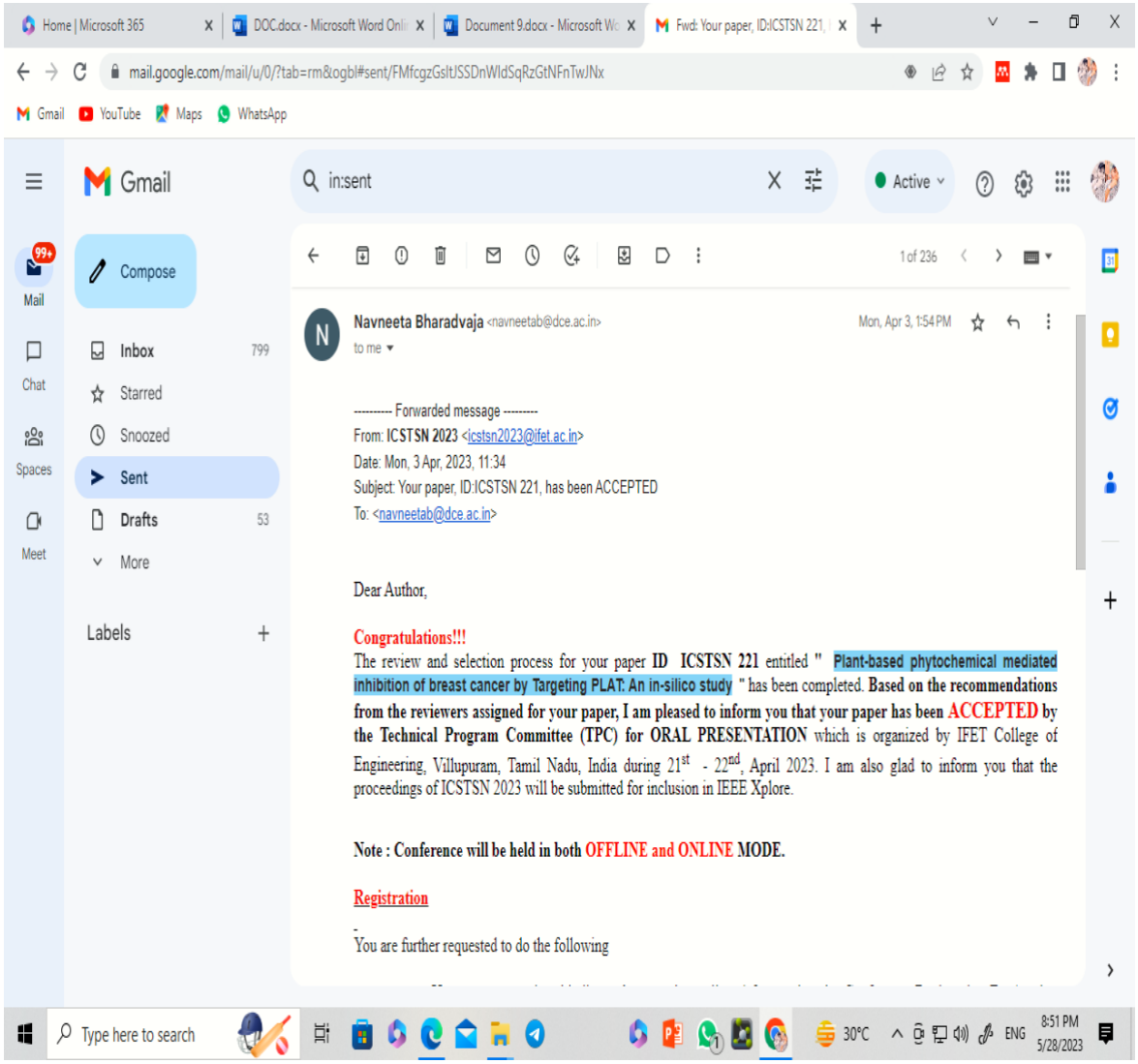

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Plant-based phytochemical mediated inhibition of breast cancer by targeting PLAT: An in-silico study

