"Computational Exploration of Molecular Interactions: Molecular Docking-Based Drug Discovery for Non-Melanoma Skin Cancer by Targeting Upregulated Gene with Curcumin Ligands"

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CANDIDATE'S DECLARATION

I hereby certify that the work which is presented in the research work entitled "Computational Exploration of Molecular Interactions: Molecular Docking-Based Drug Discovery for Non-Melanoma Skin Cancer by Targeting Upregulated Genes with Curcumin Ligand" in fulfilment of the requirement for the award of Degree of Masters of Sciences in Biotechnology and submitted to the Department of Biotechnology, Delhi Technological University, Delhi is an authentic record of my own work, carried, under the supervision of Dr. Navneeta Bharadvaja. The matter presented in this thesis has not been submitted by me for the award of any other degree of this or any other University.

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CERTIFICATE

This is to certify that Project Dissertation titled "Computational Exploration of Molecular Interactions: Molecular Docking-Based Drug Discovery for Non-Melanoma Skin Cancer by Targeting Upregulated Genes with Curcumin Ligand" which is submitted by Swati singh, Roll No. 2K21/MSCBIO/53, Department of Biotechnology, Delhi Technological University in partial fulfilment of the requirement for the award of the degree of Master of Science, is record of 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 Diploma to this university or elsewhere

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ABSTRACT

Cancer is often counted among most widespread ailment in humans and other mammals, it can be described as group of diseases where uncontrolled and abnormal cell division, which affect other neighbouring cells and tissues and can also spread through blood vessels, lymphatic nodes affecting other parts of body, it can be caused due to several environmental factors, like environmental toxins, radiations, lifestyle, lack of proper diet, genetic mutation, exposure to radiations etc. There are many distinct types of cancer like cancer of lung, prostate, colon etc and each of these have their own methods of treatments. It is advised to have test done in order for earlier detection and treat using different types of method like surgery, chemotherapy etc. One of these is non-melanoma skin cancer which can also be caused by PUVA (combination of 8-MOP and 5-MOP plus UV A) a radiation therapy used for treatment of vitiligo, by increasing the sensitivity of skin Thus increased production of melanin but it also makes the skin very sensitive to sunlight which leads to non-melanoma skin cancer, and there are certain therapeutics which can be used for treatment of this cancer, these are targeted drug delivery method where we can use small magnetic or gold nanoparticles to deliver our drug to the affected site and we can also use inhibit the NOX pathway which is upregulated in NMSC resulting in increased production of NOX mediated ROS because this ROS causes the DNA damage which leads to mutation of p53 gene

In this paper molecular docking and molecular dynamics studies are performed to find potential drug targeting the genes upregulated in NMSC using potential ligands and downregulated genes are also studied, the main ligands that were used are 2- Heptanol, Germacrone, Isobornyl acetate, Curcumin, 3(1,5-Dimethyl-4-hexenyl)-6methylene-1cyclohexene, Ar-dihydro-turmerone, these ligands are found in plant compound curcumin and a gene EGFR C797S that is upregulated in NMSC was targeted using these ligands, compatibility of ligands with the receptors present on gene was checked. Software like PyRx, auto dock Vina, RCSB PDB, PubChem, biovia studios are used. Studies are still going on curcumin; it is affective in various signalling pathways associated with growth and proliferation of cancer

KEY WORDS

PUVA, Curcumin, EGFR, PyRx, autodock Vina, NMSC, RSCB PDB, p53, ROS, NOX

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Chapter 1 : INTRODUCTION

The most prevalent kind of cancer that mostly impacts the skin is NMSC. Basal and squamous carcinoma cells carcinoma are most widespread forms of skin disease (cancer) worldwide. Continuous exposure to ultraviolet radiation which comes directly from the sun or other simulated sources like tanning bed, often leads to NMSC by inducing genetic abnormalities and abnormal skin cell growth. The cases and death rates of NMSC are on the rise, which has resulted in extensive studies on the development and growth of effective non-invasive therapies. The correlation between sun exposure patterns and basal-cell carcinoma subtypes is yet unresolved although the cumulative sun exposure affects the genesis of SCC which is evident. Proliferation of NMSC can be affected by several complex genotypic, phenotypic, and environmental factors. Squamous cell carcinomas may develop from precursor lesions, unlike basal-cell carcinomas. Non-melanoma skin cancer is determined clinically and histological testing is performed to confirm the diagnosis. The lesion and host functions, which also determine the type of therapy, affect the prognosis. Reduced sun exposure is the ultimate objective of prevention methods, although these are still not proven to be beneficial, especially when it comes to basal-cell carcinoma.[1]

1.1 POTENTIAL RISKS ASSOCIATED WITH NMSC INCLUDE:

(a) The primary risk factor for NMSC is prolonged exposure to certain radiations from the sun or tanning beds, which are quite famous in Western countries. The DNA in skin cells is damaged by overexposure to ultraviolet (UV) rays, therefore increasing the probability that cancer might develop.

(b) People with light complexion have less melanin, which safeguards against UV radiation, as well as light-coloured eyes and hair. They are therefore more susceptible to NMSC.

(c) Age: NMSC is most common in older individuals, with the increasing risks being caused by prolonged sun exposure over time.

(d) Immunosuppression: Individuals who went through some sort of treatment like recipients of organ transplant, or those who are suffering from AIDS/HIV etc have a higher risk of getting affected by NMSC

(e) Previous skin cancer patients: the patients who had NMSC previously are more prone to new type of cancers

(f) Genetic factor: NMSC are more likely to grow and develop in those individuals who are suffering from certain diseases like xeroderma pigmentosum.

1.2 TYPES OF NMSC

1. BCC: It is one of the most frequent types of NMSC. It usually looks like shiny and small sized bumps or they can even occur as tiny red patches on affected area of skin. This cancer is benign because they grow very slowly, and have very less tendency to spread to other body parts, but that does not mean it can be left untreated because if left untreated then it may spread to neighbouring tissue and cells and destroy them

2. SCC is second most frequent type of NMSC. It looks like hardened red lump or swelling, it can even be in the form of scaly patches, or an inflamed sore that remain same as new and cannot be healed overtime. As compared to BCC, SCC grow and develop more quickly, if this cancer is left untreated then can proliferate in other parts of body which is deadly for the affected individual.

