

USE OF NETWORK PHARMACOLOGY AND MOLECULAR DOCKING TO EXPLORE FRUQUINTINIB BINDING AFFINITY ON CANCER TARGETS

Submitted in partial fulfilment of the requirements for the award of
Bachelor of Science in Bioinformatics and Data Science.

BY

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**INSTITUTE OF SCIENCE AND TECHNOLOGY
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APRIL - 2024



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BONAFIDE CERTIFICATE

This is to certify that this Project Report is the bonafide work of Niveditha P (41738009), who carried out the final year project entitled "USE OF NETWORK PHARMACOLOGY AND MOLECULAR DOCKING TO EXPLORE FRUQUINTINIB BINDING AFFINITY ON CANCER" Under our supervision from January 2023 to April 2024.

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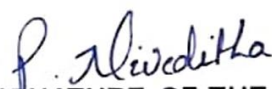
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DECLARATION

I, **NIVEDITHA.P**, hereby declare that the Project Report entitled **USE OF NETWORK PHARMACOLOGY AND MOLECULAR DOCKING TO EXPLORE FRUQUINTINIB BINDING AFFINITY ON CANCER** done by me under the guidance of **Dr. H. JEMMY CHRISTY** at Sathyabama Institute of Science and Technology, Jeppiaar Nagar, Rajiv Gandhi Road, Chennai-600119, Tamil Nadu, India, is submitted in partial fulfilment of the requirements for the award of **Bachelor of Science in Bioinformatics and Data Science**.

DATE: 27-04-2024

PLACE: CHENNAI


SIGNATURE OF THE CANDIDATE

ACKNOWLEDGEMENTS

I am delighted to express my heartfelt acknowledgement to the Board of Management of SATHYABAMA for their kind encouragement and support throughout the duration of my project. Their guidance has been invaluable in ensuring the successful completion of this project, and I am sincerely grateful for their contribution.

I convey my thanks to Dr. Rekha Chakravarthy, Dean, School of Science and Humanities for providing me necessary support and details at the right time during the progressive reviews.

I sincerely thank Dr. H. Jemmy Christy, Head of the Department, Dept. of Bioinformatics, for her unwavering support and timely provision of necessary details during the progressive reviews. Her support has been instrumental in helping me to overcome obstacles and achieve success in this project.

I am deeply indebted to my Project Guide, Dr. H. Jemmy Christy, for her invaluable guidance, suggestions, and constant encouragement throughout the project. Her expertise and insights have been instrumental in shaping my work and ensuring its successful completion.

I also wish to extend my gratitude to my family for their support and assistance in various ways, which have contributed to the successful completion of this project.

Niveditha.P



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CERTIFICATE

This is to certify that the dissertation entitled **"USE OF NETWORK PHARMACOLOGY AND MOLECULAR DOCKING TO EXPLORE FRUQUINTINIB BINDING AFFINITY ON CANCER"** Was carried out by **Ms. NIVEDITHA.P (Reg. No. 41738009)**, Department of Bioinformatics and Data Science, Sathyabama Institute of Science and Technology, Chennai in partial fulfilment of the requirements of the award of the **Degree of Bachelor of Science in Bioinformatics and Data Science** 2021- 2024, is a bonafide record of the project work done under my guidance and supervision. This thesis or part, therefore, has not been submitted elsewhere for any other degree or diploma.

Date: 27-04-2024

Place: CHENNAI

Dr. H. JEMMY CHRISTY

ABSTRACT

Fruquintinib, a potent inhibitor of vascular endothelial growth factor receptor (VEGFR), has emerged as a promising candidate in cancer treatment due to its ability to block tumor angiogenesis and inhibit tumor growth. In this study, we used a combination of network pharmacology and molecular docking techniques to explore the binding affinity of fruquintinib for cancer targets. Through pharmacological network analysis, we characterized the complex network of interactions between fruquintinib and cancer-related signalling pathways, revealing its potential as a multitarget therapy in the treatment of cancer. Cancer treatment. Molecular docking simulations further elucidated the precise binding modes and affinity of fruquintinib for key molecular targets involved in cancer progression and metastasis. Results highlight the selective binding properties of fruquintinib, disrupting key pathways involved in tumor growth and angiogenesis. This integrated approach provides valuable insights into the molecular mechanisms underlying the anticancer effects of fruquintinib and lays the foundation for future experimental validation and clinical interpretation. This comprehensive analysis highlights the molecular mechanisms underlying the anticancer effects of fruquintinib and demonstrates its therapeutic efficacy against different cancer types. Overall, our study highlights the potential of fruquintinib as a promising therapeutic agent for precision medicine approaches in oncology.

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LIST OF ABBREVIATIONS

VEGFR	Vascular Endothelial Growth Factor Receptor
NGS	Next Generation Sequencing
FDA	Food and Drug Administration
HPV	Human Papillomavirus
CRC	Colorectal Cancer
NSCLC	Non-Small Cell Lung Cancer
HUVEC	Human Umbilical Vein Endothelial Cells
HLEC	Human Lymphatic Endothelial Cells
KDR	Kinase Insert Domain Receptor
RET	Rearranged During Transfection
FGFR	Fibroblast Growth Factor Receptor
MDSC	Myeloid-Derived Suppressor Cells
MSS CRC	Microsatellite Stable Colorectal Cancer
MSI-H	Microsatellite Instability-High
DMMR	Deficient Mismatch Repair
PFS	Progression-Free Survival
PK	Pharmacokinetics
EGFR	Epidermal Growth Factor Receptor
RAS	Rat Sarcoma
ALP	Alkaline Phosphatase
FIB	Fibrinogen
TME	Tumour Microenvironment
ADME	Absorption, Distribution, Metabolism, and Excretion
CHEMBLID	Chemical Identifier in ChEMBL database

PPI	Protein-Protein Interaction
EPC	Endothelial Progenitor Cells
MNC	Mononuclear Cells
DMNC	Density Of Maximum Neighborhood Component
MCC	Maximal Clique Centrality
BN	Bayesian Network
PDB	Protein Data Bank
SRC	Proto-Oncogene Tyrosine-Protein Kinase Src

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CHAPTER 1

INTRODUCTION

Any organ in the body can develop cancer cells, and the origin of these cells varies based on the kind of tissue. Cancer is a complex disease marked by unchecked cell growth and proliferation (*Brown, J. S., Amend et al. 2020*). NGS and sophisticated computational data processing techniques are effective in preventing and treating cancer. The most prevalent malignancies are those of the breast, lungs, colon, rectum, and prostate

In spite of the fact that cancer is regularly alluded to as a single condition, it really comprises of more than 100 diverse maladies. These infections are characterized by uncontrolled development and spread of irregular cells. Cancer can emerge in numerous destinations and carry on in an unexpected way depending on its organ of beginning (*De Flora, S., & Bonanni, et al. 2011*). Breast cancer, for case, has distinctive characteristics than those of lung cancer. It is imperative to get it that cancer beginning in one body organ takes its characteristics with it indeed in the event that it spreads to another portion of the body. Cancer remains one of the foremost challenging infections all inclusive, with critical dreariness and mortality rates in spite of propels in treatment modalities. Conventional medicate revelation forms are regularly time-consuming and exorbitant, requiring broad test testing of potential compounds (*Feng, Y., Spezia, M. et al. 2018*)

The most principal characteristic of cells is their capacity to duplicate themselves. They do this essentially by isolating one cell gets to be two, the two end up four, and so on. The division of ordinary and solid cells happens in a controlled and efficient Mold. In most parts of the body, the cells persistently isolate and shape modern cells to supply the fabric for development or to supplant worn-out or injured cells. For case, after you cut your finger, certain cells isolate quickly until the tissue is recuperated and the skin is repaired. They will then return to their normal split ratio (*Duina, A. A., Miller, et al. 2014*).

In contrast, cancer cells divide randomly. As a result, they often accumulate into structureless masses or tumors. Fruquintinib, a potent inhibitor of the vascular

endothelial growth factor receptor (VEGFR), has shown promise in a variety of cancers. (Sun, Q, Zhou, J. et al. 2014)

This characteristic distinguishes cancer from generous developments, which stay within the portion of the body in which they begin. Even though benign tumors may develop very huge and press on neighboring structures, they don't spread to other parts of the body (Brown, J. S., Amend et al. 2023)

1.1 BACKGROUND

Cancers are named agreeing to the organ in which they start. Even if a cancer metastasizes to another portion of the body, it keeps its unique title. Cancer names such as breast cancer, brain cancer, lung cancer, and skin cancer are cases. In any case, cancer names may moreover be based on the sort of tissue influenced (Seyfried, T. N., & Huysentruyt, L. C. et al.2013). This segment will present you with a few essentials concerning the determination of tissues within the setting of embryology, which is the thinking about the advancement of a living being. Cancer, a multifactorial infection characterized by uncontrolled cell development and multiplication, poses a critical challenge to worldwide well-being. Conventional chemotherapy and focused treatments have made strides in cancer treatment; be that as it may, the development of medicate resistance and unfavourable side impacts requires the investigation of elective restorative procedures. (Cooper, G. M. et al.2013)

Computational reenactment strategy, empowers the expectation of ligand-receptor intuition at the atomic level, encouraging the distinguishing proof of potential medicate candidates (Rodríguez, D., & Gutiérrez-de-Terán, H. et al .2013).

