EXPLORING NATURAL COMPOUNDS TARGETING THE HIPPO PATHWAY FOR POTENTIAL TREATMENT OF MENINGIOMA

A DISSERTATION

SUBMITTED IN PARTIAL FULFILMENT OF THE

REQUIREMENT FOR THE AWARD OF THE DEGREE OF

MASTER OF SCIENCE

IN

BIOTECHNOLOGY

Submitted by:

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2K21/MSCBIO/63

Under the supervision of:

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Bawana Road, Delhi-110042

MAY, 2023

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JUNE, 2023

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CANDIDATE' DECLARATION

I, Simran Singh, Roll No., 2K21/MSCBIO/63, student of M.Sc. Biotechnology, hereby declare that the project Dissertation titled **"Exploring Natural Compounds Targeting The Hippo Pathway For Potential Treatment Of Meningioma"** which is submitted by me to the Department of Biotechnology, Delhi Technological University, Delhi in partial fulfillment of the requirement for the award of the degree of Master of Technology/Bachelor of Technology, is original and not copied from any source without proper citation. This work has not previously formed the basis for the award of any Degree, Diploma Associateship, Fellowship or other similar title or recognition.

PLACE: Delhi **SIMRAN SINGH**

DATE: **2K21/MSCBIO/63**

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CERTIFICATE

I hereby certify that the Project Dissertation titled **"Exploring Natural Compounds Targeting The Hippo Pathway For Potential Treatment Of Meningioma"** which is submitted by **Simran Singh, 2K21/MSCBIO/63,** Department of Biotechnology, Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the degree of Master of Science, is a 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.

PLACE: Delhi

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I would like to thank friends and my family for their support.

SIMRAN SINGH

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ABSTRACT

Drug development which is a bit challenging and complex process that involves the development, discovery, design, and assessment of potential therapeutic agents. Meningioma, most common among the brain tumor which are generally asymptomatic in nature is characterized by the NF2 gene loss. The current treatment options such as resection and radiotherapy have limitations, with high rates of relapse or recurrence. The lack of FDA-approved drugs specific to meningioma necessitates the exploration of alternative approaches. Currently combination of FDA approved drug for other cancer were given to patients but the side effects and failure rates were high. To battle meningioma, natural substances are being researched as potential inhibitors of particular pathways, such as the YAP/TEAD complex in the Hippo signaling pathway. YAP/TEAD complex is responsible for uncontrolled cell progression in meningioma , by targeting this complex we can make a drug or treatment of meningioma. In this study, molecular docking was used to undertake in silico work and inhibition approach was used to find naturally occurring molecules with comparable structures that might potentially interact with the target receptor. out of 50 phytochemical,10 were selected on the basis of bioavailability test and lead likeness The white mulberry *Morus alba* plant's bark flavonoid, sanggenon N, was discovered to be the study's lead substance. Sanggenon N may have lesser negative effects than synthetic medications because the Sanggenon family of chemicals has demonstrated therapeutic potential. Another flavonoid called isostaivan showed the second-highest binding affinity.. Further analysis confirmed that Sanggenon N could act as an inhibitor of the 6UYC protein, which is the TEAD complex in *Homo sapiens*, thereby inhibiting the YAP/TEAD complex. This inhibition can potentially suppress cell proliferation and tumor growth in meningioma. It is crucial to emphasize that these results are based on in silico work and that additional validation through wet lab research is required.

KEYWORDS :Meningioma, molecular docking, YAP/TEAD complex, Natural compounds, Sanggenon N, Isosativan, bioavailability test

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LIST OF ABBREVAITION

NF2	Neurofibromatosis type2
ERM	Ezrin/Radixin/Moesin
LZTR1	Leucine-zipper-like transcriptional regulator 1
CHD1	E-cadherin
EGFR	Epidermal growth factor receptor
TGF-B	Transforming growth factor-beta
GPCR	G-protein coupled receptors
ADME	Absorption, Distribution, Metabolism, and Excretion
FAT4	FAT tumor suppressor homolog 4
WNT	wingless-related integration site
P13K	Phosphoinositide 3-kinase
SCRIB	Scribble
CD44	hyaluronic acid receptor
mTOR	mammalian target of rapamycin complex
KIBR	kidney and brain protein
VS	Vestibular schwannoma
YAP	Yes- associated protein
TEAD	Transcriptional enhancer factor domain family member 1
AJUBA	LIM domain-containing protein Ajuba
PAL	Protein associated with Lin-7

CHAPTER-1
INTRODUCTION

Brain tumours are abnormal growths of brain cells. They can arise from many cell types within the brain, such as glial cells, which support and protect neurons, or from other structures within the brain, such as blood arteries. Brain tumours are divided into two category: primary and metastatic.

Primary brain tumours are those that begin in the brain and do not spread to other regions of the body. Primary brain tumours are classified as either benign (non-cancerous) or malignant (cancerous). Gliomas (including glioblastoma), meningiomas, pituitary adenomas, and medulloblastomas are common kinds of primary brain tumours.

Metastatic Brain Tumours: These are tumours that have spread to the brain from other regions of the body, such as the lungs, breast, or colon. Primary brain tumours are less prevalent than these tumours.

Indeed, the most common primary brain tumour is a meningioma. Membranes that encircles the brain and spinal cord are generally known as meninges, are where they get their start. Meningiomas specifically come from the arachnoid cells that make up the internal surface of the dura mater, one of the meninges' layers. Meningiomas are frequently categorized using the World Health Organization (WHO) classification system, which also assigns them an aggressiveness rating based on their histological characteristics.

1.1 Meningioma

Meningiomas are formally classified by the WHO into three grade groups[1]: 1- **Grade I**: Meningiomas of Grade I are the most prevalent and non-aggressive form. They usually have clearly defined borders and a modest rate of growth. The prognosis for these malignancies is typically favorable, and surgical removal is frequently curative.

2. **Grade II** (Atypical): Meningiomas of this grade are more aggressive than grade I tumours. They have a few malignancy-related traits, including increased cell density, mitotic activity (cell division), and invasion of surrounding tissue. Compared to grade I tumours, grade II meningiomas are more likely to recur[2] and may need further care, such radiation therapy[3].

3. **Grade III** (malignant or anaplastic):These are most aggressive and uncommon kind of meningiomas. These tumours show blatant signs of malignancy, such as a high rate of mitosis, cellular atypia, and invasive expansion into neighboring tissues. Grade III meningiomas having a worse prognosis and a higher probability of recurrence. Radiation therapy, surgery, and occasionally chemotherapy are common treatment options.

It is important to note that the WHO grade categorization does not exclusively rely on genetic traits, but also takes into account histological characteristics. However, recent developments in molecular research have offered new insights into the genetic variations and molecular subtypes of meningiomas, which may help us better understand the behavior of tumours and prospective treatment options[4]. With a frequency of 7.86 cases per 100,000 persons per year, meningiomas are the most prevalent primary CNS tumour, accounting for around 36% of cases and 53% of nonmalignant CNS tumours.[5][6] Most meningiomas are thought to be benign, and they are frequently discovered by chance. A larger prevalence of meningiomas is seen in the black population, and nonmalignant meningiomas are more expected in women as compared to men population. Tendency of meningioma to occur in older age group is relatively high.[7] .If imaging strongly suggests meningioma, the diagnosis is made radiologically, and biopsy is not necessary[8]. Growth rate of Asymptomatic meningiomas is linearly about a rate of 2-4 mm/year, however in other instances they might develop with no change in volume or with exponential growth [9] .This aspect highlight the significance of untreated patients with asymptomatic meningioma. Patients who have meningiomas who are symptomatic or have a high growth tendency are typically removed.[10]

The overall rates that was estimated for the benign meningiomas are 81.4%[11], compared to 57.1% for malignant ones[6]. Grade II tumours have the lowest 10-year overall survival (53%), while grade III tumours have the highest (10%).For grades II and III, the rate of recurrence is between 50% and 90%, respectively[10]. Growth of the small tumour or transformation into a higher-grade tumour are indicators of disease progression[11].