3. Other than these two non-melanoma skin cancers there are some other NMSC which are infrequent, like for example cancer that occur in Merkel cells, DFSP (Dermatofibrosarcoma

protuberans), which is also a rare kind of NMSC develop from the cells of dermis, then we have another NMSC that arise from the lymphocytes.

SYMPTOMS OF NON-MELANOMA SKIN CANCER

Appearance of brown coloured scar kind of injury, or wax like lump or the skin appears scaly. The application of therapy for this cancer depends on the site and type of cancer, it can be treated with the help on surgery, topical medication, and radiation therapy like PUVA., these radiation therapies are associated with drastic toxicity due to their inability to distinguish between normal and cancerous cells.

1.4 COMPOUNDS THAT CAN BE USED FOR TREATMENT OF NMSC

1.4.1 CURCUMIN

Curcumin is a compound that occur innately in turmeric plant, turmeric is one of the most common spices used in cooking in Indian and Asian households, it became quite popular because of its possible benefits in various aspects of healthcare and pharma industry. It is a polyphenol which anticancer, antioxidant and anti-inflammatory effects. There are researches going on curcumin some of which have shown that curcumin can be used as a treatment for cancer, it has potential to inhibit or reduce the growth of cancerous cells because of its anti-tumour property, curcumin is proved to be helpful in triggering the apoptosis of cancer cells. However, it is very important to take in account that the evidence for effect of curcumin on specific type of cancer like non melanoma skin cancer is still very limited and more research is need to be performed regarding this.

1.4.2 QUERCETIN

This compound occurs naturally and are also known as flavonoids, found in onion, citrus fruits like different types of berries, gapes, broccoli etc, it has antioxidant properties and it also protect the tissues or cells injured due to drug toxicity. Quercetin also proved itself as a possible drug for treatment in various aspects of health like for induction of proper functioning of immune system,

maintenance of cardiovascular activities and wellness,[2] there are some studies conducted which shows that quercetin is likely to have potential to treat some specific type of cancer one of which in NMSC, it inhibits the proliferation of carcinoma cells and induce their apoptosis.

1.4.3 PSORALEN

Psoralen is a naturally occurring compound, found in plants like Fig, parsley, other citrus fruits, also in medicinal plant Psoralea corylifolia, and is commonly used along with UVA a type of UV radiation. This PUVA therapy can help in targeting killing carcinoma cells, PUVA is mostly used for treatment of cutaneous T cell lymphoma.

1.4.4 GINGEROL

These are compounds found in the roots of ginger, it has anti-inflammatory, anticancer and antioxidant property. Most of the researches regarding gingerol are mainly focused on its use and effect on various cancers. No advanced clinical researches trails on humans has been done, it is only limited to preclinical research

1.4.5 RESVERATROL

Found in different plants like grapes, various berries, and peanuts. It has anti-inflammatory, anticancer, and antioxidant effects. Researches and studies on resveratrol has been performed for its potential effect on different types on cancer. The researches of resveratrol on NMSC are limited to preclinical studies performed on animal models. Resveratrol is believed to function and apply its effect through different types of mechanisms like for example regulation of signalling pathways involved growth, development and survival. However, these findings and researches cannot be used directly for treatment of humans. Clinical research needs to be performed for determination of effectiveness and safety of resveratrol for NMS

1.5 USES OF CURCUMIN IN VARIOUS SKIN DISEASES

Curcumin is a chemical compound which occur naturally and used in various skin diseases, it curcumin shows promising ability in therapeutic treatment of various skin related diseases there are researches which studied about curcumin for skin diseases are many are still happening , and more clinical studies are needed to establish its efficacy and optimal usage. Additionally, curcumin's poor bioavailability can limit its effectiveness, so using it in combination with

absorption-enhancing agents or in nano formulations may improve its therapeutic potential. It is always advisable to consult with a healthcare professional or dermatologist before using curcumin or any other natural supplement for skin conditions.[3]

1.5.1 Some of the skin disease related uses are as follows-

WOUND HEALING: Curcumin have that potential that help in inducing the process of wound healing by increasing collagen production and development of blood vessels on affected areas, it is helpful in wounds caused by cuts, burns, surgery etc.

PSORIASIS: curcumin help in psoriasis by inhibiting some specific signalling pathways that have important role in inflammatory response that occur due to psoriasis, it helps by lessening the redness, itchiness, scaling caused by psoriasis

ECZEMA: It is a skin issue where the affected individual's skin gets very dry, itchy, and sore or inflamed, so Curcumin helps in treatment of eczema by reducing the itching and inflammation caused by eczema.

Dermatitis: since curcumin has anti- inflammatory property so it is helpful in patients suffering from dermatitis (atopic and allergic dermatitis) by inhibiting the inflammatory mediators which ultimately lead to reduction of itchiness and redness of the affected area of skin

TABLE. 1 THE TABLE BELOW SHOWS VARIOUS PLANTS COMPOUNDS THEIR SOURCE AND PROPERTIES[4]

Plant Compounds	Source	Property
Curcumin	*turmeric*	*Anti-inflammatory and anti-cancerous property, have potential in treatment of breast, lung and prostate cancer*
Quercetin	*Onion, apples, berries*	*Anti-inflammatory and antioxidant property, helps in treatment of colon, breast and prostate cancer*
Psoralen	*Fig, parsley, other citrus fruits, also in medicinal plant Psoralea corylifolia*	*Used in skin disorders, anti-cancerous property induces apoptosis, breast, lung and prostate cancer*
Gingerol	*Ginger*	*Anti-inflammatory and antioxidant property, ovarian and pancreatic cancer*
Resveratrol	*Red wine, grapes, berries*	*Anti-inflammatory and antioxidant property, breast, colon and prostate cancer*

Molecular docking and molecular dynamics studies are performed to find potential drug targeting the genes upregulated in non-melanoma skin cancer with the help of ligands of curcuma longa i.e,

2-Heptanol, Germacrone, Isobornyl acetate, Curcumin, 3(1,5-Dimethyl-4-hexenyl)-6methylene-1-cyclohexene, Ar-dihydro-turmerone, and performed their molecular docking to find out their binding affinity with the gene EGFR C797S (7aei), and also the blood brain barrier crossing was identified with the help of ADME. Then the ranking of ligands performed on the basis of their binding affinity and interaction with desired protein. Different Software

like PyRx, auto dock Vina, RCSB PDB, PubChem, biovia studios are used. Studies are still going on curcumin; it is affective in various signalling pathways associated with growth and proliferation of cancer.[5]

Chapter 2 REVIEW OF LITERATURE

NMSC disease: challenges in its occurrence, etiology, and treatment.