Fruquintinib, a strong and profoundly specific inhibitor of vascular endothelial development calculate receptor (VEGFR), has appeared promising viability in different malignancies, especially colorectal cancer (Zhang, Y et al.2019).

1.2 RISK FACTORS

The explore of a cause of cancer that has been going on for centuries. Early analysts said that cancer was a normal result of maturing. As cells deteriorated, it was accepted that a few got to be threatening. Others said the cancer was innate, and examinations

into hereditary qualities started. At that point, a few started to consider chemical joins whereas still others addressed whether infections or microscopic organisms were at blame (*Blackadar C. B. et al.2016*)

for causes of cancer proposed by cancer analysts, which are accepted to be "cancer chance components." These chance variables incorporate eating propensities, way of life, living or working situations, hereditary qualities, and numerous others. a few major cancer chance variables recognized by analysts with the back of logical

(Smoking, Slim down, Hereditary qualities, Occupation and Environment, Irresistible Operators) (*Wang, Chen, P.et al. 2022*)

More than a third of all cancer deaths each year are directly due to cigarette smoking alone. The most common cause of lung cancer and the main factor in lung cancer deaths for both men and women are cigarette smoking. Additionally, most malignancies of the throat, mouth, and esophagus are caused by smoking (*Saha, S. P et al.2007*). Furthermore, it has a strong correlation with the onset and demise of bladder, kidney, pancreatic, and cervical malignancies. Thousands of chemical agents, or carcinogens are found in tobacco smoke, among these are sixty compounds that are known to cause cancer. Cigarette smoking has health concerns for non-smokers as well. The risk of lung cancer in nonsmokers is greatly increased by ambient tobacco smoke exposure (*Hecht, S. S., & Hatsukami, D. K.et al. 2022*).

Nutrition Diet is the aspect of lifestyle that has drawn the most attention lately. Research indicates that dietary factors may account for approximately one-third of cancer-related fatalities annually. These consist of food kinds, cooking techniques, serving sizes, diversity, and overall calorie balance. An elevated risk of prostate, endometrial, colon, and rectal cancer has been linked to a high-fat diet (*Donaldson M. S.et al.2004*). A high-fat diet is thought to encourage cancer, and there are a lot of theories explaining why being overweight can be harmful. For example, excess fat appears to contribute to the generation of free radicals, which are implicated in various forms of cancer. Additionally, a high-fat diet stimulates the intestinal flow of bile acids. (*Bojková, B et al.2020*).

Cancer is essentially a genetic illness. Nearly every aspect of our body is determined by the tiny molecules called genes found in our cells. Within the cell nucleus, genes

that regulate each cell's genetics and heredity are arranged along the DNA like beads on a necklace. Several of the genes controlling these pathways are aberrant (mutated) in benign or malignant tumors. Mutations in cell division, carcinogens, viruses, and other as-yet-unknown sources can all cause or inherit abnormal genes. In certain families, several prevalent diseases, such as colon, breast, ovarian, and uterine cancer, reoccur generation after generation (*Uhomoibhi, T. O et al. 2022*)

Sunlight is an environmental component that is essential to human survival. Researchers have discovered that exposure to UV radiation alters genes, which can lead to cancer. We now know that exposure to ultraviolet radiation increases the risk of cancer in individuals with light skin and that cancers can manifest years after sun damage. Annually, the number of new cases of skin cancer (squamous and basal cell carcinoma) surpasses the total incidence of all other cancer types put together. The epidermis, nasal passageways, and lungs are frequently the bodily parts exposed to carcinogens. The urine bladder is the main internal body surface that comes into touch with carcinogens (*D'Orazio, Scott, T. et al. 2013*).

It has been demonstrated that the human papillomavirus, which causes genital warts, is a major cause of cervical cancer. A close relative of the virus that causes acquired immunodeficiency syndrome (AIDS), the human T-cell leukemia virus is linked to some types of non-Hodgkin lymphomas and cancer known as Kaposi sarcoma. There are other risk factors for cancer besides those on the above list. Other risk factors include using alcohol, using specific drugs, using hormones, and engaging in sexual and reproductive activities. More cancer risk factors will be found in the future with more scientific research (*Angeletti P., Wood, C. et al. 2008*).

The common body surfaces that are exposed to carcinogens are the skin, nasal sections, and lungs. The essential inside body surface that has contact with carcinogens is the urinary bladder. cancer is caused by both outside (*Letašiová, S et al. 2012*)

(chemical, radiation, and infections) and inside (hormones, safe conditions, and acquired changes) components. Causal components may act together, or in arrangement, to start or advance carcinogenesis (*Anand, P., Kunnumakkara et al. 2008*)

1.3 TYPES BY SITE

the common open is more recognizable with cancer names based on their essential sites. The most common locales in which cancer incorporate

(Skin, Lungs, Female Breasts, Prostate, Colon and Rectum, Cervix and Uterus)

cancers named after the essential location may not be as exact. Take lung cancer in case the title does not indicate the sort of tissue included. It essentially shows where the cancer is found. Depending on how the cells see beneath a magnifying instrument, there are two major sorts of lung cancer non-small cell lung cancer and little cell lung cancer (*Selves, J., Long-Mira et al 2018*).

There are three essential sorts of skin cancer basal cell, squamous cell, and melanoma. These cancers are inferred from the epidermal layers with the same names. Melanomas are determined from the melanocytes, or shade cells, within the most profound level of the epidermis (*Hasan, N., Nadaf et al 2023*).

Basal cell and squamous cell cancers ordinarily happen on parts of the body uncovered to the sun, such as the confront, ears, and limits. These cancers are profoundly treatable, particularly on the off chance that recognized and treated early. Melanomas, which frame dim moles that spread over the surface of the skin, are more deadly since they metastasize exceptionally rapidly (*Campos, M. T., Silva et al. 2024*).

Lung cancer is exceptionally troublesome to identify at an early arrange since the side effects often do not show up until the infection has progressed. The indications incorporate determined hack, sputum streaked with blood, chest torment, and rehashed assaults of pneumonia or bronchitis.

Around 1 in 8 ladies will inevitably create breast cancer in their lifetime. Most breast cancers are ductal carcinomas. Ladies most likely to create the illness are those over the age of 50 those who have as of now had cancer in one breast; and those whose mother or sister had breast cancer (*Feng, Y., Spezia i et al. 2018*).

Cancer of the prostate is found primarily in more seasoned men. As men age, the prostate may broaden and piece the urethra or bladder. Frequently there are no side effects of early cancer of the prostate.

Of the cancers that influence the large digestive system, almost 70 percent happen within the colon and about 30 percent within the rectum. These cancers are the third most common cancers by and large. Side effects incorporate blood within the stool, which can be tried for by a basic faecal mysterious blood test, or an alteration in bowel propensities, such as extreme obstruction or loose bowels (*Sun, Y. S., Zhao et al 2017*).

Cancer of the uterus is the foremost common gynecologic danger. This cancer happens occasionally in ladies under 40 a long time of age. It happens most frequently after the age of 60. The showing side effect is as a rule anomalous uterine dying. numerous other cases such as brain cancer, testicular cancer, bladder cancer, and so on.

1.4TREATMENTS

varieties of these organizing strategies exist. For case, a few cancer registries utilize observation, the study of disease transmission, and comes about programs named rundown arranging. bunches cancer cases into five fundamental categories:

In situ: Irregular cells are shown as they were within the layer of cells in which they were created.

Localized: Cancer is constrained to the organ in which it started, without proof of spread.

Territorial: Cancer has spread past the essential location to adjacent lymph hubs or organs and tissues.

Removed: Cancer has spread from the essential location to removed organs or far-off lymph nodes (*White, M. C., Babcock et al 2017*).

Obscure: There are not sufficient data to decide the arrangement. Organizing cancer is critical; it helps the doctor to choose the most compelling and helpful conventions, gives a premise for evaluating the forecast for understanding, and gives a framework to communicate the patient's condition. Although patients may get a one-of-a-kind sequenced treatment, or convention, for their cancer, most medications have one or more of the taking after components: surgery, chemotherapy, radiation treatment, or combination medicines (a combination of two or all three medications). People get a variety of these medications for cancer. Patients with cancers that cannot be cured

(totally expelled) by surgery ordinarily will get combination treatment, the composition decided by the cancer sort and organize (*Tamirisa, N. P., Goodwin et al 2017*).

Palliative treatment (therapeutic care or treatment utilized to decrease disease symptoms but incapable of remedying the understanding) utilizes the same medicines portrayed over. It is done to amplify and make strides in the quality of life of the terminally sick with cancer understanding. numerous cancers can either be avoided or the hazard of creating cancers can be uniquely decreased. A few of the cancer anticipation strategies are straightforward; others are generally extraordinary, depending on an individual's (*Khosla, D., Patel et al. 2012*)

There are two antibodies right now affirmed by the U.S. Nourishment and Medicate Organization (FDA) to avoid particular sorts of cancer. Vaccines against the hepatitis B infection, which is considered a cause of a few liver cancers, and antibodies against human papillomavirus (HPV) sorts 16 and 18 are accessible (*Enokida, T., Moreira et al 2021*).