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***Abstract*—Cancer refers to a group of diseases in which some cells of the body start growing abnormally and in an uncontrolled manner causing deaths in millions worldwide. Tumor cells spread or invade to other parts of body or tissue and the process is called metastasis. Genetic and environmental factors like arsenic, alcohol, and tobacco cause cancers in the human body. Studies show antioxidants have potential anticancer effects and are used to design therapeutic tactics to fight cancer. Several computational tools, including Autodock Vina, Pymol, Protein Drug Bank, and PILP, are used in this study. (Protein-Interaction Ligand Profiler). By using PILP and molecular docking of the protein and ligand, the interactions between Tissue type Plasminogen-Activator and plant phytochemicals are investigated. Drug discovery is facilitated by research into protein and ligand interactions. The purpose of this study is to identify the most effective plant phytochemicals that have demonstrated promise in preventing cancer in humans.**

Keywords*— *Bioinformatics, Drug discovery, Pymol, Protein-Ligand Interactions, Docking, Computational biology.

I. *INTRODUCTION*

Breast cancer a serious threat to human health. It mostly affect women worldwide, also affect men. There are several proteins that are upregulated (i.e., increased in expression) in breast cancer, Estrogen receptor, Progesterone receptor,p53,Ki-67. Breast cancer can start in different parts of the breast, such as the milk ducts, lobules, or other breast tissue[1]. Risk factors for breast cancer include being a woman, getting older, having a family history of breast cancer, having certain gene mutations, having dense breast tissue, being overweight or obese, drinking alcohol, and not having children or having children after age 35.Symptoms of breast cancer may include a lump or thickening in the breast or armpit, a change in the size or shape of the breast, nipple discharge or inversion, redness or swelling of the breast, or skin changes on the breast. Early detection and treatment are important for improving the chances of survival from breast cancer. Screening tests such as mammograms can help detect breast cancer before symptoms appear. Treatment options for breast cancer may include surgery, radiation therapy, chemotherapy, hormone therapy, or targeted therapy, depending on the type and stage of the cancer. There are several proteins that are upregulated (i.e., increased in expression) in breast cancer. Estrogen receptor (ER) - This is a protein that is present on the surface of some breast cancer cells. ER-positive breast cancers depend on estrogen to grow and are typically treated with hormone therapy. Progesterone receptor (PR) - This is another protein that is present on the surface of some breast cancer cells. PR-positive breast cancers also depend on hormones to grow and are typically treated with hormone therapy. Ki-67- This is a protein that is present in the nucleus of dividing cells. t's important to note that there are many other proteins that may be upregulated in breast cancer, and the specific proteins that are involved can vary depending on the individual tumor. Plasminogen activator tissue (tPA) is a protein utilized in the degradation of blood clots. It is produced by various cells in the body, including cancer cells. In breast cancer, tPA protein suggest role in tumor growth, invasion, and metastasis. tPA able to activate plasminogen, a precursor protein, which then converts to plasmin, an enzyme that can break down the extracellular matrix and other proteins that hold cells together. This process is important for cancer cells to invade and spread to other parts of the body.

Phytochemicals in cancer prevention

Resveratrol - Resveratrol has been studied for its potential health benefits, particularly in relation to its antioxidant and anti-inflammatory properties. In laboratory studies, resveratrol has been shown to have anti-cancer effects, such as inhibiting the growth of cancer cells and inducing apoptosis (cell death) in cancer cells. However, its efficacy in humans is still under investigation and more clinical studies are needed to confirm its anti-cancer properties. Resveratrol is also known for its potential anti-aging effects. It has been shown to activate a protein called SIRT1, which is involved in cellular aging and may help to protect against age-related diseases[2]. However, its effects on human lifespan are not yet clear. Resveratrol is available in supplement form and is also found in foods such as red wine, grapes, berries, and peanuts. It is important to note that while resveratrol has shown promise in laboratory studies, its long-term effects and safety in humans are still being investigated, and it should not be used as a replacement for conventional medical treatment.

health benefits, particularly for liver health[3]. Silymarin is believed to exert its beneficial effects through several mechanisms, including antioxidant, anti-inflammatory, and hepatoprotective (protective of liver cells) properties. It is thought to help protect liver cells from damage caused by toxins, drugs, and alcohol, and to promote liver regeneration. Silymarin has been studied for its potential therapeutic effects in a variety of liver diseases, including hepatitis, cirrhosis, and non-alcoholic fatty liver disease. It has been shown to improve liver function tests and reduce inflammation in some clinical trials, although results have been mixed and more research is needed to confirm its efficacy. Silymarin is available in supplement form and is generally considered safe when used as directed.