NMSC is a very big trouble to the wellbeing of humans around the world, with its increasing rate of incidence. This kind of disease incorporates BCC and SCC are the two types which represent most of carcinomic diseases related to skin. It is important to understand the rate, etiology, and treatment challenges related with NMSC because it is essential for creating successful anticipation systems and working on persistent results.[6]

The occurrence of NMSC shifts geologically, with higher rates saw in areas with more prominent sun openness. Lighter looking people, especially those with a background marked by exorbitant sun openness and burns from the sun, are at higher gamble. Other gamble factors incorporate old age, immunosuppression, openness to specific synthetic compounds, and a family background of skin disease.

Bright (UV) radiation from the sun is one the significant etiological factor in proliferation of NMSC. Persistent exposure to UV radiation causes harm to the DNA of skin cells, which causes genetic mutation that result in initiation of proliferation and development of cancer cell. The combined impacts of continuous exposure, contribute to development of NMSC[6].

Diagnosis of NMSC basically includes a combination of certain clinical assessment, like dermoscopy, and biopsy of affected area of skin, and some histopathological investigations. Early recognition is pivotal, as it takes into consideration brief intercession and better treatment results. Nonetheless, challenges exist in distinctive NMSC from harmless skin sores, particularly in situations where the clinical show is abnormal or sores are little and unpretentious.

Treatment approaches for NMSC rely upon different variables, including the cancer type, size, area, and individual patient qualities. Careful extraction is the essential treatment methodology for most cases, offering amazing fix rates. Notwithstanding, challenges emerge while managing huge or forceful growths, repetitive cases, or cancers situated in cosmetically delicate regions or physically testing destinations.

Lately, non-careful therapy choices like effective chemotherapy, immunotherapy, photodynamic treatment, and radiation treatment have arisen as options or assistants to medical procedure. These modalities offer benefits in unambiguous cases yet additionally present their own constraints and possible secondary effects.

So, NMSC is a typical kind of disease with worldwide increase in rate of cases. So, understanding the elements adding to its turn of events, like exposure to UV radiations, along with its difficulty looked in its conclusion and therapy, is very important for real time successful administration.[7]

The Role of Upregulated Genes in proliferation of NMSC

Non melanoma skincancer is a type of very complex disease which is described by the undifferentiated development and expansion of skin cells. The proliferation of NMSC includes many different molecular modifications, which often includes the increased activity in affected cells as compared to normal cells. The upregulated genes have a very vital role in driving the movement and development of NMSC.

One of the vital processes by which upregulated genes helps in proliferation of NMSC is by advancing the uncontrolled cell proliferation and development. These genes are often related to certain signaling pathways that are associated with regulation of cell cycle and its proliferation, someof the genes upregulated in NMSC are EGFR and other pathway is MAPK that is mitogen-activated protein kinase. When these genes get overexpressed in the mentioned pathways which activate the downstream process of signalling, which ultimately leads to advanced cell division and growth of tumor.[8]

Upregulated genes in NMSC also helps in angiogenesis, it is the mechanism by which the new blood vessels in order to supply oxygen and nutrients to growing tumors. Genes such as vascular endothelial growth factor (VEGF) and hypoxia-inducible factor 1-alpha (HIF-1α) are frequently upregulated in NMSC, promoting the formation of new blood vessels that fuel tumor growth and metastasis.[9]

Furthermore, upregulated genes can modulate the tumor microenvironment in NMSC, facilitating immune evasion and resistance to therapy. For example, genes involved in the production of

immunosuppressive factors or in the downregulation of immune response pathways can create an immunosuppressive environment that allows tumors to evade immune surveillance.

The therapeutics performed are usually based of upregulated gene targeting whether it is NMSC or any other cancer, but if we talk about NMSC then this method has a very good compatibility. What we can do is identify the genes and study their role in causing disease and then desired therapy can be performed in order to inhibit the activity of upregulated.[10].

2.4 Importance of computer-based methods in drug discovery mechanisms

Computer based methods and software have become a distinct part of the field of drug discovery, it can used for accelerating the process of identification and production of new therapeutic mechanism. With the ever-increasing availability of computational power and advanced algorithms, these methods have revolutionized the drug discovery process and significantly reduced the time and cost involved in bringing new drugs to market. Here, we explore the importance of systematical methods in discovery of drug and their impact on the field.

The systematic or computational techniques have one of the major role and contribution it accelerates the primary stages need to be performed in drug discovery. With the help of these systematic and computational techniques one can evaluate and analyze chemical compound required for therapeutic purpose of protein of interest, and helps in better understanding of therapeutic approach required for the desired outcome. This also helps researches to work on even very smallest compound which have desired pharmacological and medicinal. These computer-based methods are time saving and also gives high throughput results.

These computer-based approaches also help in finding the specific behavior of drug molecules which are present in the biological system. It can also help in analysis of interaction takin place between the desired protein-ligand complex, their binding affinities, and assess their pharmacokinetic properties. This information aids in the selection and optimization of lead compounds, guiding the design of more potent and selective drugs.[11]

Moreover by integrating computational methods with experimental techniques, scientists can efficiently explore chemical space, optimize drug properties, and ultimately bring safer and more effective drugs to patients in a shorter timeframe.

Non-Melanoma Skin Cancer Targeting Upregulated Genes:

Identification of key upregulated genes in NMSC

NMSC is a very common type of cancer with its cases increasing worldwide. It is important to understand the molecular changes or mutations that triggers proliferation of NMSC, the understanding is also important for development of therapy and improving patients health.