Several factors that corresponds to disease progression are characterized below:

- Growth of the shred tumor: After surgical removal of a meningioma, there may be residual tumor cells left behind. If these cells continue to grow over time, it indicates disease progression which are further observe by Regular follow-up imaging studies, such as MRI
- Transformation into a higher-grade tumor: Meningiomas have the tendency to transform from a lower-grade (benign or atypical) to a higher-grade (malignant) tumor over the years. This transformation is correlates with more aggressive behavior and a poorer prognosis. To confirm the tumor histological examination is needed.
- Recurrence: Meningiomas can reoccur or relapse after initial treatment, even if they were completely removed. The recurrence can be local (at the site of the original tumor) or distant (in other locations within the central nervous system). Recurrence is a sign of a developing disease and may call for more therapeutic measures.

Risk factors associated with meningioma include ionizing radiation,[12]–[15] sex hormones , smoking , diabetes mellitus , atrial hypertension, and mobile phone usage[11].

Meningiomas can be caused by multiple endocrine neoplasia type 1, NF2, and the Li-Fraumeni, Gorlin, Cowden, and von Hippel-Lindau syndromes[16]; these tumours are frequently numerous and usually affect children.

Recent treatment includes surgery (resection)and radiotherapy , whereas the relapse's rate is usually high after 5 years for all grades/type of meningioma. NF2 is almost inactive in 50% of sporadic meningiomas.

1.2 Meningioma and NF2 link

(NF2) provided the first evidence that meningiomas can be genetically influenced[17], [18]. Autosomal dominant mutation disorder also called as NF2 are cause by loss of merlin gene which is the tumor suppressor gene which are further cause by Pathogenic mutations in the NF2 gene.[19]–[21]. NF2 are feature by the Tumours of the central and peripheral nervous systems [21]. On chromosome 22q12.2, the tumour suppressor gene NF2 is located. It has 17 exons and two splicing isoforms. The protein Merlin which contains 595 amino acid is encoded by it[21]. There is evidence to suggest that Merlin, a member of the (ERM) family of linking proteins membrane-cytoskeleton, which, by blocking signals from the PI3kinase/Akt, Raf/MEK/ERK, and mTOR signaling pathways, helps to stabilize the membrane cytoskeleton interface. [22]–[24].

NF2 is comprised of intracranial or spinal Meningiomas.. Spinal meningiomas occurs in about half of NF2 patients [25], [26], while about 20% of individuals have intracranial meningioma.

1.3 Schwannomatosis

VS are tumours that form from the vestibular branches of the vestibulocochlear nerve (cranial nerve VIII)[27]. Hearing loss, tinnitus, unbalance, face numbness/paraesthesia's, and facial paresis are the most typical VS symptoms. Multiple schwannomas developing in the absence of NF2-defining lesions like bilateral vestibular schwannomas or ependymomas is known as schwannosis[28]. Compared to NF2, it is a more uncommon condition with an estimated incidence of 1/40,000 to 1/70,000.[29]. The gene NF2, which is found at position 22q12.2 on Human chromosome no. 22, produces the protein Merlin,[30]–[32]. (LZTR1) and SWItch/ (SWI/SNF)- (SMARCB1) are the genes, and both of the genes are situated on chr22q next to NF2gene[1][33], [34].

CHAPTER-2
LITERATURE REVIEW

Indeed, the absence of Merlin, also known as NF2, are the major factor in the emergence of both syndromic and sporadic meningiomas. The meninges, which are the protective membranes that wrap around CNS, which further give rise to tumours known as meningiomas. [1].

The protein Merlin, which is produced by the tumour suppressor gene NF2, controls cell growth and proliferation by obstructing signalling pathways involved in cell division. Merlin is rendered inactive as a result of NF2 gene mutations or loss of function, which causes unchecked cell proliferation and the development of meningiomas[1]. Studies using next-generation sequencing (NGS) have improved our knowledge of the genetic makeup of meningiomas. Based on their genetic abnormalities, these studies have given us a framework for classifying meningiomas into two broad groups: non-NF2 mutants and NF2 mutants.

Meningiomas with mutations in other genes, such as SMARCB1, TRAF7, AKT1, and others, are referred to as non-NF2 mutants. These mutations can cause the activation of particular signalling pathways, which can aid in the growth and spread of tumours. Non-NF2 mutant meningiomas often develop ad hoc and are not connected to any recognised genetic disorders. However, the NF2 gene is selectively altered or lost in NF2 mutant meningiomas. The genetic condition Neurofibromatosis type 2 (NF2), which is characterised by the growth of many tumours in the nerve system, is frequently linked to these tumours. Both sporadic examples of the NF2 gene being somatically altered and patients with NF2 syndrome can develop NF2 mutant meningiomas.

Researchers can acquire understanding of the underlying molecular pathways causing tumour formation and find new therapeutic targets for individualised treatment approaches by classifying meningiomas into these two groups based on their genetic trait

2.1 MERLIN

The Merlin protein, sometimes called schwannomin, is synthesised by the NF2 gene. It is a member of the protein 4.1 family and functions to link plasma membrane proteins to the actin cytoskeleton[35]. Studies have demonstrated that the absence of merlin in fibroblasts and Schwann cells causes an increase in soft agar growth, tumour development in mice, and a loss of the contact-dependent regulation of cell proliferation[36], [37].

Merlin has been discovered to be involved in a number of cellular activities in these cell types. Epidermal growth factor receptor[38], 1-integrin[39], CD44[40], and intracellular signalling pathways including Ras, Rac1, phosphatidylinositol 3-kinase, mitogen-activated protein kinase[41], and signal transducer and activator of transcription have all been linked to its activity.

2.2 MERLIN SIGNALLING

2.2.1 Contact inhibition

Neurofibromin also called as merlin which is the antioncogenes, is essential required for controlling cell division and contact inhibition[42]. When cells reach a particular density or confluence, a phenomenon known as "contact inhibition" occurs where they stop multiplying and begin creating stable interactions with nearby cells.

Early research revealed that merlin's capacity to cause contact-induced proliferation inhibition is related to its tumor-suppressor action. Merlin is elevated and experiences hypo phosphorylation (lower phosphorylation), which results in its activation, as cells grow more confluent.[43] Dephosphorylated, active merlin interacts primarily with CD44, a hyaluronan receptor and cell-to-cell adhesion molecule that is a major part of the extracellular matrix (ECM)[44].