Mitomycin C - Mitomycin C is a drug that is used to treat cancer, including breast, lung, stomach, and bladder cancer. It induce DNA damage in cancer cells, so that they can not divide and multiply. Mitomycin C is typically administered intravenously and is often used in combination with other chemotherapy drugs. It is generally reserved for use in advanced or metastatic cancers, or in cases where other treatments have been unsuccessful. Mitomycin C is a potent chemotherapy drug and must be used with caution. It is important for patients to discuss the potential benefits and risks of this treatment with their healthcare provider before beginning therapy[4].

Berberine - Berberine is a natural alkaloid compound found in a variety of plants, including the barberry plant, Oregon grape, and goldenseal. It has been used in traditional Chinese medicine and Ayurvedic medicine for centuries to treat a variety of conditions, including diarrhea, diabetes, and infections. Berberine has been studied extensively in recent years for its potential health benefits[5]. It has also been shown to have effects on blood sugar levels and cholesterol and may have potential benefits for cardiovascular health. Some studies have suggested that berberine may be effective in treating certain conditions, such as type 2 diabetes, metabolic syndrome, and high cholesterol. It may also have potential benefits for cognitive function and neurological disorders. Berberine is available as a dietary supplement and is generally considered safe when used as directed.

Andrographolide - Andrographolide is a bioactive compound derived from the leaves and stems of the Andrographis paniculate plant, also known as the "king of bitters". It has been used in traditional medicine in Asia for centuries to treat a variety of conditions, including infections, inflammation, and digestive disorders. Andrographolide has been studied for its potential health benefits, and it has been found to have a number of pharmacological effects, including anti-inflammatory, antioxidant, and immunomodulatory properties. Andrographolide is available as a dietary supplement and is generally considered safe when used as directed[6].

Hesperidin - (3,5,7 – trihydroxyflavanone 7- rhamnoglucoside) was first isolated in 1828 by chemist from france named lebreton, it is isolated from inner white peel of oranges(citrus). Hesperidin is reported for various biological and pharmacological effects, such as anticancer, anti-oxidant, anti-inflammation properties. Hesperidin and it's aglycone hesperitin, possesses anticancer activity and reported effective against various cancers like breast cancer,liver cancer, colon cancer, gastric cancer, lung cancer and Prostate cancer[7].

I. MATERIAL AND METHODOLOGY

A. Materials

A 10th generation i6 core with 8.0 GB of RAM and a 64-bit operating system are needed for in-silico study of proteins and ligands. Protein of plasminogen activator (tissue type) with receptor structure found in protein databank (pdb). A docking utility called Auto Dock 1.6.3 is needed. The interaction of protein-ligand is visualized using PLIP and the protein and ligand are generated and converted into pdbqt format in Open Babel GUI..

Methodology

1. Protein and ligand (phytochemicals) selection from the IMPPAT database
2. After receiving the protein's structure from the Protein Data Bank, make the protein. The protein was created using the auto dock 1.6.3 tools, and then the water molecules were removed, Kolman's charge was added, and polar hydrogen was added before the file was saved in the pdbqt format.
3. Protein and ligand molecular docking is initiated by formatting the x, y, and z centers in 6.084, 45.738, and 38.252 points, respectively. This is done by Auto Dock Vina 1.4.6. X, Y, and Z are each 40, 40, 40 in size. In auto dock vina software, all phytochemicals (ligands) are docked with proteins.

4. Analysis: Using the auto dock vina tools, an output file is created. This output is then run via the pymol software to create a pdb file, and the results are analyzed using PLIP. On the basis of binding energy, the protein and phytochemical (ligand) and protein and conventional inhibitor (ligand) were compared and chosen.