CHAPTER - 2

LITERATURE SURVEY

Network pharmacology and molecular docking have ended up as effective instruments in sedate revelation and improvement, especially in investigating the intuition between little particles and their target proteins.

When it comes to examining the official partiality of Fruquintinib on cancer targets utilizing these procedures, a few consider having contributed profitable bits of knowledge.

- Matt Shirley et al. (2018) Fruquintinib is an orally accessible, powerful, and profoundly specific little particle inhibitor of VEGFR-1, -2, and -3 that was found and created by Hutchison Medi Pharma for the treatment of strong tumors.

In September 2018, fruquintinib got its to begin with worldwide endorsement, in China, for utilization within the treatment of metastatic colorectal cancer (CRC) in patients who have fizzled at least two earlier systemic anti-neoplastic treatments.

Fruquintinib is in progressing stage III clinical development for utilization within the treatment of progressed NSCLC and advanced gastric cancer. This article summarizes the breakthroughs within the advancement of fruquintinib driving this, to begin with, an endorsement for the treatment of metastatic CRC.

- Junning Cao et al. (2018) investigated fruquintinib as a novel verbal little particle compound that specifically represses vascular endothelial development figure receptors 1, -2, and -3 with strong inhibitory impacts on different human tumor xenografts.

This first-in-human consideration was conducted to survey the greatest endured dosage and dose-limiting toxicities, security and tolerability, pharmacokinetics, and preparatory anti-tumor action of fruquintinib. Forty patients were selected into 5 cohorts in a ceaseless regimen and 2 cohorts within the 3-week-on/1-week-off regimen. The foremost common review 3/4

antagonistic occasions were hand-foot skin response, hypertension, and thrombocytopenia.

PK examination appeared great and fast retention was taken after moderate terminal disposal with a cruel half-life of roughly 42 h which was steady over all dosage bunches. Thirty-four patients were evaluable for tumor reaction, counting 14 with halfway reaction and 14 with steady malady.

Fruquintinib appeared a worthy security profile and preparatory proof of anti-tumor movement in patients with progressed strong tumors.

- Huaqing Cai et al. (2023) investigated Fruquintinib speaks to an unused era of little atom VEGFR inhibitors with solid power and tall kinome selectivity focusing on VEGFR1, 2, 3.

In in vitro enzymatic and cellular tests, it repressed VEGFR family kinases and smothered VEGF/VEGFR cell signalling in human umbilical vein endothelial cell (HUVEC) and human lymphatic endothelial cell (HLEC) with IC₅₀ at moo nanomolar level.

Fruquintinib was found to hinder VEGFR2 (KDR) with an IC₅₀ of 25 nmol/L within the Z-lyte measure.

The kinase selectivity of fruquintinib was assessed against a board of 253 kinases utilizing the [p-ATP] joining test by Upstate Biotechnology Inc.

The comes about appeared that fruquintinib repressed the VEGFR family part (VEGFR1, 2, 3) with IC₅₀s of 33 nmol/L, 35 nmol/L, and 0.5 nmol/L, individually with powerless hindrance of RET, FGFR-1, and c-kit kinases.

No critical restraint was found against all other kinases The selectivity of fruquintinib against FGFR-1 was advanced evaluated in a cellular test. Compared with the hindrance of KDR phosphorylation IC₅₀ of 0.6 nmol/L, the cellular action against FGFR phosphorylation was much weaker and over 1000-fold, affirming that fruquintinib is profoundly specific for VEGFR1, 2, 3 tyrosine kinase.

- Qingli Li et al. Fruquintinib Upgrades the Antitumor Safe Reactions of Anti-Programmed Passing Receptor-1 in Colorectal Cancer- Qingli Flexible combination of fruquintinib and sintilimab shown the most grounded hindrance of tumor development and accomplished the longest survival time in mice

bearing MC38 or CT26 xenograft tumors, compared to fruquintinib and sintilimab alone.

Robotically, the combination of fruquintinib and sintilimab diminished angiogenesis reprogramed the vascular structure, improved the invasion of CD8+T cells

T cells and decreased the proportions of MDSCs and macrophages in mice. There was no self-evident harmfulness observed within the primary organs of the tumor-bearing mice with the combined treatment.

Besides, the treatment utilizing the combination of fruquintinib and sintilimab accomplished a viable reaction in five patients with hard-headed progressed MSS CRC.

the combination of fruquintinib and sintilimab enormously hinders CRC development by modifying the tumor's resistant microenvironment. This consideration gives the method of reasoning for utilizing the combination of fruquintinib and anti-PD-1 counteracting agent for the treatment of progressed CRC.

Colorectal cancer is the moment the most common cause of cancer-related passing around the world, the most recent investigations come about have appeared that the utilization of pembrolizumab as the first-line treatment for metastatic colorectal cancer (mCRC) with tall microsatellite flimsiness (MSI-H) or lack jumble repair (dMMR) quality few treatment-related antagonistic occasions.

Fruquintinib (HMPL-013) may be a little particle inhibitor with solid strength and tall selectivity against VEGFR1, 2, and 3 and was endorsed for third-line treatment in metastatic colon cancer in China.

Fruquintinib is as of now being enlisted in a clinical ponder for third-line treatment in metastatic colon cancer

It has great security and effectiveness in clinical patients. Be that as it may, it isn't known whether combining fruquintinib and anti-PD-1 treatment could enhance its adequacy in CRC. The impact of the combination of fruquintinib and anti-PD-1 in MSS colon cancer has not been inspected and the nitty gritty instrument of activity has not been explained. The REGONIVO think about found that nivolumab additionally regorafenib had an ORR of 36% and a middle

PFS of 7.9 months in 25 patients with metastatic colorectal cancer who advanced after standard treatments.

- Yi Gu et al. (2023) Preclinical pharmacokinetics and mien of novel inhibitor fruquintinib and the expectation of its human pharmacokinetics It has tall penetrability without efflux. No critical nourishment impact is on pooch PK. HMPL-013 has tolerably tall tissue dispersion. It is majorly disseminated within the gastrointestinal tract, liver, kidney, adrenal, and fat.

The plasma protein official division is 88–95 % in mice, rats, mutts, and people, perpetual up to 10 μ M. The in vivo clearance of HMPL-013 is low, and steady with the in vitro scaling.

Three major oxidative metabolites were distinguished in liver microsomes of mice, rats, pooches, monkeys, and people. Pooches are for the most part comparable to people concerning the in vitro digestion system. Demethylation, hydroxylation, and successive glucuronidation are the major in vivo metabolic responses.

Coordinate urinary and biliary excretion of HMPL-013 is irrelevant. Metabolizing to M1 (demethylation), consecutively glucuronidation, taken after by biliary excretion.

illustrates great preclinical PK and empowers effective human PK and measurement projection. It is important for advance clinical advancement.

- Rui-Hua Xu et al. (2017) investigated on Security and viability of fruquintinib in patients with already treated metastatic colorectal cancer stage Ib ponder, 42 patients took fruquintinib 5 mg for 3 weeks on/1 week off. The middle PFS was 5.80 months, and the middle general survival was 8.88 months. Within stage II think about, 71 patients were randomized (47 to fruquintinib, 24 to fake treatment). was essentially moved forward with fruquintinib also Fruquintinib showed a significant PFS good thing at about 3.7 months in patients with treatment-refractory mCRC. The security profile was steady with that of VEGFR tyrosine kinase inhibitors.

- Zhongguang Chen et al. (2019) investigated the clinical application of fruquintinib on colorectal cancer Anti-angiogenetic specialists are right now the

foremost commonly utilized drugs for the treatment of colorectal cancer (CRC) patients, counting different inhibitors focusing on the epidermal development figure receptor (EGFR), vascular endothelial development calculates (VEGF), and VEGF receptors (VEGFRs). Fruquintinib (HMPL-013), a profoundly specific and long-term small-molecule inhibitor of VEGFR (VEGFR1, 2, and 3) was as of late affirmed in China for CRC treatment. the atomic structure, instrument of activity, pharmacokinetics, clinical adequacy, and security of fruquintinib are presented in detail. The potential clinical application for non-small cell lung cancer (NSCLC) and gastric cancer is additionally examined. Fruquintinib was endorsed for patients with metastatic colorectal cancer (RAS wild sort) who have already gotten fluorouracil, oxaliplatin, and irinotecan-based chemotherapy and who have gotten or are not reasonable for anti-VEGF treatment and anti-EGFR therapy. a helpful approach to CRC, Fruquintinib may well be utilized as a third-line medication for the treatment of CRC patients. Due to medication resistance amid long-term treatment, the combination of fruquintinib with other focused treatment drugs may be a viable choice for CRC treatment.

- Kanchi Patel et al. (2024) investigated on poisonous quality and administration of fruquintinib and gives an outline of the pre-clinical information, pharmacokinetics, clinical adequacy, and security profile of fruquintinib, as well as the administration of clinical toxicities related to fruquintinib. Fruquintinib could be an important extra treatment choice for patients with hard-headed mCRC. The significant part of watchful poisonous quality administration cannot be downplayed. Whereas fruquintinib offers a helpful and in general, well-tolerated treatment choice, continuous research is basic to decide its viability in numerous quiet subsets, assess it in combination with chemotherapy and immunotherapy, and decide its part in prior lines of treatment.