Through wide range of analysis are performed using genomics and transcriptomics, researchers have successfully identified several key upregulated genes in NMSC. These genes are involved in diverse many biological activities and signaling pathway that contribute to tumor growth, invasion, angiogenesis, and resistance to treatment. Their identification provides valuable insights into the underlying molecular mechanisms of NMSC and offers potential targets for therapeutic intervention.[12]

Among the upregulated genes in NMSC, the EGFR and its downstream signaling pathways have been broadly studied over a certain period of time. In cases of NMSC it was observed that there was overexpression of EGFR and it was noted that EGFR is always linked with metastasis, undifferentiated cell growth, as well as angiogenesis. So, a targeted therapy performed by inhibiting the signaling pathway of EGFR, which gave very promising results.[13]

Another important group of upregulated genes in NMSC includes those involved in cell cycle regulation and proliferation. Cyclin-dependent kinases (CDKs) and their regulatory partners, such as cyclins and CDK inhibitors, play a critical role in controlling cell cycle progression. Dysregulation of these genes can lead to uncontrolled cell proliferation and tumor development. Targeting CDKs has emerged as a potential therapeutic strategy in NMSC.[14]

Furthermore, genes associated with immune modulation and evasion are upregulated in NMSC. Immune checkpoint molecules, including programmed cell death protein 1 (PD-1) and its ligand

PD-L1, are frequently expressed in NMSC and play a role in immune evasion. Immune checkpoint inhibitors targeting PD-1/PD-L1 have demonstrated significant clinical benefits in certain subsets of NMSC patients.[15]

In conclusion, the identification of key upregulated genes in non-melanoma skin cancer has provided crucial insights into the molecular alterations underlying tumor progression. These genes are involved in various cellular processes and signaling pathways that contribute to tumor growth, angiogenesis, and immune evasion. Targeting these genes and their associated pathways holds promise for the development of more effective and personalized therapeutic approaches in NMSC treatment. Further research is warranted to fully elucidate the functional significance of these upregulated genes and to translate these findings into clinically meaningful interventions.

Biological pathways and molecular mechanisms associated with upregulated genes

In NMSC, the dysregulation of gene causes upregulation of certain genes, which triggers the proliferation of disease. These upregulated genes have a very important role in tumor proliferation and growth. It is important to understand the various pathways to find out the processes taking place in NMSC and the pathways are also helpful in identification of compatible targets for therapeutic approach.[16]

The EGFR Signaling Pathway:

The signaling pathway is uncontrolled in NMSC it was observed that in many cases there was overexpression of EGFR. And the genes that are upregulated in EGFR pathway, induce the downstream signaling, like the Ras/Raf/MEK/ERK and PI3K/AKT pathways, all these pathways help in tumor cell growth, proliferation, development.so, we can try to inhibit the EGFR pathway as a therapeutic approach for NMSC.[17]

Angiogenesis:

Upregulated genes in NMSC often include those involved in angiogenesis, the formation of new blood vessels that support tumor growth and metastasis. Vascular endothelial growth factor (VEGF) and its receptors are key regulators of angiogenesis in NMSC. Overexpression of VEGF and increased angiogenic signaling contribute to the development of a tumor vasculature network that supplies nutrients and oxygen to the growing tumor.[18]

Immune Modulation and Evasion:

The genes that are related to regulation of immune were found to be upregulated in NMSC. it consists of molecules like programmed cell death protein 1 (PD-1) and the ligand PD-L1. While upregulation of these immune regulatory genes can cause immunosuppressive effect. If we target the pathways of these genes, it gives the immune cells power to recognize and attack the tumor cells.[19]

DNA Repair and Genomic Stability:

The genes that are upregulated in NMSC may be a cause of damaged caused to the healthy DNA leading to gene mutation, due to this mutation proliferation and development of tumor cell starts understanding this molecular mechanism can lead help in better understanding of therapeutics processes need to be performed on NMSC.[20]

Significance of targeting upregulated genes for therapeutic interventions

The significance of targeting upregulated genes for therapeutic interventions in various diseases, including cancer like non-melanoma skin cancer (NMSC), cannot be overstated. These upregulated genes play a critical role in driving disease progression and are often associated with key molecular pathways and cellular processes that contribute to tumor growth and survival. Here are some reasons why targeting upregulated genes is significant for therapeutic interventions:[21]

Upregulated genes can serve as valuable targets for drug development. By inhibiting or modulating the activity of these genes or the proteins they encode, therapeutic interventions can disrupt the

dysregulated signaling pathways, cellular processes, or molecular interactions that drive disease progression.[22]

Curcumin as a Ligand for Non-Melanoma Skin Cancer:

Introduction to Curcumin and Its Anti-Cancer Properties

Curcumin is a natural compound derived from the rhizome of the turmeric plant (Curcuma longa). It has been used for centuries in traditional medicine due to its various therapeutic properties. In recent years, curcumin has garnered significant attention for its potential anti-cancer effects. Numerous studies have highlighted its ability to inhibit tumor growth, induce apoptosis (cell death), and suppress metastasis in various types of cancer, including breast, lung, colon, prostate, and skin cancer.

The anti-cancer properties of curcumin can be attributed to its diverse mechanisms of action. Firstly, curcumin has been shown to have potential antioxidant and also anti-inflammatory function. It was noted that when someone suffer from chronic inflammation or even oxidative stress that accumulation reactive species of oxygen, are prone to cancer. Curcumin help in inhibition of various cancers.[23]

Another notable aspect of curcumin's anti-cancer effects is its ability to induce apoptosis in cancer cells. It can activate various pathways that regulate apoptosis, including the intrinsic mitochondrial pathway and the extrinsic death receptor pathway. Curcumin can stimulate the release of pro-apoptotic proteins and inhibit anti-apoptotic proteins, promoting programmed cell death in cancer cells.[24]

Curcumin has anti-angiogenic properties embedded in it, which produce hindrance in formation of new blood vessels due to which the supply of oxygen to tumor cells get affected leading to their death. Curcumin also inhibits the expression of VEGF which is an angiogenic factor and inhibit

the activity of enzymes involved in angiogenesis which lead to inhibition of activity of enzymes involved in angiogenesis resulting in reduction of blood supply to the tumor cells which causes their death.