1	Hesperidin	-8.5	190 A	3.80
2	Silymarin	-8.5	192 A	3.66
3	Berberine	-7.7	213 A	3.78
4	resveratrol	-6.7	215 A	3.67
5	Mitomycin c	-6.8	190 A	3.80
6	andrographolide	-6.8	192 A	3.66
7	Tranexamic acid (standard inhibitor)	-5.0	215 A	3.78

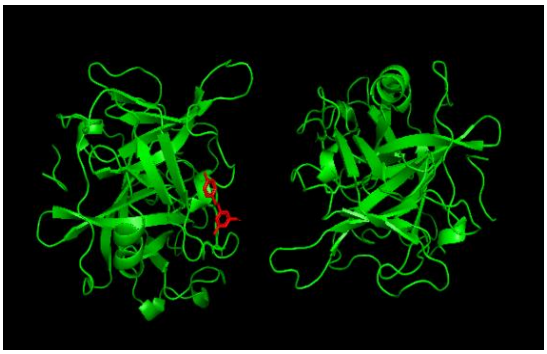

Figure 1. Interaction between protein (PLAT) and ligand (Hesperidin) in pymol

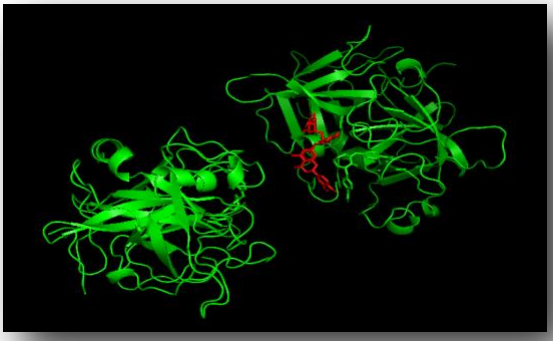

Figure 2. Interaction between protein (PLAT) and ligand (Silymarin) in pymol

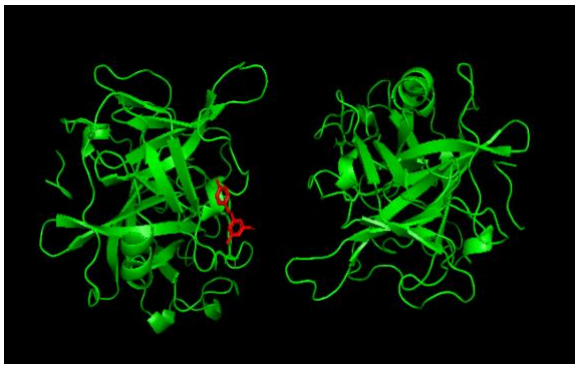

Figure 3. Interaction between protein (PLAT) and ligand (berberine) in pymol

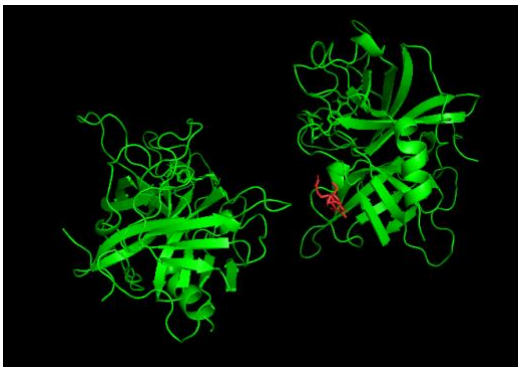

Figure 4. Interaction between protein (PLAT) and ligand (resveratrol) in pymol

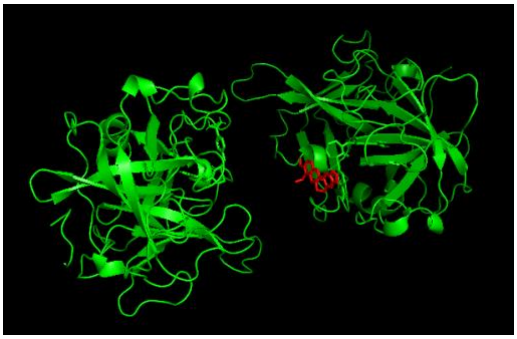

Figure 5. Interaction between protein (PLAT) and ligand (Mitomycin-c) in pymol

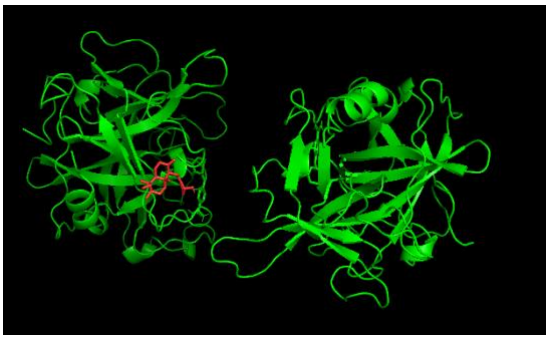

Figure 6. Interaction between protein (PLAT) and ligand (andrographolide) in pymol