- Weijie Zhang et al. (2022) investigated on Adequacy, security and indicators of fruquintinib Inquire about discoveries have uncovered that combining anti-angiogenesis inhibitors with modified inhibitors can switch the immunosuppressive tumor microenvironment and upgrade the antitumor-resistant reaction. To investigate the restorative alternatives for breaking

resistant resilience in microsatellite solidness Fruquintinib combined with PD-1 inhibitors has antitumor action and sensible security in treating patients with progressed CRC. Liver metastases, High Mountain level, and Lie level may be a forecast of the patient's reaction to this treatment. Concurring to developing proof, anti-angiogenic treatment combined with immunotherapy fortifies vascular normalization and safe reconstructing, switching the immunosuppressive tumor microenvironment and actuating a long-lasting antitumor-safe reaction within the body. By hindering VEGFR, fruquintinib normalizes tumor blood vessels, progresses the TME's hypoxic environment, and invigorates T-cell invasion, all of which offer assistance invert the immunosuppressive microenvironment. Fruquintinib has appeared critical selectivity for tumor cells and great antitumor action in both preclinical and clinical considerations This consideration had a few restrictions. To begin with, being a review think about, it was inclined to predispositions due to constrained information collection and inadequate information, coming about one-sided comes about. Moment, the OS seems not to be decided due to the brief follow-up term and insufficient information collected. penetration of cytotoxic T-cells in tumors has appeared to foresee immunotherapy reactions differently consider.

CHAPTER 3

AIM AND SCOPE OF THE STUDY

3.1 AIM

- The objective of this project is to recognize the medicate repurposing and understand the intuitive and official partiality towards the cancer targets, to utilize arranged pharmacology and atomic docking methods to explore the official fondness of Fruquintinib on cancer targets.
- By utilizing atomic docking simulations, we look for to explain the exact official modes and affinities of Fruquintinib with key atomic targets involved in cancer movement and metastasis.

3.2 SCOPE

This study, comprehensively investigates the official partiality of Fruquintinib on a differing cluster of cancer-related targets utilizing arranged pharmacology and molecular docking approaches.

At first, build an arrangement of Fruquintinib-associated proteins and their interactions inside cancer flagging pathways utilizing bioinformatics devices. Along these lines, atomic docking recreations will be conducted to foresee the official modes and affinities of Fruquintinib with these targets.

The understanding of Fruquintinib's mode of activity against cancer. Through this investigation, we point to contribute to the headway of accuracy medication by encouraging the rational plan and optimization of Fruquintinib-based restorative procedures for cancer treatment.

CHAPTER – 4

METHODOLOGY

4.1 Chemical Candidates

The chemical candidates were at that point screened utilizing the Swiss ADME database (<http://www.swissadme.ch/>) based on two key ADME GI absorption and drug-likeness.

The GI absorption record demonstrates the capacity of the medication to be processed and ingested within the stomach and digestion tracts after verbal organization.

The medicate resemblance file surveys the probability of a particle getting to be a verbal medicate concerning bioavailability.

Hence, as it were compounds with tall “Gi absorption” and positive “drug-likeness” were considered candidates The sedate resemblance record evaluates the probability of an atom getting to be a verbal sedate about bioavailability. compound with tall “Gi absorption” and great “drug-likeness” were considered. They were high (*Daina, A., Michielin.et al. 2017*)

4.2 RELATED TARGETS

the dynamic candidate compounds were inputted into PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) (gotten to on 6th December 2022) to gather the chemical structures utilizing the Simplified Molecular Input Line Entry System.

SwissTargetPrediction is a web instrument, on-line since 2014, that points to anticipate the foremost likely protein targets of little atoms. Forecasts are based on the similarity principle, through switch screening (*Zoete, V et al 2017*).

The major data displayed in this result page comprises within the organized list of plausible protein targets as anticipated by the double score ligand-based invert screening of the inquiry particle towards the collect0ion of known actives.

The targets comprising in protein complex are given in full title (connected to a special ChEMBL ID), whereas their subunits/components are connected exclusively to Quality card and Uniport (Bento, A. P., Gaulton et al.2014)

The anticipated targets for the compound fruquintinib 100 targets got recorded. With the gene l'd and common names and target course and likelihood.

4.3 Construction and analysis of the protein–protein interaction (PPI) network

Cytoscape adaptation 3.10.2 (<https://cytoscape.org/>), an open-source program, was utilized for visualizing the systems and coordinating systems to discover their atomic intuitive and related natural pathways.

Numerous interaction databases are as of now actualizing PSICQUIC. You'll be able to check the Registry to see the foremost up-to-date list of suppliers and their status PSICQUIC by utilizing this plugin the interaction organized was seen by the Cytoscape.

An organization was built by that plugin with the inquiry of the focused-on qualities within the table down in that each detail almost those edges and hubs which id's, and quality names were recorded. This plugin was utilized for module clustering of the PPI arrangement (*del-Toro, N., Dumousseau et al 2012*).

4.4 IDENTIFICATION OF HUB GENES

Cytohubba is an open-source program, was utilized to discover the center qualities

Investigate vital nodes/hubs and delicate themes in an interactome arrange by a few topological calculations counting Degree, Edge Permeated Component (EPC), Greatest Neighborhood Component (MNC), Density of Greatest Neighborhood Component (DMNC), Maximal Clique Centrality (MCC) and centralities based on most brief ways, such as Bottleneck (BN), Eccentricity, Closeness, Radiality, Betweenness, and Stress.

CytoHubba gives a user-friendly interface to investigate critical hubs in natural systems. It computes all eleven strategies in a one-stop shopping way. Other than that, analysts can combine CytoHubba with other plugins into a novel examination plot.

These strategies add up to beat ten positioned qualities and after that, the topological strategies get the center qualities.

4.5 Verification with molecular docking

To analyze the interaction and liking of the fruquintinib compound, a molecular docking approach was utilized. After finding the positioned qualities and after that sifting the center qualities by the common, 10 qualities were obtained.

The 3D structures of the center target were downloaded from the PDB database (<http://www.rcsb.org/>) (gotten to on 11th December 2022), and we have chosen the protein 3D structure with tall quality based on the taking after criteria:

The source life form is “Homo sapiens”, and the total protein structure arrangement with data of little atom ligands.

Utilizing BIOVIA Discovery Studio Visualizer is a comprehensive program suite for analysing and modeling atomic structures, groupings, and other information of significance to life science analysts. This docking handle was done and the structures came about (*Martiz, R. M., Patil et al.2022*)

CHAPTER – 5

RESULTS AND DISCUSSION

5.1 CHEMICAL CANDIDATES OF FRUQUINTINIB

The chemical candidates were at that point screened utilizing the Swiss ADME database (<http://www.swissadme.ch/>) based on two key ADME

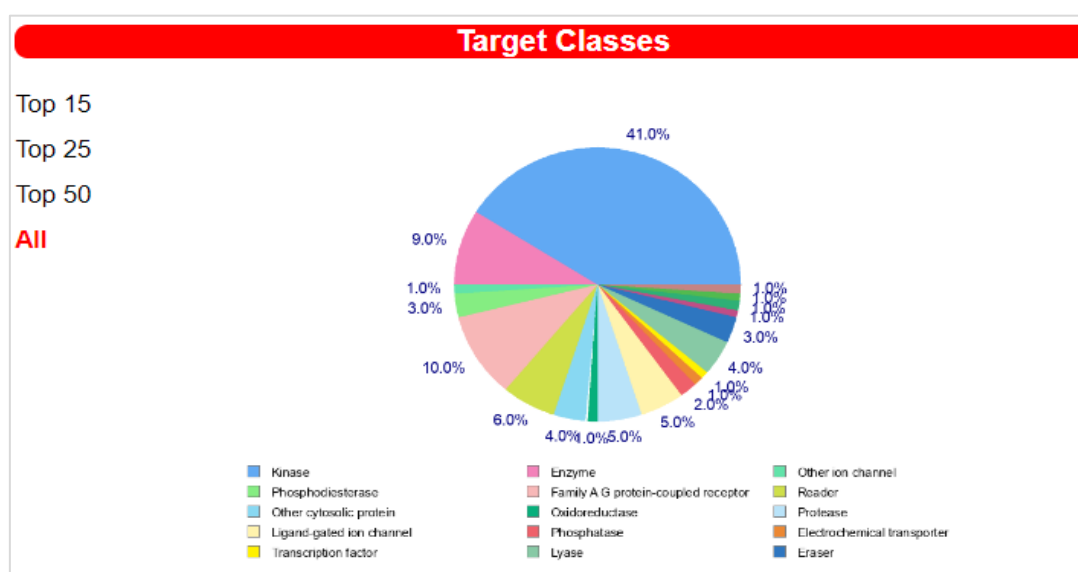
GI absorption and drug-likeness. The GI absorption list demonstrates the capacity of the drug to be processed and retained within the stomach and digestion tracts after verbal organization.