It was found that Curcumin has the ability to weaken the tumors cells to unlike normal chemotherapy and radiotherapy. It can also improve the anti-tumors effects of these treatments, reduce treatment resistance, and it also provides protection to the healthy cells during the procedure of therapy.[25]

Overall, curcumin possesses a wide range of anti-cancer properties, making it a promising candidate for cancer prevention and treatment. Its multi-targeted approach, along with its low toxicity and affordability, has generated considerable interest in harnessing its potential in combating various types of cancer. However, it is very important to keep in mind that the bioavailability of curcumin is relatively low, and efforts are being made to enhance its absorption and effectiveness through various formulation and delivery strategies. Ongoing research aims to further elucidate the mechanisms underlying curcumin's anti-cancer effects and explore its potential in combination therapies and clinical applications.[25]

Biological activities and mechanisms of curcumin relevant to non-melanoma skin cancer

The curcumin, a phytochemical which is derived from the plant Curcuma Longa, we all know that turmeric is one the most considerable Indian medicinal plant and it has been very broadly used and studied in various ailments for its therapeutic ability, it can also be useful in NMSC.

1. Curcumin have potential to help reduction of very long term as well as new mutations inflammation plays a very important role development and proliferation of NMSC. curcumin have the inhibit various signalling pathways and proinflammatory responses as well, which lead to NMSC

2. Curcumin is also known to antioxidant activity, and it was found that proliferation and development of NMSC induced by oxidative stress, which is improper accumulation of reactive species of oxygen. Since curcumin antioxidant property it helps in reduction or destruction of these reactive oxygen species which is also known as ROS these reactive free radicals often cause damage and mutation to the DNA.[23], [24]

4. Curcumin also has a property to cause programmed cell death in NMSC affected cells it performs apoptosis by triggering the extrinsic and intrinsic pathway that causes apoptosis, which ultimately lead to death of cells affected with NMSC.[26]

5. It is very important to keep in mind the incase of Curcumin there is very limited bioavailability and there are researches going on to overcome this issue and and increase the absorption of curcumin more research in needed to find the required dosage of curcumin for patients suffering from NMSC.[27]

Drug discovery using curcumin with the help of molecular docking

Selection of target gene and ligand and preparation of their complex structure with the help of molecular docking, this step should be performed very carefully as one minute mistake can cause failure of accurate result.

1. The selection of target protein and ligand like for example upregulated genes taken in account in many diseases, this step is also very crucial.:

2. the structure of desired protein and ligand are obtained with the help of various methods like X-ray crystallography and other similar methods. And if the structure is not available then a method called homology technique can be used to find or analyze structure based on already available similar structure.

3. The structure that was selected, go through some more steps in order to make sure that the structure is suitable for docking. In these we remove molecules of water, add hydrogen bonds, add kaumanns charge, revise and evaluate the structure and geometry, check the bond order, check whether some atoms are missing or not, all these are performed with the help of software tool PyMOL, and chimera can also be used but PyMOL is easier.

4. the identification of binding site of ligand is also a very crucial step: this analysis can be done by finding whether there are active sites in the protein or not, and also analysis of protein's residue that are functional

5. With the help of Grid generation, we can generate a 3D grid all around the site where binding of our protein ligand complex occur, it is also necessary to determine the search space so that the docking and simulation of the ligand can be performed easily. the grids basically help in exploring symmetrical and measurable coordinates within which the ligands can be analyzed. And the spacing of the grid should be done carefully

6.We also need to minimize the energy of all ligands before performing docking, so that any steric hinderance does not occur which can even cause deformity in our selected structure. And this step helps in improving the accuracy of docking

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6. So it is compulsory to check whether our structure is compatible or not and for this we can use, Ramachandran plot analysis, it is helpful in evaluating whether the structure of protein is compatible or not we can also use experimental data present online.[28]

CHAPTER 3 MATERIAL AND METHODS

MATERIALS USED

PubChem : It is a chemical database which is accessible for everyone and this database is maintained by the NCBI (National Centre for Biotechnology Information), NCBI is important part of National Library of medicine of United States (NLM). It is a global resource which produce the information about biological activities, characteristics of smaller molecules, and their chemical structure as well.

The main of this chemical database is to help with the discovery of new drugs and also in exploring the biological effects of different types of compounds. PubChem contains information of millions and billions of chemical substances like peptides, proteins, organic and inorganic compounds, natural products etc. these chemical compounds are arranged into records that contain all required data like chemical structure, physical properties, links of genuine scientific literature is also available. PubChem also have a feature of unique identifier PubChem CID, compound identifier for each compound, which make referencing and search for desired compound very easy, there are several other tools also available which helps in analysis of chemical data, performing similarity search etc[11], [29]

IMPPAT : It stands for Indian Medicinal Plants, Phytochemistry and Therapeutics, which is manually organized database which is produced with the help of digital form of information from about more than 100 books written and available on traditional Indian medicine and medicinal plants, and more than 7000 research literature. It is one of the largest database that is available digitally on phytochemicals of wide variety of traditional Indian medicinal plants, and the latest version that is IMPPAT 2.0 have database of 4010 traditional Indian medicinal plants, 1095 are those which have some or other therapeutic use, and 17967 phytochemicals.

For 17967 phytochemicals which are in the database, we have 3D (three dimensional) and 2D (two dimensional) chemical structure, it also has cheminformatic tools which help to compute the physicochemical properties and drug similarity, multiple scoring and predicted with the of ADMET properties (Absorption, distribution, metabolism, excretion, toxicity).[30]

RCSB PDB : It is a resource which have three-dimensional structure of biomolecules like protein, nucleic acids and other complex arrangements. PDB is a worldwide bank that have collection and access to structures of biomolecules that are experimentally resolved and obtained with the help of techniques like NMR spectroscopy, cryo-EM, X-ray crystallography, etc. these structures produce important information about functioning and organization of biological macromolecules.
It allows user, researchers and scientists to analyse, search and visualize the stored structures, it also provides great amount of information about each structure like ligand binding sites, methods of experiment, atomic coordinates, references to publication etc. This website also provides the tutorials and required materials in order to help users study and perform the effective use of these structural information. RCSB PDB have a wide range of application some of them are research in the field of, drug discovery, molecular biology, protein engineering, and study of molecular basis of diseases. This storehouse or database is continuously growing because scientists from all over the world are depositing new structures.[31]

AUTODOCK VINA : It is a molecular docking software used worldwide. It is mostly used for computational drug designing and their virtual screening. It is more advanced version of AutoDock and is developed by same group at the Scripps Research Institute. Molecular docking is a systematic technique which is used to analyze the model and the binding interactions between a small molecule (ligand) and a target receptor or protein. AutoDock Vina automates this process by exploring the conformational space of the ligand and the receptor and predicting the most favorable binding pose and affinity.[32]

Some important characteristics of Autodock Vina are: -

1. Provides flexibility in ligand docking: Autodock Vina gives users easy access to wide range of ligand, which makes it easier for the user to research various it to explore various shapes and configurations like polyhedral, spherical, ball and stick etc., while performing the process of docking

2. Other characteristic it that the software autodock vina uses a function of verifiable and factual scoring in order to find out the binding affinity of the protein ligand complex. It also helps in analysis of multiple configurations and also the most compatible binding position.