It is well known that CD44 interacts with a number of RTKs that control growth factor signalling. Merlin reduces the accessibility of RTKs at the plasma membrane and lowers

their signalling activity by interacting with CD44. This implies that merlin works to reduce RTKs' output of signalling, which is essential for cell growth and proliferation[45]. Furthermore, RAC1 and its downstream kinase PAK1 are involved in the regulation of merlin-mediated contact inhibition through their reciprocal interactions. The arrival of RAC1 to the plasma membrane is inhibited by active, dephosphorylated merlin, which prevents the activation of RAC1 and its downstream effector PAK1[46]. Cellular activities like cytoskeletal reorganisation and cell motility are impacted by RAC1 and PAK1.

Interestingly, Serine 518 is the location at which PAK1 phosphorylates the protein merlin. Merlin is rendered inactive as a result of this phosphorylation, which also hinders its movement towards the cell membrane. As a result, RAC1 and PAK1 are able to become active and may help promote cellular activities related to proliferation and motility. This reduces the inhibitory impact of merlin on RAC1[46].

In conclusion, these results indicate that merlin regulates cell proliferation, inhibits contact formation, and modifies the RTK and RAC1/PAK1 signalling pathways, all of which are associated with its tumour suppressor action. Tumour formation may be influenced by dysregulation of merlin function, such as its loss or inactivation, especially in diseases like schwannoma where merlin mutations are common.

2.2.2 PI3K/AKT/mTOR Pathway

It is widely known that the merlin protein interacts with the PI3K signalling pathway and is important for cell growth and expansion[47]. Merlin functions as an inhibitory protein in healthy cells by attaching to PIKE-L (a PI3K enhancer) and suppressing PI3K signalling, which stops the cell cycle.

However, merlin has been found to be downregulated in meningioma, a particular type of brain tumour. The progression of tumour cells is brought on by the stimulation of the PI3K/AKT pathway, which in turn stimulates mTORC[48].

Akt, a protein kinase associated in the PI3K pathway, is one of the major regulators of merlin. Merlin is phosphorylated by Akt at particular sites, including S315 and T230. Since PIKE-L cannot connect with merlin due to phosphorylation, merlin becomes polyubiquitinated, which then causes its destruction[49].

Inhibiting AKT activation and regulating the PI3K pathway could be a possible therapeutic strategy for treating meningioma, given the significance of the PI3K pathway in meningioma and the Merlin's role as a tumour suppressor gene
It is possible to avoid or restrict the polyubiquitination and degradation of merlin and preserve its tumor-suppressive properties by regulating the PI3K signalling pathway and restricting Akt activation.

Utilising particular PI3K pathway inhibitors or modulators is one strategy to accomplish this. These drugs can target the PI3K protein itself or downstream effectors like Akt, among other pathway elements. Merlin's phosphorylation and subsequent degradation can be stopped, preserving merlin's tumor-suppressive properties, by decreasing or regulating the activity of Akt.
Another approach is Targeting the PI3K pathway's upstream regulators, such as growth factor receptors or other signalling molecules that activate PI3K, may be another tactic. It is possible to manage Akt activity and keep merlin stable and functional by inhibiting or lowering PI3K activation.

2.2.3 HIPPO SIGNALLING PATHWAY

The Salvador-Warts-Hippo signaling network, commonly known as the Hippo signaling network, is a route that controls cellular functions and organ size. It regulates immunity, cancer, tissue regeneration, cell development, proliferation, and apoptosis[50]. Genetic screenings in Drosophila were used to discover the route. The Hippo signaling network is remarkably preserved in mammals, according to later research[51]. Numerous inputs, both at the plasma membrane and upstream intracellularly, control the Hippo kinase cascade. The Crumbs polarity complex, CHD1, Wnt, AJUBA, FAT4, CD44 , growth factor receptors, and GPCR are proteins that regulate the Hippo pathway at the plasma membrane[52].

- Crumbs polarity complex- Cell polarity is established and maintained by the Crumbs polarity complex, which is made up of the proteins CRB, Pals1, and SCRIB. Activity and localization of the hippo pathway is achieve through this complex

- CHD1– it is a cell adhesion molecule that contributes to tissue integrity and cell-cell adhesion. It can influence the signaling activity of the Hippo pathway by interacting with its constituent parts.
- Wnt- Wnt proteins are secreted signaling molecules that regulate various cellular processes, including the Hippo pathway. Wnt signaling can influence the activity of the Hippo pathway through the regulation of downstream effectors.
- AJUBA- It is a scaffold protein that interacts with multiple components of the Hippo pathway. It modulates the activity of the pathway and is involved in regulating cell proliferation and organ size.
- FAT4: Itis a member of the atypical cadherin family and acts as a tumor suppressor. It can regulate the Hippo pathway by interacting with other components and affecting downstream signaling events.
- CD44 : CD44 is a cell surface glycoprotein involved in cell-cell and cell-matrix interactions. It can influence the Hippo pathway through its interaction with other proteins and the extracellular matrix.
- Growth factor receptors: Various growth factor receptors, such as the EGFR and TGF-β receptors, can activate downstream signaling pathways that intersect with the Hippo pathway and regulate its activity.

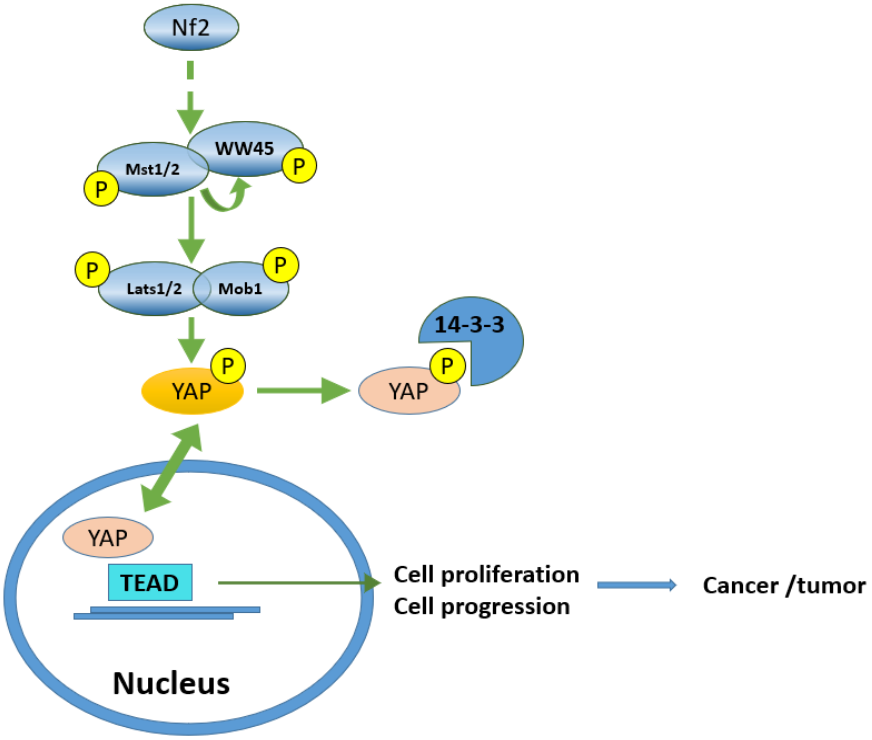


Fig 2.1: Hippo signalling pathway

These proteins, with other components of the Hippo pathway, work together to control cell growth, proliferation, progression and tissue homeostasis. Their interactions and signaling activities at the plasma membrane are crucial for proper regulation of the Hippo pathway.