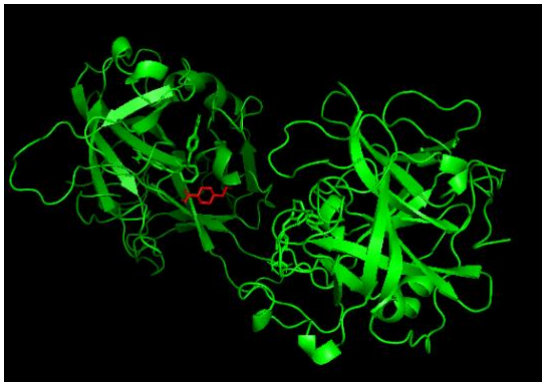

Figure 1. Interaction between protein (PLAT) and ligand (Tranexamic acid) in pymol

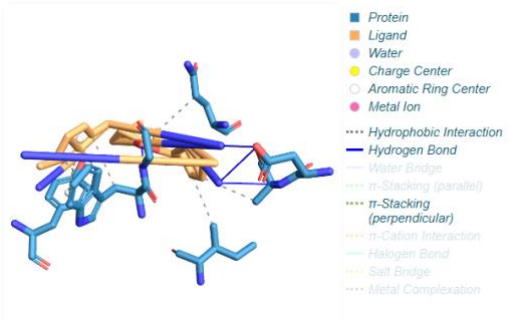

Figure 2. Interaction of protein (PLAT) and ligand (Tranexamic acid) in Protein-Ligand Interaction Profiler PLIP

Figure (1–7) are images obtained in pymol, a software which require pdb file and show interaction of protein with ligand in visual form. Green (protein) and Red (ligand) in these figures, depicts interactions between them. Figure 8 obtained from online tool also show interactions among them.

IV. Observation

The most energetic molecules for binding are chosen. Hesperidin and silymarin in table 1 exhibit maximum binding energy (-8.5 kcal/mol), allowing for their usage in the development of drugs that inhibit the PLAT protein in breast cancer and function as therapeutic agents for the disease

V. Conclusion

Studies have shown that high levels of tPA expression are linked with poor prognosis in breast cancer patients, indicating that it can be used as biomarker agent for predicting disease outcome. Additionally, inhibition of tPA by ligand inhibitor have been shown to reduce growth of cancer cells and metastasis in breast cancer models, suggesting that targeting tPA may be a potential therapeutic strategy for treating the disease.Overall, the role of tPA in breast cancer appears to be significant, and further research is needed to understand its mode of action and potential as a therapeutic target. Targeting multiple targets inhance the quality data and utilized in drug design.

.