3. It is also famous for its very fast and high throughput result delivery

4. It is user friendly, because individuals with less expertise in this field can also perform molecular docking very easily

It helps in analysis and evaluation of binding affinity and energy between protein and ligand complexes or ligand- ligand complexes and even protein- protein. With the helps these interactions researchers or users can get an idea about the structural activities of ligands and help in improvement of binding energy and biological activities of selected compounds.

BIOVIA: it is a software specifically designed to provide solutions of scientific researches and also help in simulation for life sciences research and other related researches. It provides a wide range of software tools and platforms that help in scientific research, management of laboratory, and product management.

BIOVIA is a software which is embedded with many different types of solutions that are specifically designed to fulfill the research needs

1. **BIOVIA Discovery Studio**: This is a software which helps in integration of molecular modeling, simulation, and it also help as a visualization tool for the process of drug discovery, protein modeling etc. It allows scientists and researcher scholars to explore and analyze the molecular structures, anticipate the binding interactions, and also to perform simulations so that it gets easier to understand various biological systems.[33]

PyMOL: PyMOL is a powerful software and it is used globally for molecular visualization. It helps research scholars and scientists in visualization and analysis of three-dimensional (3D) molecular structures, like proteins, nucleic acids, small molecules, and many other complexes.[34]

Some key features of PyMOL are as follows:

1. Molecular rendering: PyMOL also have a feature of producing high-quality exhibits, which gives users a wide variety of interesting presentation of molecules. it provides styles like space-filling, and ball-stick models, and also cartoon presentations.

2. Molecular editing: Users can easily manipulate or edit the structures of molecule directly within PyMOL. The process includes steps such as addition or deletion of atoms, modification of desired bond angles or even lengths, and it can even build or modify surface of molecules.

3. Molecular analysis: PyMOL provides wide variety of tools for analysis of molecular structures. With the help of PyMOL users can easily measure the angles, and distances

within a molecule, it was also found to be useful in calculating the electrostatic surfaces, and also helps to perform alignments of protein structure, and also perform studies related to molecular docking.

PyMOL is widely used in various scientific fields, including structural biology, biochemistry, drug discovery, and computational chemistry. It is employed for tasks such as protein structure visualization, molecular docking, virtual screening, molecular dynamics simulations, and research presentations.

PyMOL offer both open-source as well as commercial versions. The open-source version also known as PyMOL Open-Source, it provides user the requirements of functions that can be used for molecular visualization. Whereas the commercial version that is PyMOL Professional, provides some more advanced features, to help the scientists and research scholars to perform advanced processes

It is very important to keep in mind that yes PyMOL is a very useful tool for visualization and analysis of structures of molecules, it should be used along with other methods and other techniques in order to support and have more accurate and clarified research findings.

MEHODOLOGY

So first of all PyRx virtual screening tool software was installed from the official website of PyRx python prescription, then the protein of interest was taken form the website RSCB protein data bank, where protein 7AEI which is upregulated in NMSC, this upregulation is caused by mutation EGFR C797S where serine get attached at cysteine at 797 codon within the ATP binding site. So, this gene was searched.

Then this protein was downloaded in PDB format. Next the molecule of ligand was downloaded from was downloaded from IMPPAT where phytochemicals of *curcuma longa* was searched and six of them were downloaded in the SDF(3D) format,

PROTEIN PREPARARTION

BIOVIA discover studio was used for protein preparation, in the biovia discovery studio the protein of interest was loaded or opened and a 3D structure appeared on the screen then in the hierarchy tab the detail about the protein appeared which provide a better analyzation of the protein structure, there were both A and B chains, water molecules, first of all water molecules were deleted, then polar hydrogen atoms were added by clicking on the chemistry tab and the polar hydrogen atoms were added and then the protein was saved in PDB format.

Fig 1. protein before and after addition of hydrogen atoms

Now open the PyRx window, it has autodock, autodock wizard, vina wizard, run vina etc embedded in it, which provides better results in short amount of time, so first of all click on the file and load molecule then the file containing protein was opened then protein was selected and with help of autodock option it was converted to macromolecule which convert the protein form pdb to pdbqt format. Then in open babel all six ligands were inserted one by one with the help of insert new items, the formula, number of atoms, weight observed in the table. Then minimize the energy of all ligand, by doing this the format of all ligands changed from sdf to pdb and then all these were converted to pdbt format with the help of autodock ligand option. Now vina wizard in PyRx was open to start the docking by adding ligand and protein together and forwarded, after which a grid box appears around the protein and ligand complex, the size of the grid can be increased by covering the whole protein ligand complex if someone want to perform blind docking, then forwarded to start docking. Once the docking process ends, one can analyse the results using PyMOL, BIOVIA discovery studio etc. now after getting the docking score of ligands, it was saved in excel format. Then it was observed that the ligand Germacrone had the highest score, then the selected ligand was saved in a separate file and the conformation of the ligand was analysed.