NF2, KIBRA, and members of the RASSF all have an impact on the Hippo pathway intracellularly. These upstream intracellular pathway elements participate in the regulation of the Hippo pathway's activity. The Hippo pathway is started by phosphorylation of the activation loop of mammalian STE20-like kinase 1/2 (MST1/2) on threonine 183/180[53].Afterward, MST1/2 phosphorylates to activates LATS1/2, a major tumour suppressor kinase[54]. AJUBA and NF2 can also directly activate LATS1/2[55], [56]. MST1/2 and LATS1/2 protein kinases are phosphorylated in accordance with the regulation of these kinases by regulatory proteins Salvador family WW domain containing protein 1 (SAV1)[57] and MOB kinase activator 1[58]. This kinase cascade controls the phosphorylation of YAP and how it interacts with the coactivator with the PDZ-binding motif. A binding site which is on 14-3-3 proteins is created when LATS kinases phosphorylate YAP proteins at certain locations such as in case of Human YAP1 it is on Serine(Ser127) and Serine(ser 89) in human TAZ, which causes YAP to localize to the cytoplasm[59].

YAP TEAD COMPLEX

The 488 amino acid YAP protein comprises two WW domains[57], an SH3-binding motif, a CC domain in the TAD, a PDZ-binding motif in the C-terminus, a P-rich domain, TEAD and 14-3-3 binding sites in the N-terminal region[60]. TAZ protein contain 400 amino acid[61].

In case of active hippo pathway Dephosphorylated of YAP molecule is needed to enters the nucleus. It binds to transcription factors from the TEAD family as well as other transcription factors there[62]. Among the target genes regulated by the TEAD family members are connective tissue growth factor and cysteine-rich angiogenic inducer 61.[63]. This encourages a number of cellular functions, including cell progression, survival, tissue expansion, and apoptosis inhibition. The active Hippo pathway is essential

in controlling the development and growth of tumours as well as normal organ growth. It accomplishes this by preventing cell proliferation, encouraging apoptosis, and limiting stem cell growth[62]. The retention of YAP/TAZ proteins in the cytosol that results from phosphorylation slows the growth of tumours. On the other hand, unphosphorylated YAP/TAZ proteins enter the nucleus, encourage the growth of progenitor cells, aid in tissue regeneration, and raise the risk of tumour development[64]. In the absence of the NF2 gene and merlin protein, the Hippo pathway can lead to the formation and expression of the YAP/TEAD complex, promoting cell growth and proliferation, potentially leading to a cancerous condition such as meningioma.

2.3 NATURAL COMPOUNDS USED FOR DOCKING

2.3.1 SANGGENON N (PUBCHEM CID-42608044)

Sanggenon is a isoprenylated flavonoids with molecular formula (C25H26O6) found from the of white mulberry pant *Morus alba* specially from their root barks[65].molecular weight is around 422.5g/mol

Sanggenon N has been the focus of research studies and exhibits a variety of biological functions. Numerous pharmacological characteristics, such as antioxidant, anti-inflammatory, and anticancer activities, have been demonstrated. Sanggenon N has also demonstrated potential in blocking certain enzymes and pathways linked to disorders including cancer and inflammation.

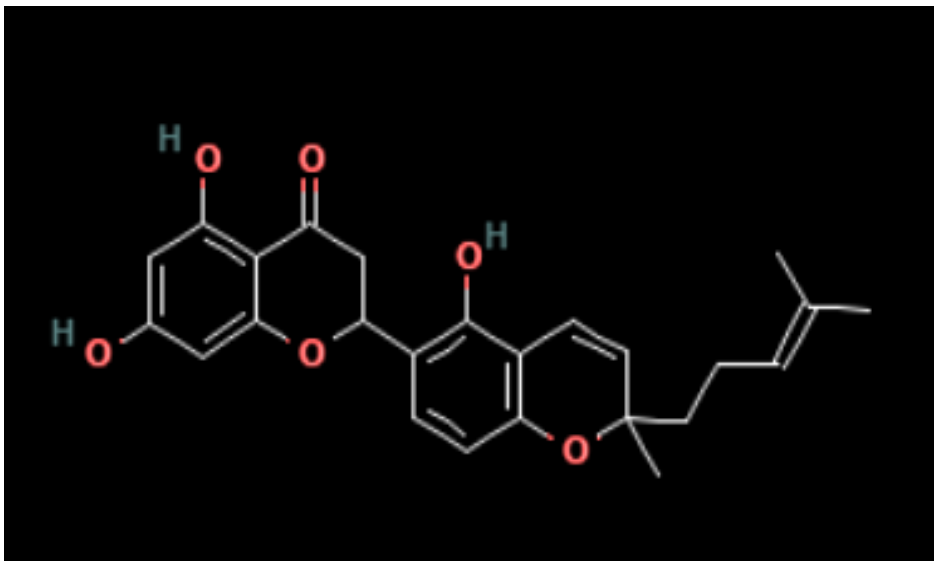


Fig 2.2 - 2D structure of Sanggenon N

2.3.2 ISOSATIVAN (PUBCHEM CID-591624)

Isosativan is an isoflavonoids with molecular formula . It is an isoflavone derivative containing methoxy and hydroxyl substituents in particular places. Molar weight is around 286.32g/mol.A category of organic substances called flavonoids, which includes isoflavonoids, can be found in a variety of plants. They are recognized for their potential health advantages and are linked to anti-inflammatory and antioxidant characteristics. The potential effects of flavonoids on human health are the subject of extensive research.

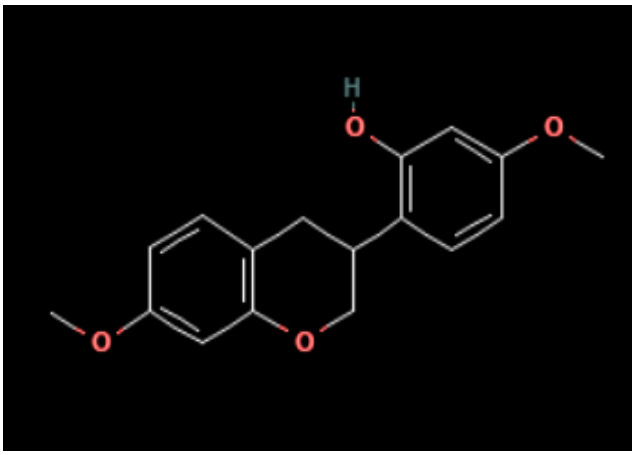


Fig 2.3- 2D structure of Isosativan

2.4 FOR PERFORMING MOLECULAR DOCKING WE HAVE 2 APPROACHES

In the Hippo signaling pathway, the NF2 gene encodes the protein merlin. Merlin activates MST1/2, which are protein kinases. MST1/2, in turn, activate LATS1/2 and other proteins. This cascade of activations leads to the phosphorylation and subsequent inactivation of the YAP/TEAD complex. By inhibiting the YAP/TEAD complex, cell proliferation and growth can be halted.

TEAD is a transcription factor that associates with YAP/TAZ to form a heterodimer. This complex, when hyperactivated, can lead to excessive cell growth and contribute to cancer development. In the case of meningioma, the NF2 gene is absent or lost, resulting in the absence of merlin protein. Without merlin, the YAP/TEAD complex remains active, promoting continued cell growth and proliferation, which can lead to the formation of tumors or cancer.