The medicate resemblance file surveys the probability of an atom getting to be a verbal medicate about bioavailability. Subsequently, compounds with high “GI absorption” and great “drug-likeness” were considered. They were high

5.2 RELATED TARGETS OF FRUQUINTINIB

Related targets with a likelihood more prominent than anticipated utilizing the Swiss Target Forecast database (<http://www.swisstargetprediction.ch/>)

The targets comprising of a protein complex are given in full title (connected to an interesting ChEMBL ID), whereas their subunits/components are connected separately to Quality card and Uniport. The anticipated targets for the compound fruquintinib 100 targets were recorded. With the



gene ID and common names target lesson and probabilit.

FIG 5.1. The Target Classes of The Compound Fruquintinib

5.3 PPI NETWORK

Cytoscape adaptation 3.10.2 (<https://cytoscape.org/>), an open-source computer program, was utilized for visualizing the systems and coordinating systems to discover their molecular intuitive and related organic pathways.

By using the PSICQUIC plugin the network was constructed and visualized.

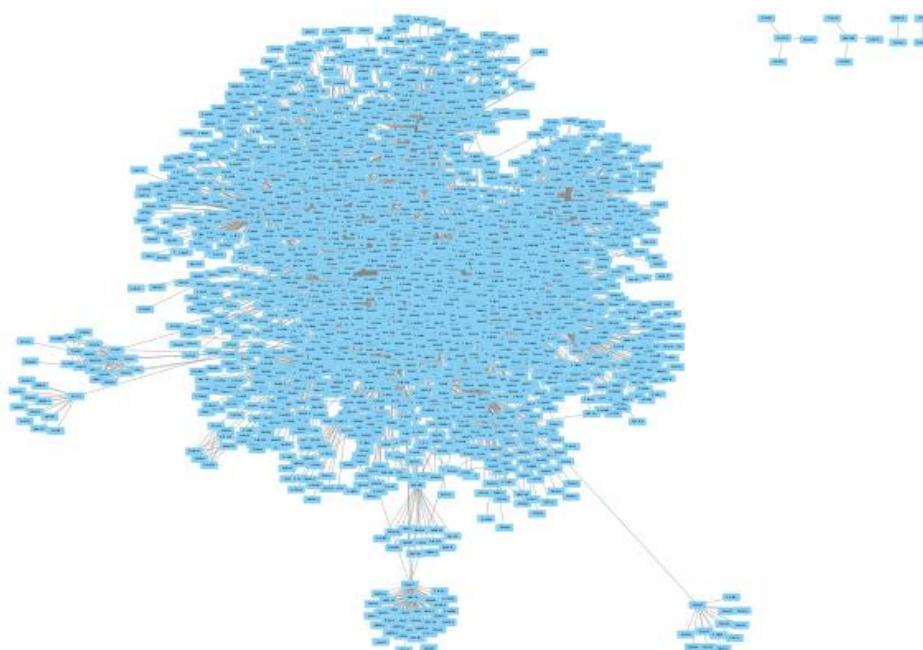
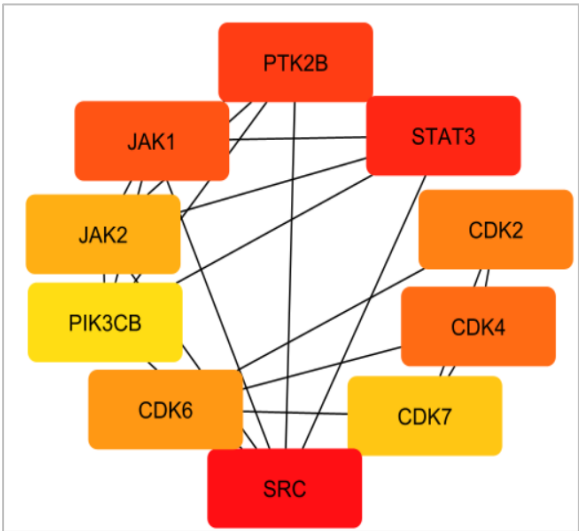


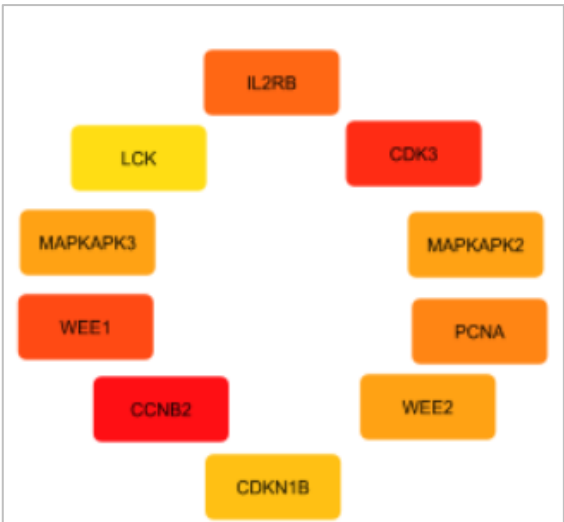
FIG 5.2. Visualization of PPI network using Cytoscape. The nodes represent the proteins and the edges represent the protein interactions

5.4 CytoHubba Network - Identification of Hub Genes

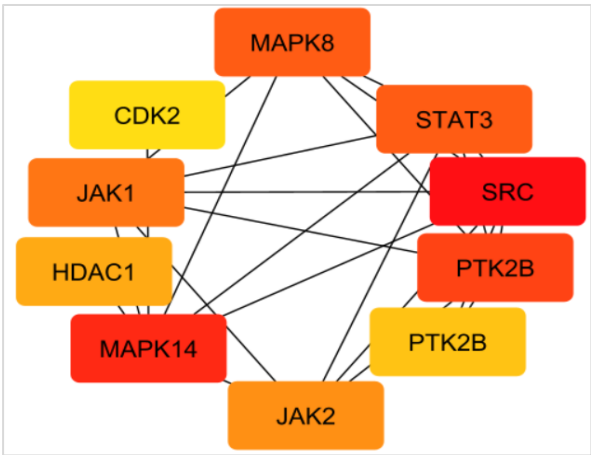
Genes having more interactions with other genes are defined as hub genes These are the results of 12 topological methods.