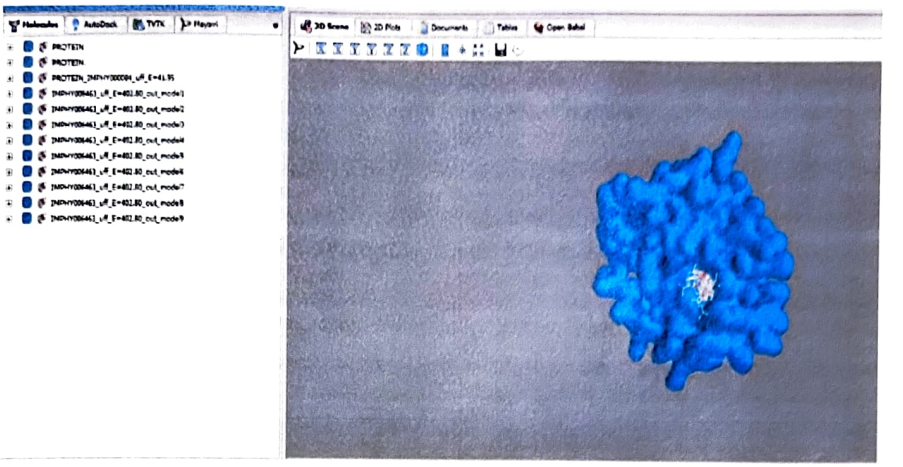

Fig 2. A molecular surface image of protein 7AEI and ligand Germacrone interaction in PyRx

The docked protein with compatible ligand was saved in pdb format and then it was further analysed using BIOVIA discovery studio and then the protein file was open and similarly the file of desired docked protein ligand opened, ligand was placed in the protein by clicking on view and hierarchy, the hierarchy of ligand was copied and pasted in the hierarchy of ligand, then analysis was done.

CHAPTER 4 RESULT

Protein 7AEI has been found to exhibit significant relations with various ligands, namely 2-Heptanol, Germacrone, Isobornyl acetate, Curcumin, Ar-dihydro-turmerone and . 3(1,5-Dimethyl-4-hexenyl)-6methylene-1cyclohexene, all these are found in These ligands interact with the protein with binding affinity -4, -6.8, -5, -6.7, -5.6, -5.4 K_D (equilibrium dissociation constant) respectively.

Binding affinity have an important role in protein-ligand binding and these are often characterized by the stability of nonpolar or hydrophobic groups in an aqueous environment. In the case of protein 7AEI, these interactions occur among specific regions of the protein receptors and the hydrophobic moieties of the ligands. The observed binding affinity provides a very good understanding about the binding property between protein 7AEI and the selected ligands. Understanding these interactions is a very important step for further elucidation of the structural and functional characteristic of the complex of protein and ligand. Further investigation and analysis of these relationships could contribute to the development of novel therapeutic interventions or the design of specific ligands that target the protein 7AEI.

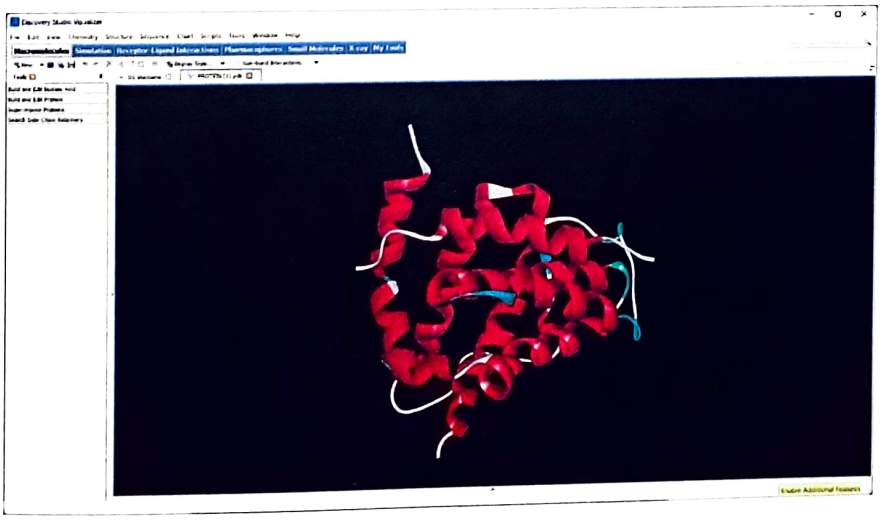

Fig 3. 3D Structure of desired protein (7aei which is an EGFR, one of the upregulated gene in NMSC) visualised in BIOVIA

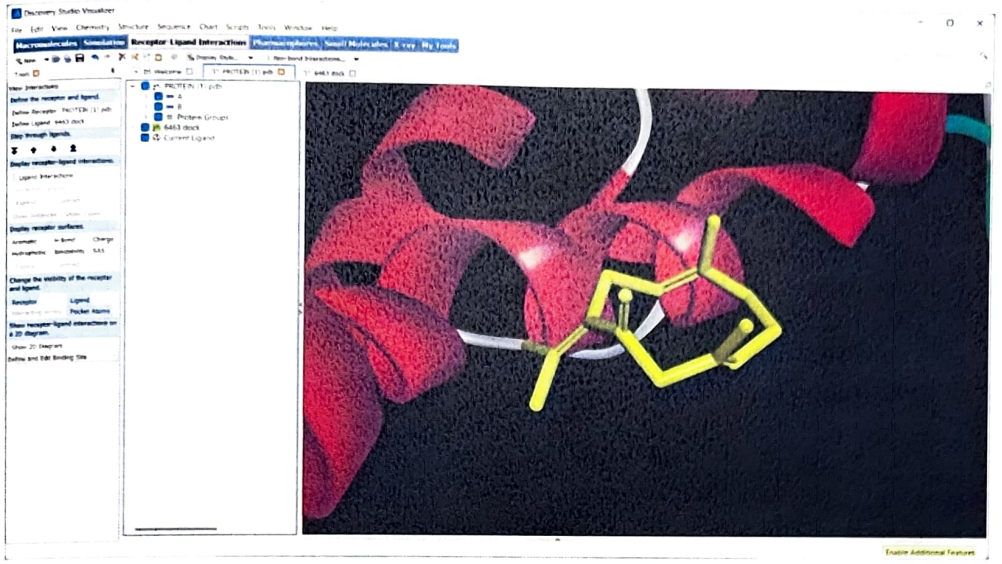

Fig 4. interaction of 7AEI protein with the ligand having highest binding affinity that is Germacrone