2.4.1 1ST APPROACH STIMULATION

To activate MST1/2 and achieve inactivation of the YAP/TEAD complex, one approach is to identify a stimulatory gene or molecule that can enhance the activity of MST1/2. This process typically involves various techniques and environments for performing molecular docking and screening.

A computer-based approach called molecular docking is used for predicting the interactions that will occur when a small molecules (the ligand) and a target protein (MST1/2) link together. Researchers can find possible MST1/2 activators by analyzing known biological molecules or virtually screening a library of chemicals.

In order to verify the expected binding and evaluate the functional impacts of the stimulatory molecules on the Hippo signalling pathway, experimental validation is also required.

In general, the hunt for a stimulatory gene or chemical that can activate MST1/2 and deactivate the YAP/TEAD complex can be a difficult and time-consuming endeavor that involves computational analysis and experimental validation.

2.4.2 2ND APPROACH INHIBITION

Directly targeting the YAP/TEAD complex may be a potential strategy to reduce activity and terminate the signalling cascade. Finding inhibitors that can stop the formation or stability of the YAP/TEAD complex, causing YAP to dissociate and the subsequent deactivation of its transcriptional activity, is the aim.

Researchers may use a variety of techniques to find possible YAP/TEAD complex inhibitors. High-throughput screening, rational small molecule creation, virtual compound library screening, and medication repurposing are a few examples. These methods can include computational modelling, molecular docking, and experimental validation to assess the discovered inhibitors' binding affinities and functional effects.

While it may be difficult, the discovery of YAP/TEAD complex inhibitors holds significant potential for therapeutic approaches in disorders involving deregulation of the Hippo signalling system and excessive cell proliferation.

CHAPTER-3
METHODOLOGY

3.1 PROTEIN PREPARATION

The 3D conformation of the target protein 6UYC (Crystal structure of TEAD2 bound to Compound 2) was downloaded from the (PDB) website (http://www.rcsb.org/pdb/home/home.do), along with the inhibitor[41]. Heteroatoms like water and the inhibitor complex were removed using Biovia DS Visualizer 2021, and the coordinates of the inhibitor binding were recorded. Additional polar hydrogen atoms were added to the protein. The protein structure was then energy minimized using Swiss PDB Viewer. Finally, the structure was downloaded in PDB format.

Fig 3.1 - PDB structure of 6UYC Protein

3.2 LIGAND PREPARATION

The PubChem ID 146171270 for the discovered Protein 6UYC inhibitor, QLV which is also known as **N-5-[€-2-(4,4-difluorocyclohexyl)ethenyl]-6-methoxypyridin-3-ylmethanesulfonamide**, was retrieved in 3d SDF format from the PUBCHEM database (https://pubchem.ncbi.nlm.nih.gov). The structure was translated into .mol2 format using Biovia Discovery Studio Visualizer to get the ligand ready for molecular docking , selection of ligands and preparation for the same. This conversion enables the ligand to be compatible with molecular docking studies

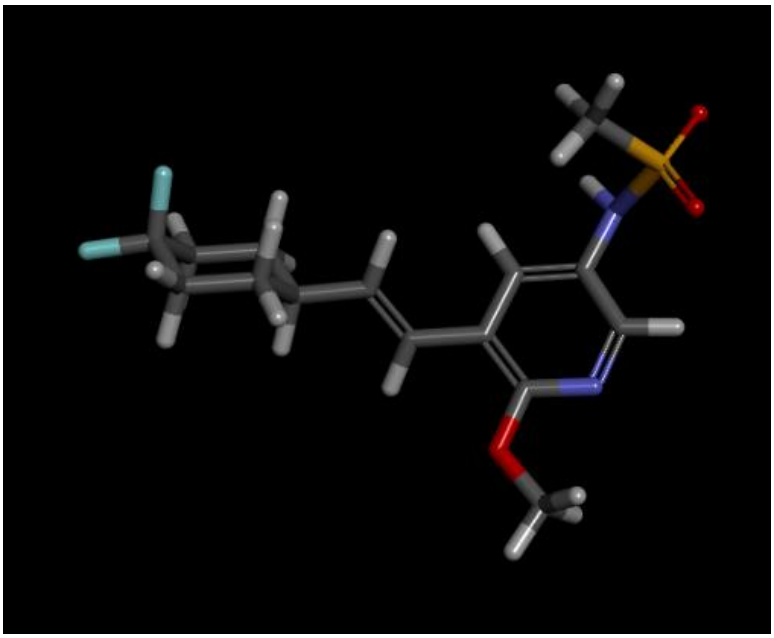


Fig 3.2: PDB structure of QLV

3.3 PROTEIN PREPARATION FOR DOCKING

The protein that was prepared for the control after removing the ligand was used as the protein which has to be dock in Swiss dock

3.4 LIGAND SELECTION AND PREPARATION

Using the IMPPAT database along with relevant research publications, **fifty** permeable phytochemicals that can penetrate the blood-brain barrier were found. These phytochemicals' chemical structures were retrieved from the PUBCHEM database in 3D SDF format. at https://pubchem.ncbi.nlm.nih.gov.The SDF files were modified into .mol2 and.pdb formats using the Biovia Discovery Studio Visualizer program

(https://discover.3ds.com/) to get the ligands ready for molecular docking. The ligands are appropriate for subsequent molecular docking experiments as a result of this conversion process.