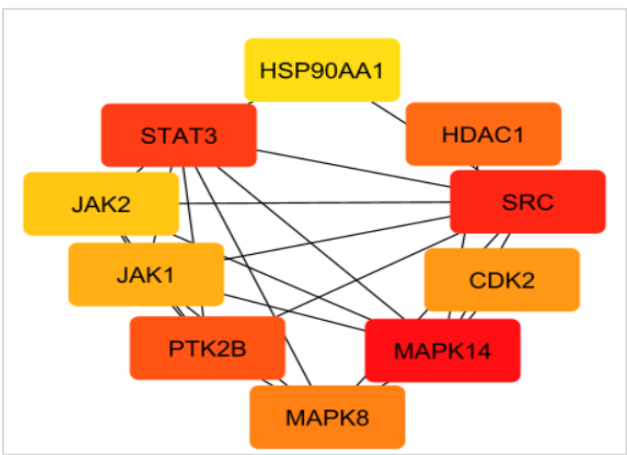
MCC



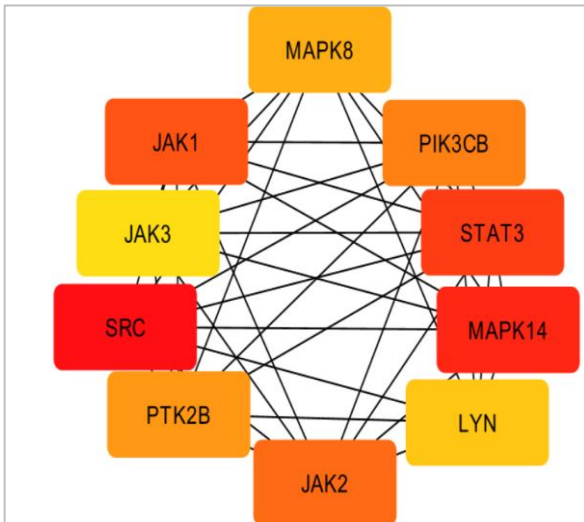
DMNC



MNC

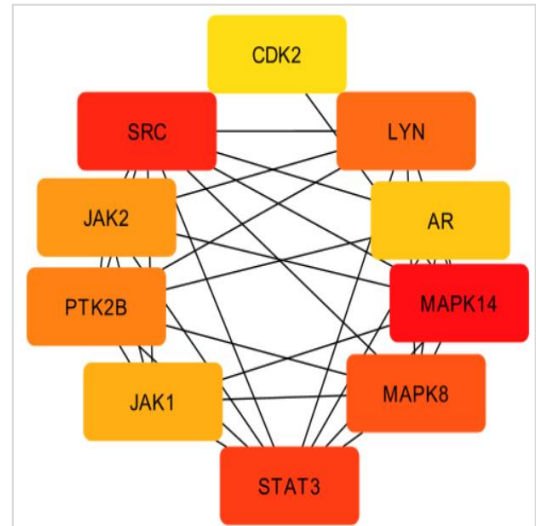


DEGREE

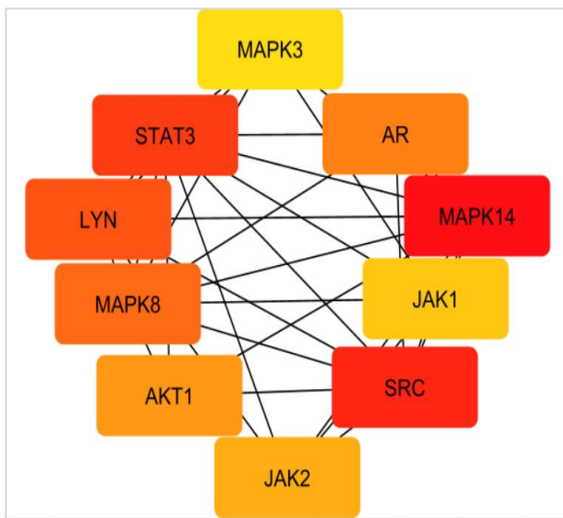


EPC

CLOSENESS

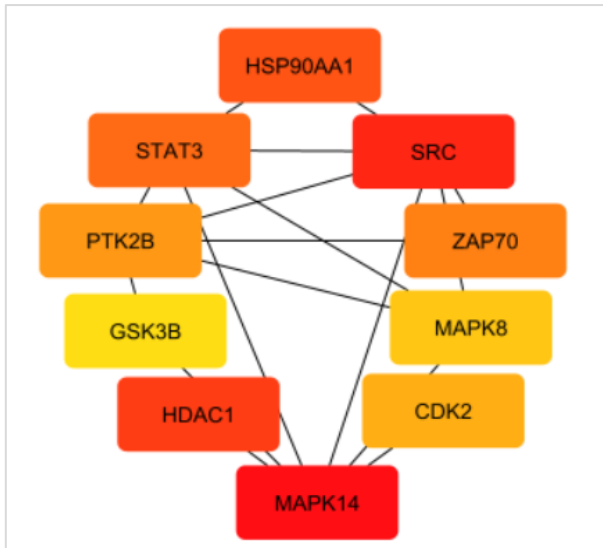


RADIALITY

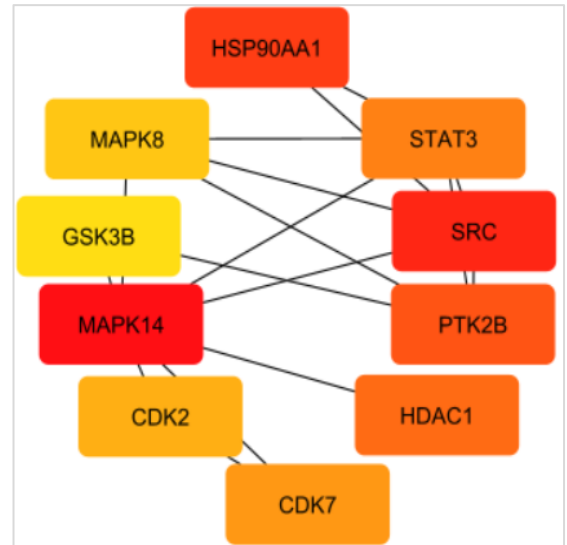


BOTTLENECK





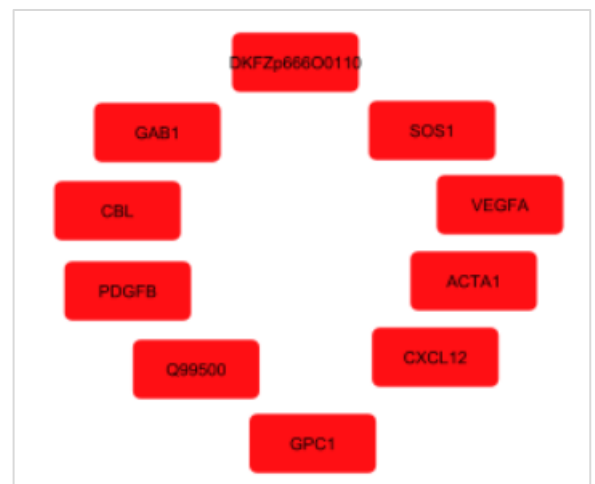
STRESS



BETWEENNESS



CLUSTERING CO-EFFICIENT



ECCENTRICITY

FIGURE 5.3. The common hub genes network generated using CytoHubba, where the color gradient from red to yellow represents the connection degree ranking from 1 to 10.

TABLE 5.1. Graph Theory Method Results

GENES	MCC	DMNC	MNC	EPC	DEGREE	BOTTLE NECK	ECCENTRICITY	CLOSENESS RADIALLY	BETWEEN NESS	STRESS	RADIALLY	CLUSTERING COEFFICIENT
SRC	✓	✓			✓	✓		✓	✓	✓	✓	
PTK2B	✓	✓		✓	✓	✓		✓	✓	✓		
JAK1	✓	✓		✓	✓			✓	✓		✓	
JAK2	✓			✓	✓			✓	✓		✓	
CDK2	✓	✓		✓				✓				
STAT3	✓	✓		✓	✓	✓		✓	✓		✓	
HDAC1	✓					✓						
LYN					✓	✓		✓	✓		✓	
MAPK8	✓			✓	✓	✓		✓	✓	✓	✓	
AR								✓	✓		✓	

TABLE 5.2. Common Hub Genes Identified in the Study

HUB GENES

UNIPROT ID	GENE
P12931	SRC
Q14289	PTK2B
P23458	JAK1
O60674	JAK2
P24941	CDK2
P40763	STAT3
Q13547	HDAC1
P07948	LYN
P45983	MAPK8
P10275	AR

5.5 MOLECULAR DOCKING

In this study, molecular docking was utilized to assess the interaction and affinity of the Fruquintinib compound with three specific target genes: JAK1, SRC, and JAK2.

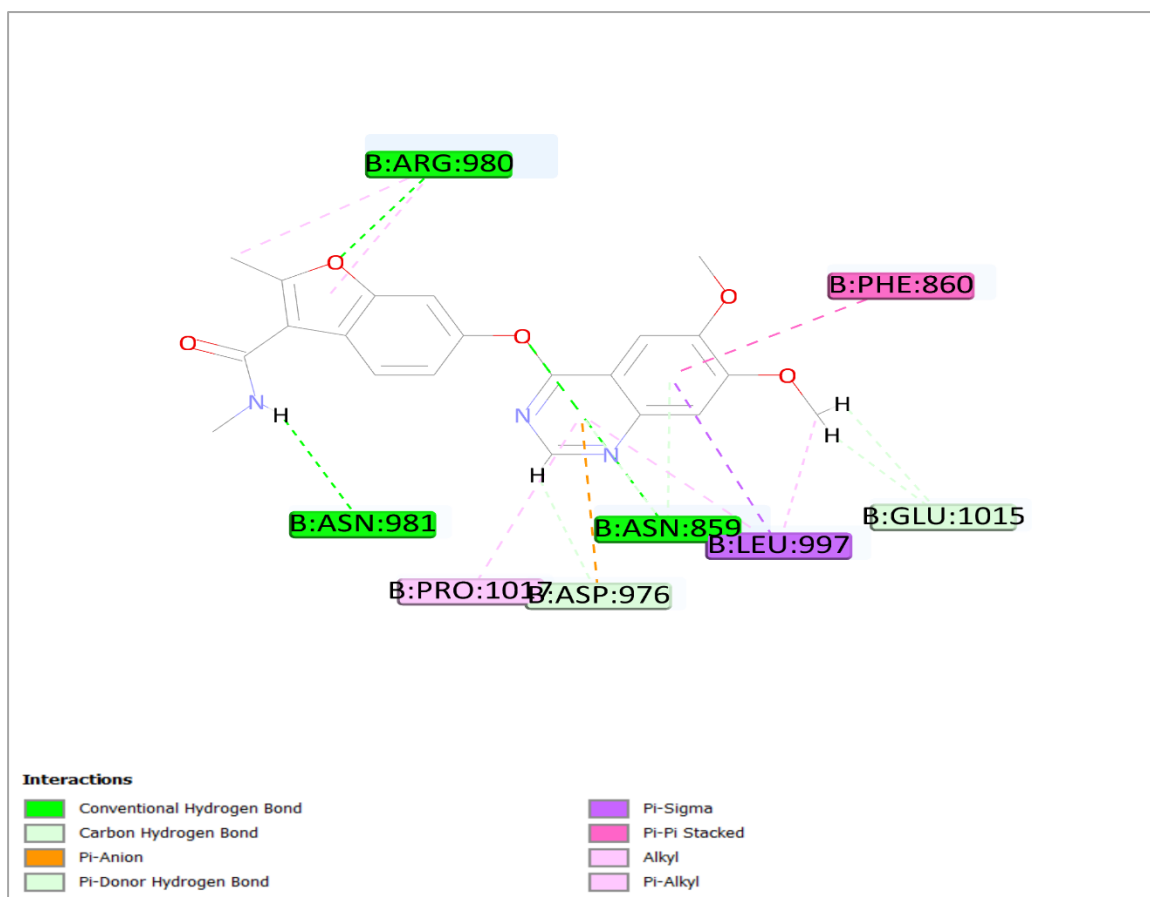


Figure 5.4. 2D structure of JAK2 Docked with Fruquintinib. The optimised pose, determined using BIOVIA CDOCKER, reveals various types of molecular interaction highlighted through color-based representation with the associated amino acid residues binding to Fruquintinib