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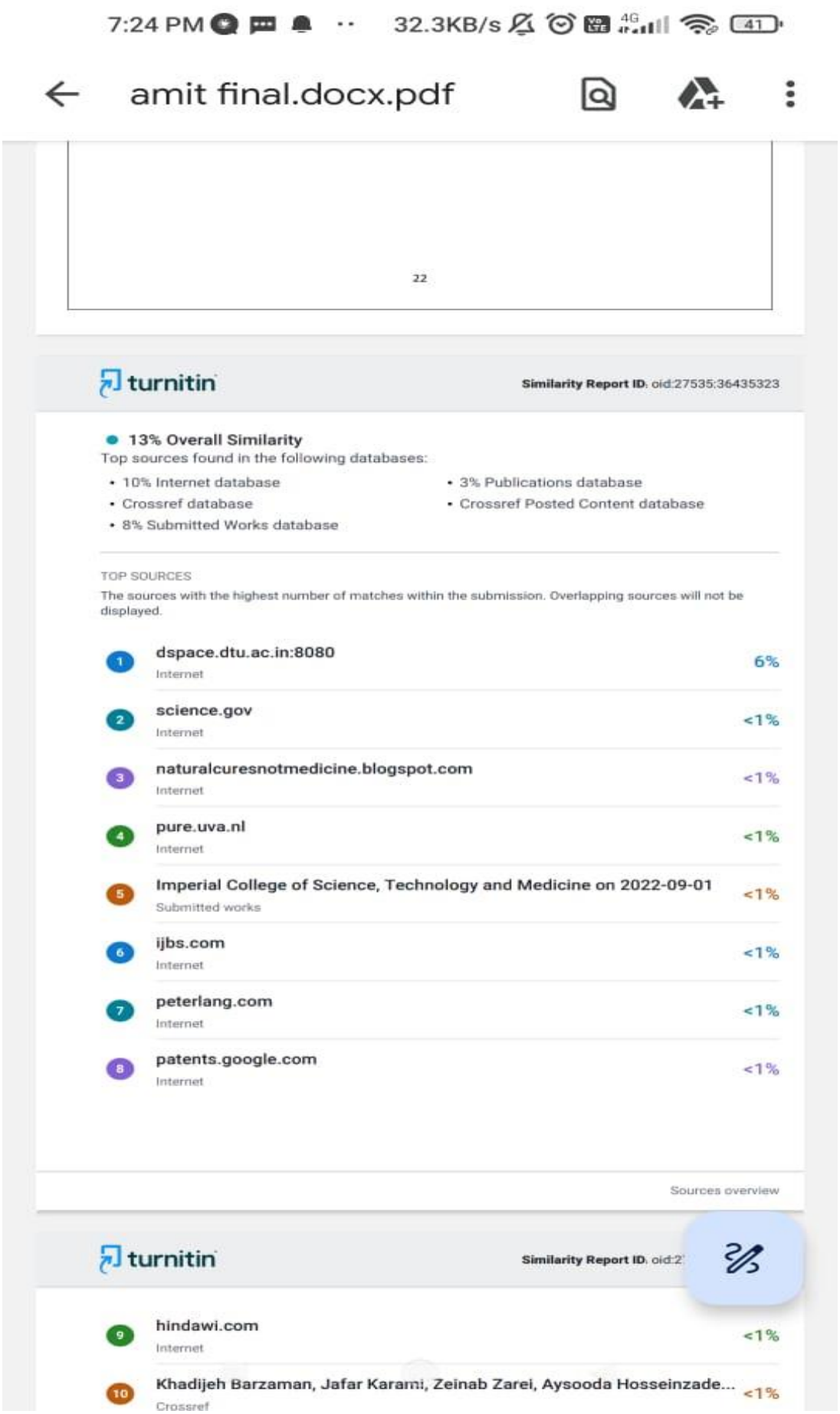
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CANDIDATE'S DECLARATION

I Amit, Roll Number: 2K21/MSCBIO/04, student of M.Sc. Biotechnology, hereby declare that the work which is presented in the Major Project entitled — "EXPLORING THE THERAPEUTIC POTENTIAL OF PHYTOCHEMICALS: MOLECULAR DOCKING STUDIES IN BREAST CANCER" in the fulfilment of the requirement for the award of the degree of Master of Science in Biotechnology and submitted to the Department of Biotechnology, Delhi Technological University, Delhi, is an authentic record of my own carried out during the period from January- May 2023, under the supervision of Assistant Prof. Navneeta Bharadvaja

The matter presented in this report has not been submitted by me for the award for any other degree of this or any other Institute/University. The work has been accepted in IEEE Conference with the following details:

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Name of Conference- "Smart Technologies and System for Next Generation Computing(ICSTSN 2023)" -IEEE Conference

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Status of Paper: Accepted

Date of Paper Communication: 17th March 2023

Date of Paper Acceptance: 29th March 2023

Amit

Date: 30-05-2023

CERTIFICATE

I hereby certify that the Project Dissertation "EXPLORING THE THERAPEUTIC POTENTIAL OF PHYTOCHEMICALS: MOLECULAR DOCKING STUDIES IN BREAST CANCER" Amit, Roll No. 2K21/MSCBIO/04, Department of Biotechnology, Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the degree of Master of Science is recorded for the project work carried out by the student under my supervision. To the best of my knowledge this work has not been submitted in part or full for any degree or any diploma to this university or elsewhere.