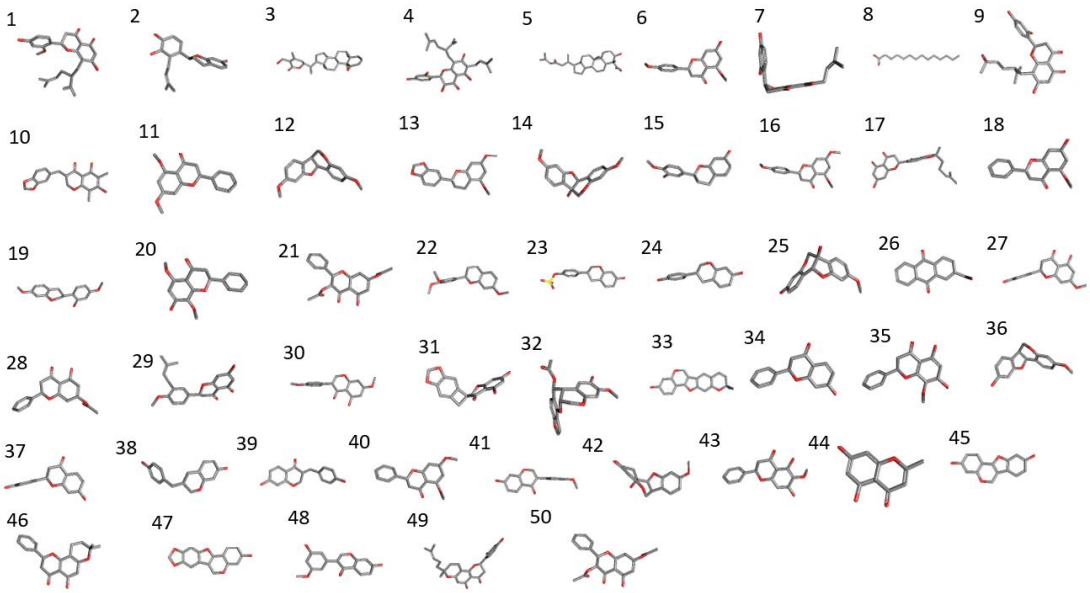


Fig 3.3: 3-D Structures of 50 phytochemicals

(1)leachianone A, (2)Kazinol U, (3) Withaferin A, (4)Kushenol M,(5) Gardenolic acid B, (6)Tsugafolin, (7) Cudraflavanone B, (8)Myristic acid,(9)Kurarinol,(10)Alpinetin,(11) Methylophiopogonanone A,(12) Chrysin dimethylether,(13) Homopterocarpin, (14)3-Hydroxy-5,7-dimethoxy-3', (15)4' methylenedioxyflavan, (16)(-)-Variabilin, 7,(18)3'-Dihydroxy-4'-methoxyflavan,(19) Naringenin trimethyl ether, (20)Sanggenon N,(21) Isosativan, (22)7-Hydroxy-5,8-dimethoxyflavanone,(23) 3,7-O-Diacetylpinobanksin, (24)3',4',7-Trimethoxyflavan,(25) 4',7-Isoflavandiol,(26) EQUOL, (27)6alpha-Hydroxymedicarpin,(28) 2-hydroxymethyl-anthraquinone, (29)Sakuranetin,(30) Pinocembrin 7-acetate,(31) 4'-O-Methyllicoflavanone, (32)7-O-Methylbiochanin A,(33) Scillascillin , (34)12-Deoxo-12alpha-acetoxyelliptone, (35)Anhydrotuberosin, (36)2H-1-Benzopyran-7-yloxy, (37)5-Hydroxy-7,8-dimethoxyflavanone, (38)Isomedicarpin,(39)Liquiritigenin, (40)7-Hydroxy-3-(4-hydroxybenzyl)chroman, (41)7,4'-Dihydroxyhomoisoflavanone, (42)Dihydrobonducellin, (43)5,7-Dimethoxyflavanone,(44) Calycosin, (45)1,11b-Dihydro-11b-hydroxymedicarpin,(46) Dihydrooroxylin A, (47)Noreugenin,(48) Anhydroglycinol, (49)Dihydroobovatin, (50)Dehydromaackiain,

3.5 BIOAVAILABILITY TESTING

Phytochemicals with high or favorable binding energies were evaluated for bioavailability using SwissADME (http://www.swissadme.ch/index.php)[66], a tool that assesses various parameters including molecular weight, Lipinski's Rule of Five (which determines drug candidacy)[67], molecular refractivity, solubility, and more. The SMILES notation of the compounds is provided as input to SwissADME, which then identifies the compounds that meet the specified criteria and are suitable for further wet lab experiments.

3.6 DOCKING ANALYSIS

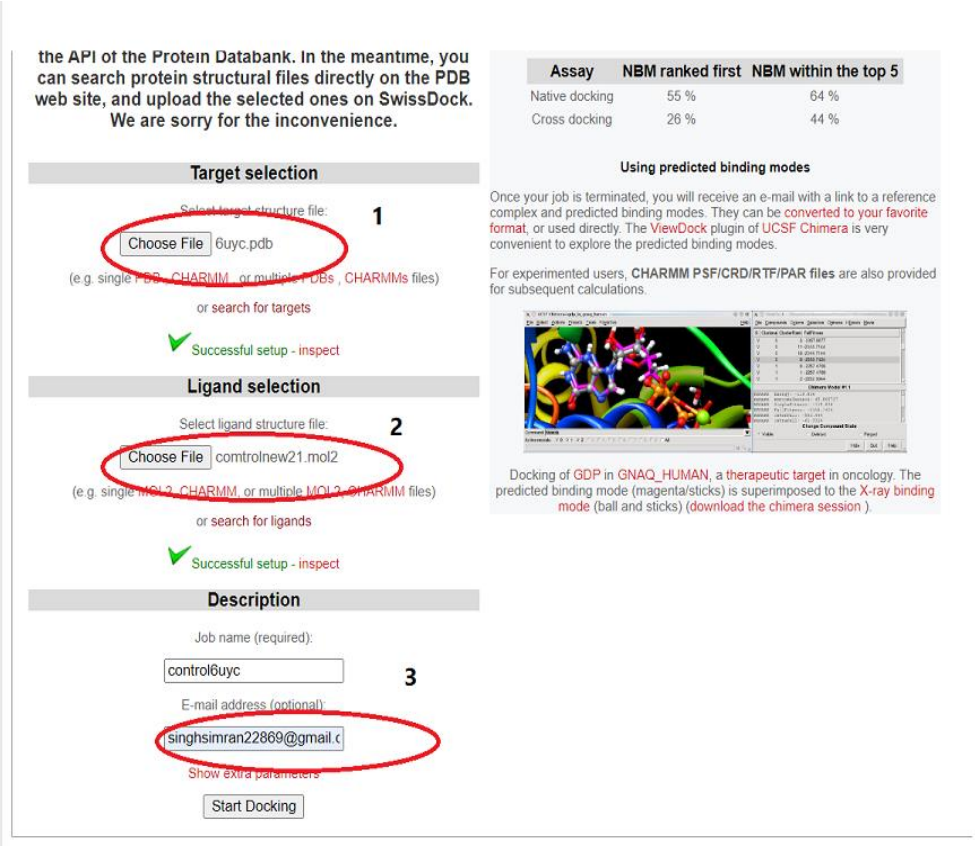
Permeability-tested compounds underwent molecular docking using Swiss Dock (http://www.swissdock.ch/docking/) .Swiss Dock is a molecular docking software used for predicting the binding affinities of small molecules to protein targets. After docking interaction were checked.

3.6.1 Control docking

- After eliminating all ligands and heteroatoms, the target protein in.pdb file was submitted to the target selection window.

- In the ligand selection window, a.mol2 file containing the inhibitor of the 6UYC protein i.e. QLV with the PubChem ID 146171270 was submitted.

- The results were interpreted from the email sent by SwissDock, which included the binding energies of the docking calculations.



1-target upload **2**- ligand upload **3**- E-mail

Fig 3.4: Steps involved in Swiss docking

3.6.2 Experimental docking

- The target protein (receptor), 6UYC protein, was uploaded to the target selection window in .pdb format.
- Fifty phytochemicals that were BBB permeable were selected and uploaded separately in .mol2 format in the ligand selection window.
- The same steps were repeated for each ligand and receptor(6UYC protein) combination.
- SwissDock was initiated, and the docking calculations were performed. The results were obtained via email, which was provided during the docking process.

- The binding energies of the compounds were compared, and the ones with the best results were separated. Further swissADME analysis and bioavailability testing are done
- The interactions between the selected compounds and the receptor(target protein) were further examined. Different software tools like Plip, PyMOL, and Chimera were used for visualization and interaction analysis.
- The 3D structures of the complexes were downloaded and assessed using UCSF ChimeraX 1.16 software (https://www.cgl.ucsf.edu/chimera/)

  The interactions were compared with the control, and compounds with higher binding energy compared to the control were identified.