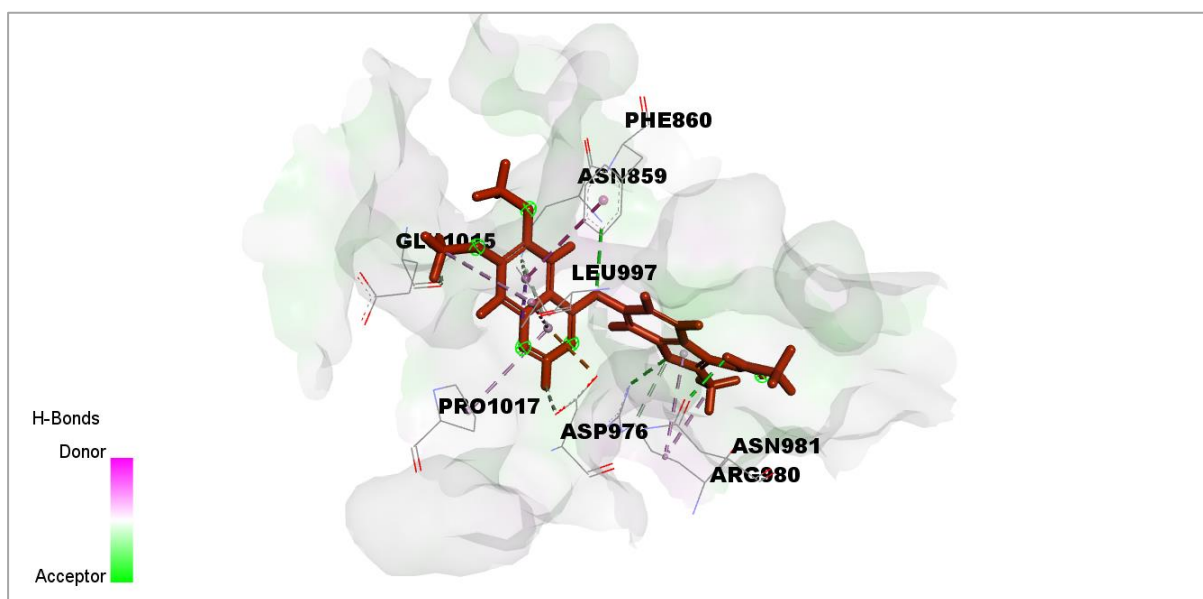


FIGURE 5.5. 3D representation of JAK2 and Fruqintinib Docking. The image shows the molecular docking of the JAK2 obtained using BIOVIA CDOCKER. The optimised 3D pose also highlights the amino acid residues binding to Fruqintinib

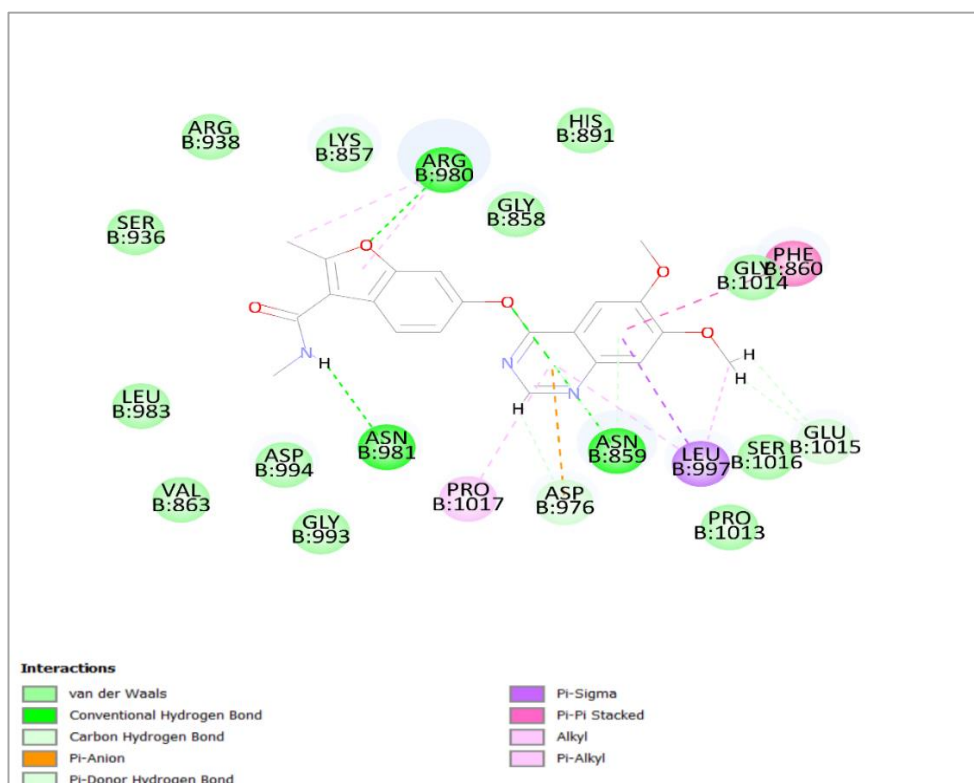


FIGURE 5.6. 2D structure of SRC Docked with Fruqintinib. The optimised pose, determined using BIOVIA CDocker, reveals various types of molecular interaction highlighted through color-based representation with the associated amino acid residues binding to Fruqintinib

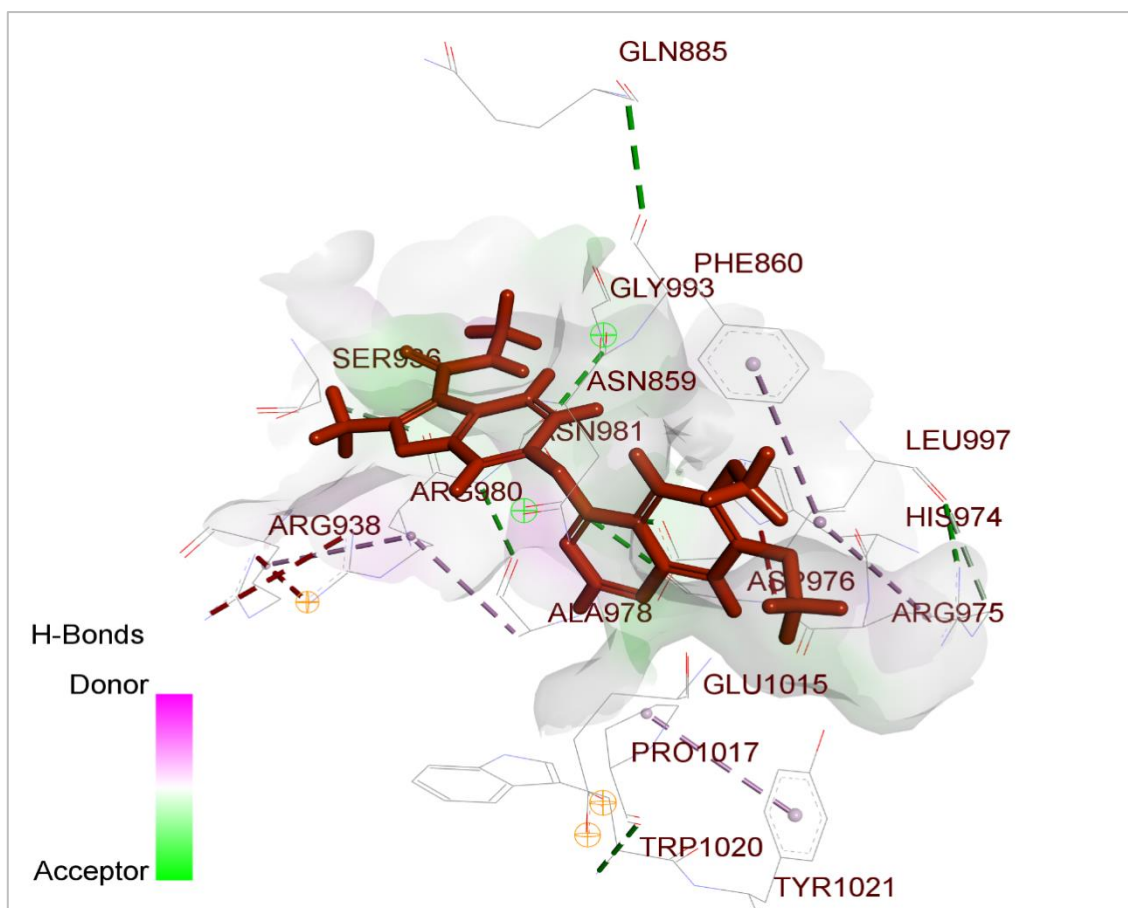


FIGURE 5.7. 3D representation of SRC and Fruqintinib Docking. The image shows the molecular docking of the SRC obtained using BIOVIA CDOCKER. The optimised 3D pose also highlights the amino acid residues binding to Fruqintinib