Date: 30-05-2023

Place: Delhi

Dr. NAVNEETA BHARADVAJA

SUPERVISIOR

Assistant Professor

Department of Biotechnology

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30/05/2023

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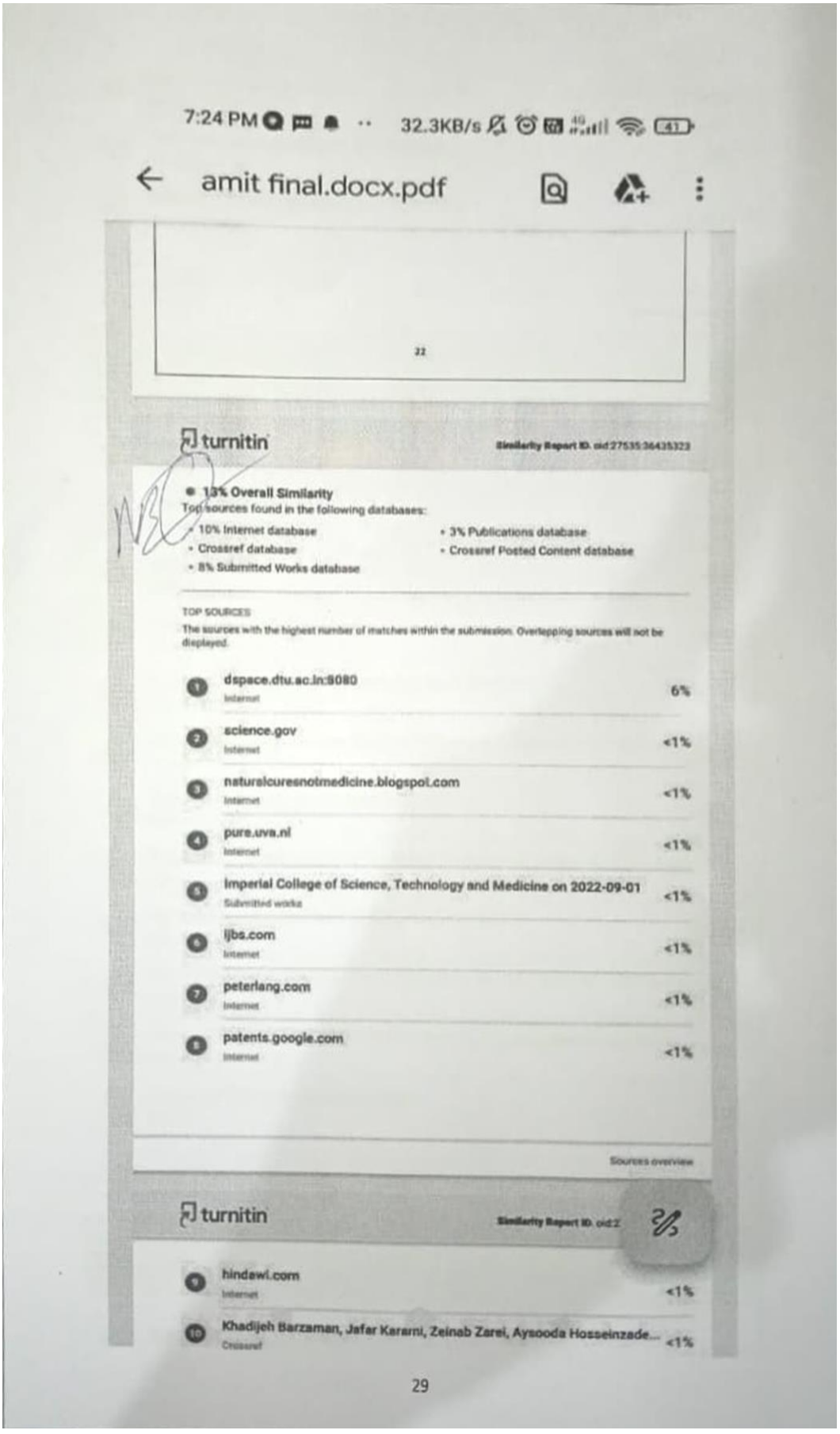
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