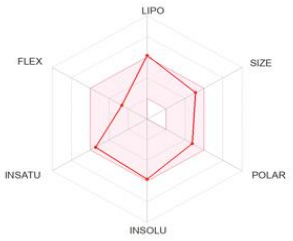
CHAPTER-4
RESULT

A major factor in the onset and spread of cancer, particularly meningioma, is the absence of the gene known as NF2. It is associated with merlin, which acts as a precursor to the merlin protein. Since there is currently no FDA-approved drug for meningioma, it is necessary to develop drugs that target different signaling pathways Our research focuses on the Hippo signaling pathway, where merlin degradation leads to the hyperactivation of the YAP/TAZ complex, a transcriptional factor that promotes cell growth and progression. It is crucial to develop a drug that can directly inhibit the YAP/TEAD complex within the Hippo signaling pathway, thereby deactivating the pathway and preventing the growth of cancer or tumors in the body.

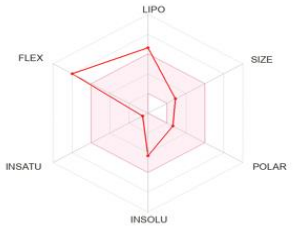
For this analysis, 50 phytochemicals were obtained, and binding energy was used to compare the ligands' and receptors' binding affinities.out of 50 phytochemicals 10 phytochemicals were selected with high binding affinities

4.1 BIOAVAILBILTY TESTING

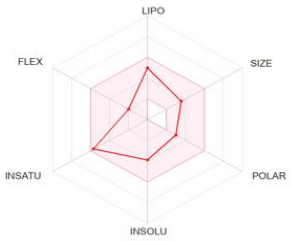
The phytochemicals that were obtained from IMPPAT were subjected to bioavailability testing to identify the lead compounds ,the compounds which proves to be promising treatment for the disease and often lead to drug discovery. Out of 50 tested we have selected 10 which shows zero lead likeness violation. The radar plots of these were shown below



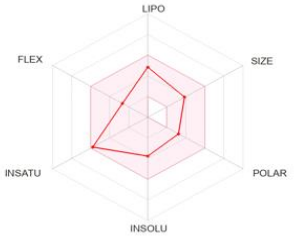
Sanggenon N



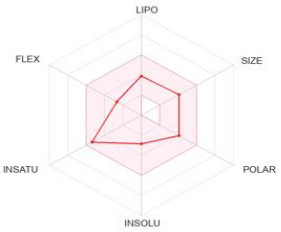
Myristic acid



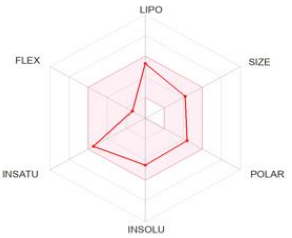
Isosativan



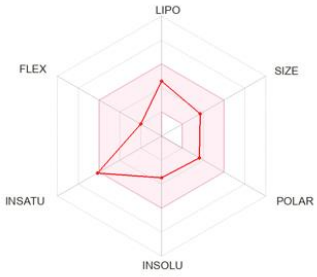
Naringenintrimethylether



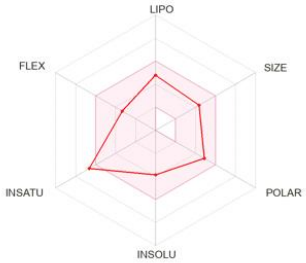
Trimethoxyflavan



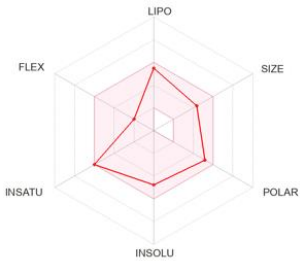
Methylophiopogonanone A



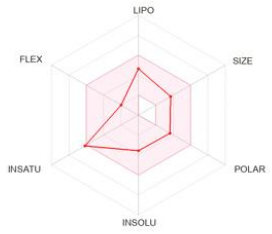
7-Hydroxy-5,8-dimethoxyflavanone



3,7-O-Diacetylpinobanksin



Cudraflavanone B



Tsugafolin

Fig 4.1: Phytochemicals satisfying bioavailability parameters

4.2 DOCKING STUDIES

Docking analysis were performed from the phytochemicals obtained from the IMMPAT database.

Reference -The binding results of our target protein 6UYC protein with its inhibitor comes out to be **-8.42**

Docking result- The binding energy of the 10 best phytochemicals falls under the range of -7.84 to -9.42

TABLE 4.1 COMPARED PHYTOCHEMICALS

Phytochemicals	Binding Energy	H acceptor	H donor	Mol. Wtg.
Sanggenon N	-9.42	6	3	422.47
Isosativan	-8.54	4	1	286.32
Myristic acid	-8.32	2	1	228.37
Trimethoxyflavan	-8.31	6	2	332.35
MethylophiopogonanoneA	-8.23	6	2	342.34
Naringenintrimethylether	-8.12	4	5	314.33
7-Hydroxy-5,8-dimethoxyflavanone	-7.98	5	1	300.31
3,7-O-Diacetylpinobanksin	-7.90	7	1	356.33
CudraflavanoneB	-7.86	6	4	356.37
Tsugafolin	-7.84	5	1	300.31

4.3 PHARMACOKINETICS SCREENING OF PHYTOCHEMICALS

The Lipinski rule and ADME in silico screening of the ten phytochemicals revealed information about their drug-likeness and bioavailability. With the exception of myristic acid, all of the substances had a bioactive score of 0.55. This rating reflects the likelihood that the chemicals will demonstrate biological activity.

All of the phytochemicals can be employed with ease in wet lab investigations because they are water soluble, have low bioactive scores, and are non-toxic. This implies that they can be put to the test in a lab environment to learn more about their characteristics and prospective uses. The medication made from these compounds can be given via several ways depending on its pharmacodynamics. Intravenous administration, which involves a bloodstream injection, is one choice. As an alternative, the substances can be enclosed in nanoshells or nanocapsules made of non-toxic nanomaterials. This encapsulation protects the molecules and regulates their release, enabling the delivery to be targeted and managed.

TABLE 4.2: USING SWISS ADME, IN-SILICO PHARMACOKINETICS OF LIGANDS

Phytochemicals	Binding energy	BBB testing	Bioavailability score	Mol refractivity	LOGP
Sanggenon N	-9.42	permeable	0.55	119.25	3.70
Isosativan	-8.54	permeable	0.55	80.09	2.74
Myristic acid	-8.32	permeable	0.85	71.18	3.32
Trimethoxyflavan	-8.31	permeable	0.55	87.74	3.18
MethylophiopogonanoneA	-8.23	permeable	0.55	90.35	3.09
Naringenintrimethylether	-8.12	permeable	0.55	84.98	3.08
7-Hydroxy-5,8-dimethoxyflavanone	-7.98	permeable	0.55	80.51	2.54
3,7-O-Diacetylpinobanksin	-7.90	permeable	0.55	89.92	2.64
CudraflavanoneB	-7.86	permeable	0.55	97.31	2.64
Tsugafolin	-7.84	permeable	0.55	80.51	2.45

This in silico work offers a framework for evaluating the drug-likeness, safety, and possible pharmacological applications of the phytochemicals. It is followed by wet lab investigations and later formulation procedures.