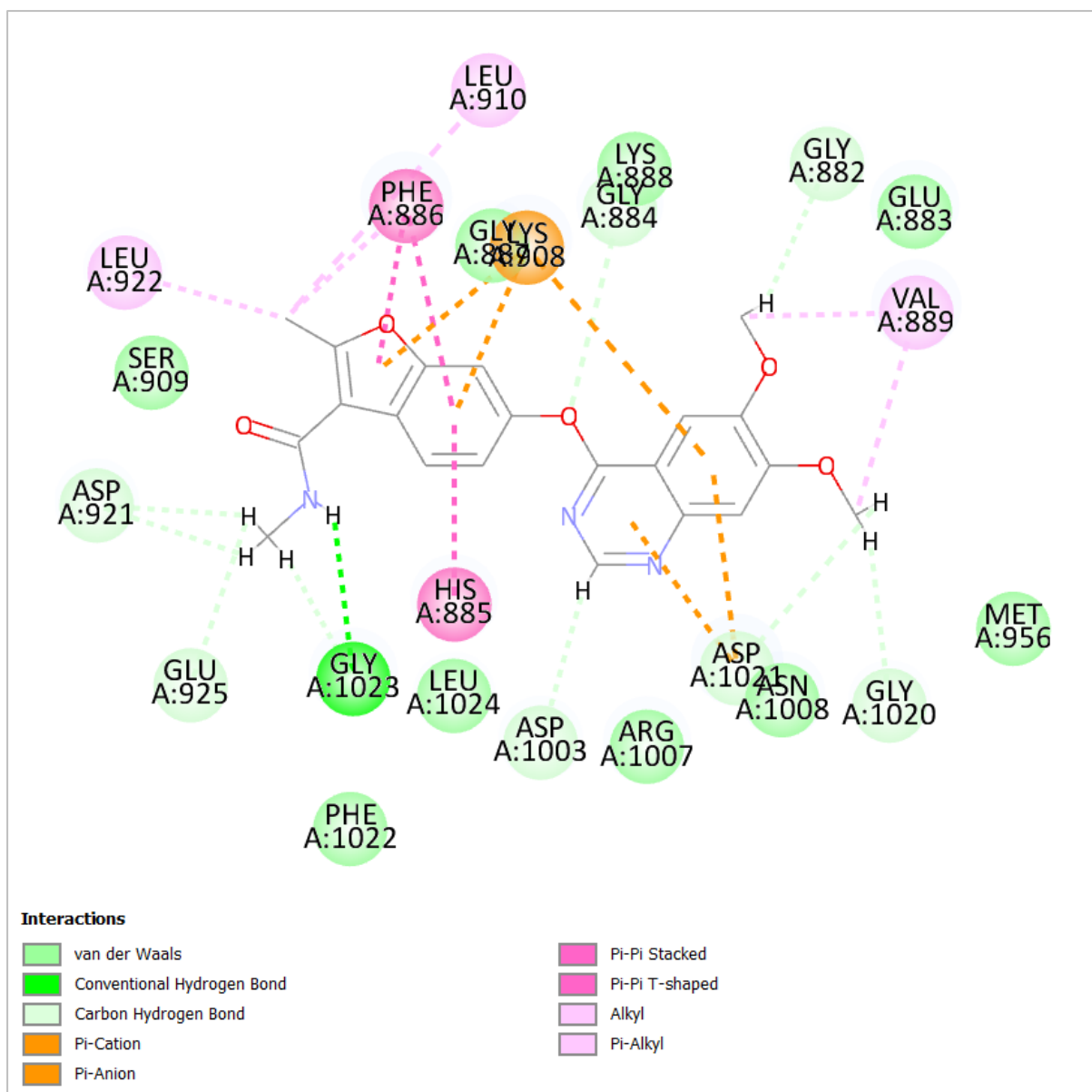


FIGURE 5.8. 2D structure of JAK1 Docked with Fruquintinib. The optimised pose, determined using BIOVIA CDOCKER, reveals various types of molecular interaction highlighted through color-based representation with the associated amino acid residues binding to Fruquintinib

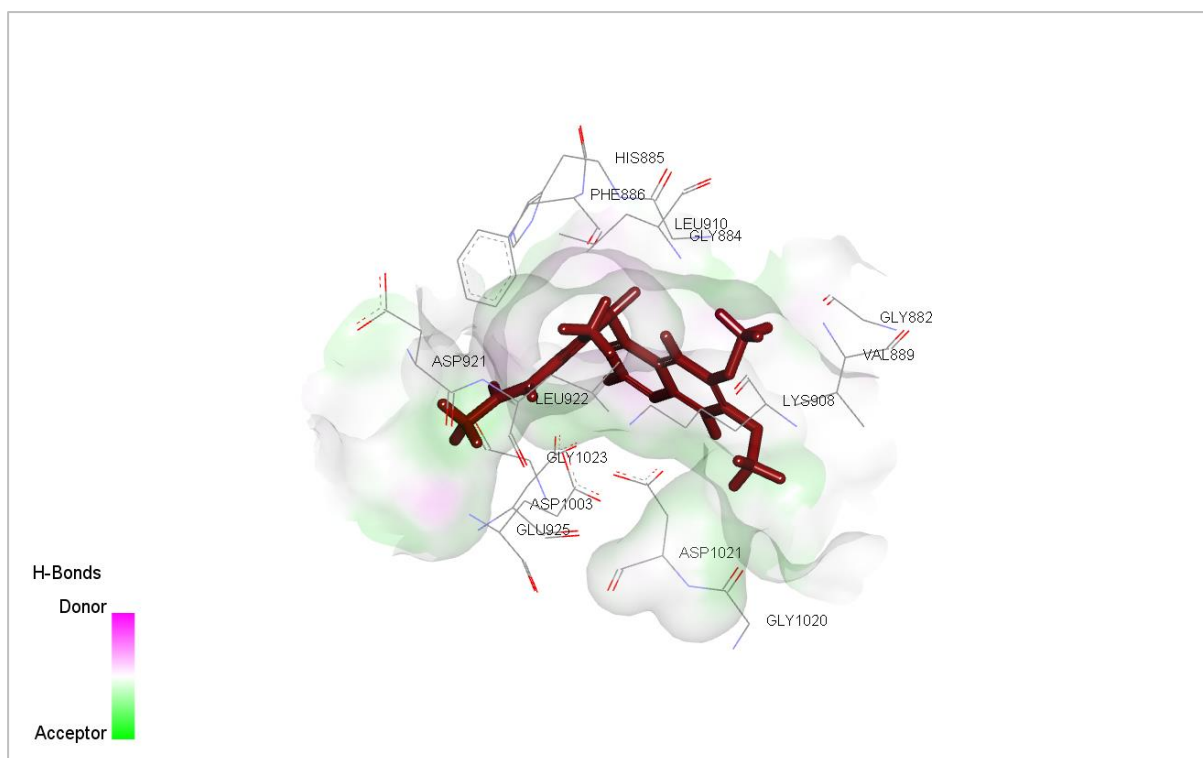


FIGURE 5.9. 3D representation of JAK1 and Fruqintinib Docking. The image shows the molecular docking of the JAK1 obtained using BIOVIA CDOCKER. The optimised 3D pose also highlights the amino acid residues binding to Fruqintinib

CHAPTER – 6

SUMMARY AND CONCLUSION

6.1 SUMMARY

This study, utilized network pharmacology and molecular docking strategies to examine the binding affinity of Fruquintinib, a strong inhibitor of vascular endothelial development calculates receptor (VEGFR), on different cancer targets.

Through organized pharmacology investigation, we comprehensively investigated the intelligence between Fruquintinib and its potential targets inside cancer-related signalling pathways.

After sifting utilizing the chart hypothesis strategy 10 center qualities were recognized: AR, SRC, JAK1, JAK2, PTK2B, MAPK8, LYN, HDAC1, STAT3, CDK2.

Atomic docking reenactments were utilized to illustrate the exact authoritative modes and affinities of Fruquintinib with key atomic targets involved in cancer movement and metastasis.

discoveries uncovered that Fruquintinib shows solid authoritative partiality towards numerous cancer targets, The auxiliary bits of knowledge given by atomic docking recreations highlighted the key buildups included in Fruquintinib official and shed light on the atomic instruments basic its anticancer movement.

underscored the capacity of Fruquintinib to specifically tie to particular target proteins, subsequently restraining their movement and disturbing significant pathways included in tumor development and angiogenesis.

6.2 CONCLUSION

The study illustrates the potential of Fruquintinib as a promising helpful operator for cancer treatment.

Its intuitive with different cancer targets utilizing organized pharmacology and atomic docking approaches picked up important experiences into the molecular premise of Fruquintinib's adequacy and selectivity.

These discoveries not as it were upgraded our understanding of Fruquintinib's pharmacological profile but also cleared the way for the rational design of optimized helpful procedures for cancer administration.

Exploratory approval of Fruquintinib's anticancer properties is justified to approve our computational expectations and development of its clinical advancement as a novel anticancer treatment.

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