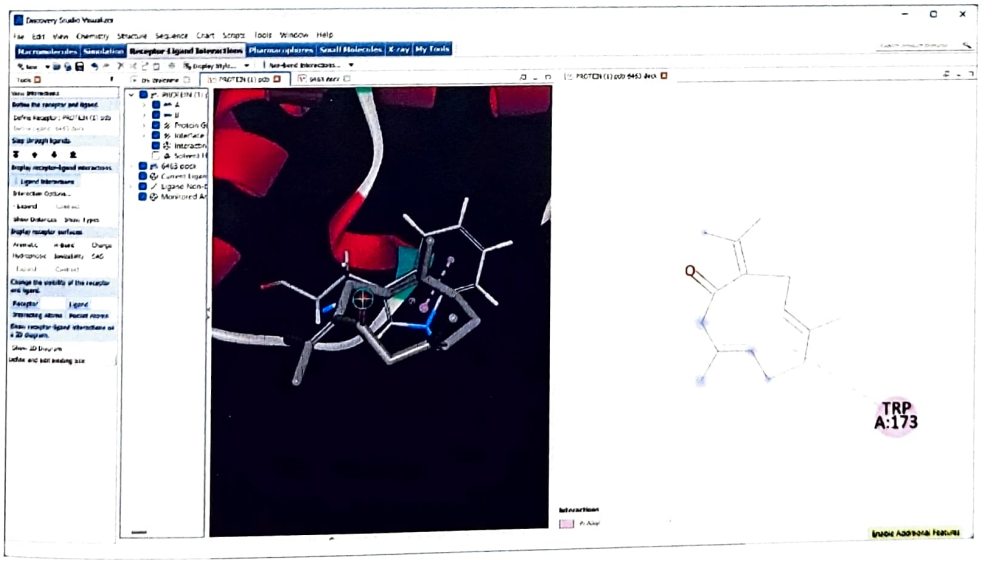

Fig 5. structure of the ligand Germacrone and the amino acid with the help of which it is bound to the protein

Molecule no.	Protein	Ligand	Binding Affinity (kcal/mol)
1	7aei	2-Heptanol	-4
2	7aei	Germacrone	-6.8
3	7aei	Isobornyl acetate	-5
4	7aei	Curcumin	-6.7
5	7aei	3(1,5-Dimethyl-4-hexenyl)6-methylene-1-cyclohexene	-5.6
6	7aei	Ar-dihydro-turmerone	-5.4

Table 2. binding affinity of ligands of curcumin

The ranking of binding affinity of various ligands obtained from the leaves, root, rhizomes, whole plant of the Indian medicinal plant Curcuma Longa, with one of the upregulated gene 7AEI in Non-Melanoma-Skin-Cancer, this result was obtained after performing, autodocking tool PyRx. With the help of this table, we can see that the protein 7AEI has the highest binding affinity with the ligand Germacrone, which has an affinity of -6.8 kcal/mol. The results of the docking made it easy to analyse the receptors of protein and ligands interactions, the red helical structure is the representation of protein 7AEI, which consist of two chains, chain A and chain B, the ligand is connected to the protein at site where receptor is present with the help of amino acid Tryptophan ($C_{11}H_{12}N_2O_2$).This representation gives a clear understanding of how the ligands interacted with protein at the site of receptor.

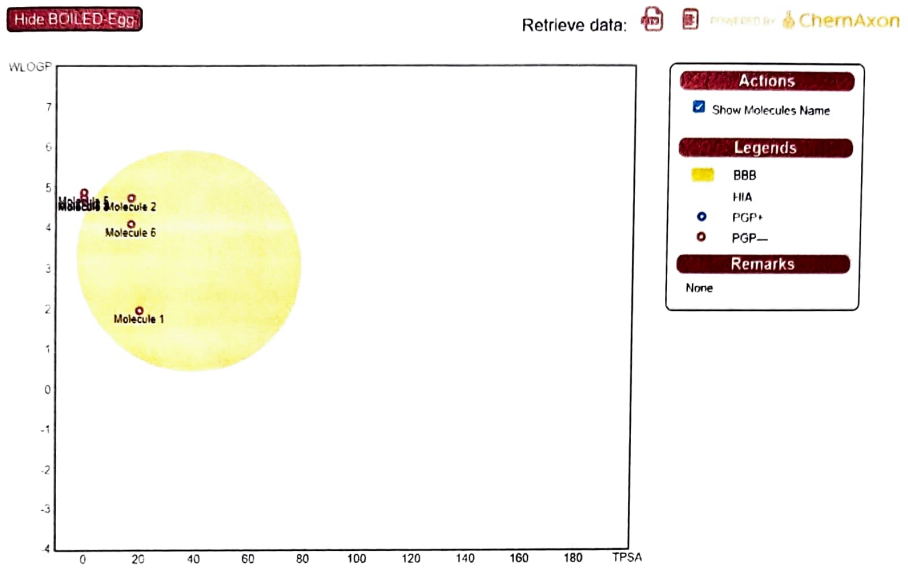

Fig 6. The blood brain barrier crossing analyzed with the help of Boiled egg, in SwissADME

It can be seen that the molecule 1, 2 and 6 will not cause any harm to the blood brain barrier or will also not cause any neural disease in future, these three molecules are safe to use, so the ligands 2-Heptanol, Germacrone and Ar-dihydro-turmerone are the most compatible as a drug for NMSC and the binding affinity of Germacrone is highest.

CHAPTER 6 CONCLUSION

The upregulated genes were taken selected with the help of GEO, and evaluated with the help of tables which was available on GEO on the basis of experiment performed from the patient's samples. This analysis was shown on the site of GEO as different types of chats and graphs. The main aim of this dissertation was to get a view on molecules like ligands and proteins interact with each other, and by performing molecular docking and it was found that the ligands are bound to the receptors of proteins with the help of specific amino acids. With the help these tools the binding affinity of each ligand with protein of interest was analysed which were -4 kcal/mol for 2-Heptanol, -6.8 kcal/mol for Germacrone, -5 kcal/mol for Isobornyl acetate, -6.7 kcal/mol for curcumin, -5.6 kcal/mol for 3-(1,5-Dimethyl-4-hexenyl)-6-methylene-1-cyclohexene and -5.7 kcal/mol for Ar-dihydro-turmerone. Based on these results Germacrone was found to be most compatible based on these results, and the three molecules that is Isobornyl acetate, curcumin, 3(1,5-Dimethyl-4-hexenyl)-6methylene-1-cyclohexene can cross the blood brain barrier. There are very few research for NMSC, so this paper may help in further research.

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A DISSERTATION

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE AWARD OF THE DEGREE

OF

MASTER OF SCIENCE

IN

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