4.4. RECEPTOR – LIGAND INTERACTION

From the above tables we can intrepret that sanggenon N and isosativan shows more binding affinities as compared to our control (refernce) . the values were sanggenon N (-9.42) and Isosativan(-8.54)

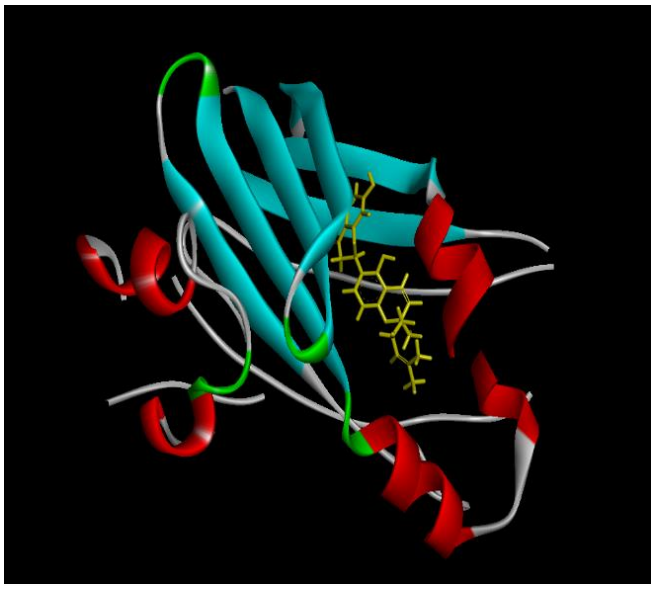


Fig 4.2:Target protein 6UYC with QLV

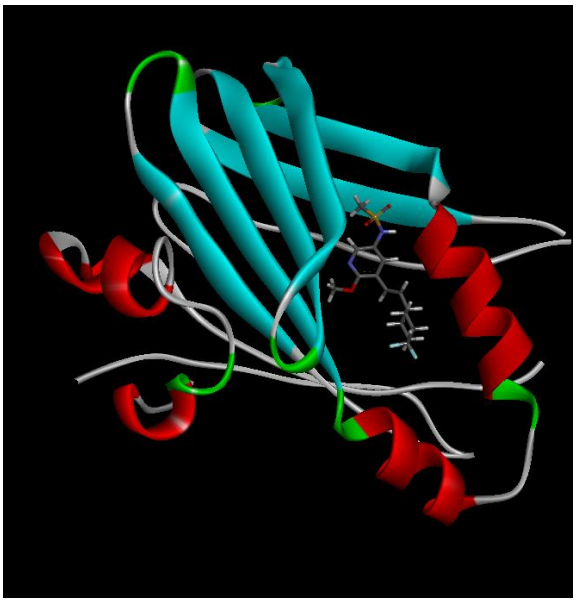


Fig 4.3: Target protein 6UYC with SANGGENON N

4.4.1. 2D RECEPTOR LIGAND INTERACTIONS OF QLV WITH 6UYC PROTEIN

Following interactions were shown i.e. the binding site of sanggenon N as well as 6UYC inhibitor

Protein 6UYC with its inhibitor PubChem ID 146171270 shows the binding energy of -8.42

The inhibitor interacts with the target protein 6UYC in several methods. It interacts with the amino acids leucine 306 (Leu306), leucine 403 (Leu403), phenylalanine 386 (Phe386), phenylalanine 406 (Phe406), methionine 379 (Met379), lysine 357 (Lys357), and glutamate 359 (Glu359) in eight different van der Waals interactions.

In addition, the inhibitor forms nine alkyl bonds with the amino acids isoleucine 408, leucine 383, alanine 235, phenylalanine 302, phenylalanine 428, tyrosine 426, and valine 329. These amino acids include leucine 387, alanine 304, phenylalanine 302, phenylalanine 302, phenylalanine 428, and tyrosine.

Additionally, the inhibitor and the amino acid phenylalanine 233 (Phe233) interact in a pi-pi manner.

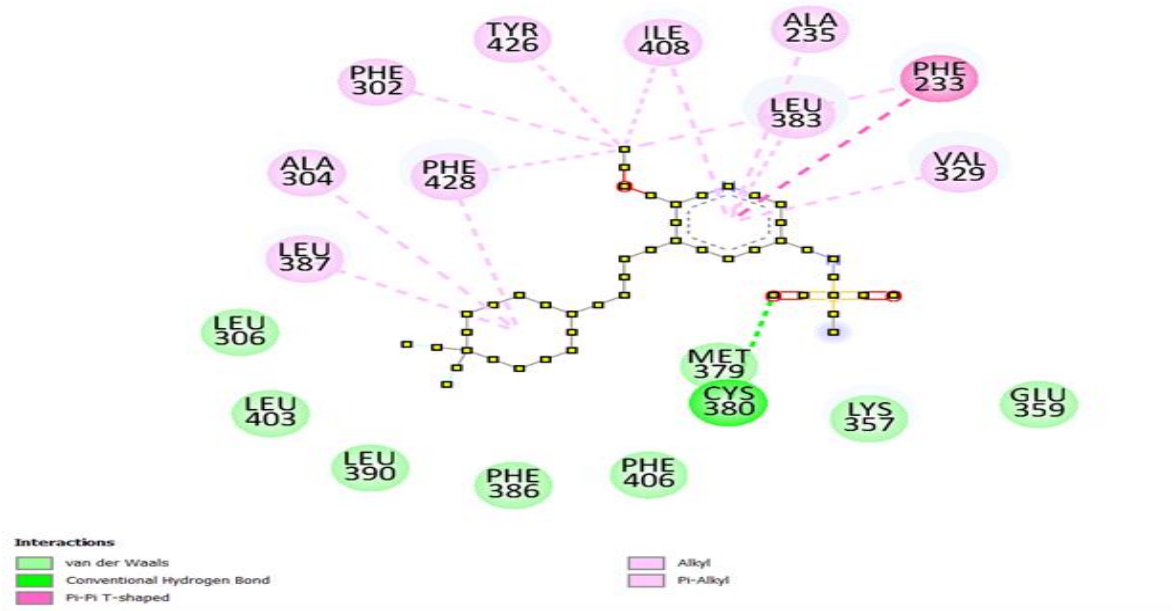


FIG 4.4- Interaction between QLV with 6UYC protein

4.4.2 2D RECEPTOR LIGAND INTERACTIONS OF SANGGENON N WITH 6UYC PROTEIN

Sanggenon N and **Isosativan** have more highest Binding affinity towards target protein 6UYC than its own inhibitor

Sanggenon N demonstrates the highest binding efficiency among the compounds, with a binding affinity of -9.42 kcal/mol.

Sanggenon N forms various interactions with the target protein 6UYC. It engages in van der Waals interactions with eight amino acids: valine 329 (Val329), alanine 235 (Ala235), methionine 379 (Met379), leucine 383 (Leu383), leucine 390 (Leu390), phenylalanine 386 (Phe386), alanine 304 (Ala304), and leucine 306 (Leu306).

Furthermore, Sanggenon N also establishes alkyl bonds with 12 amino acids: valine 329 (Val329), alanine 235 (Ala235), methionine 379 (Met379), leucine 383 (Leu383), leucine 390 (Leu390), phenylalanine 386 (Phe386), alanine 304 (Ala304), leucine 306 (Leu306), leucine 403 (Leu403), phenylalanine 406 (Phe406), isoleucine 408 (Ile408), and leucine 387 (Leu387).

Sanggenon N also interacts with the amino acids glutamate 359 (Glu359), serine 331 (Ser331), and glutamine 410 (Gln410), forming three typical hydrogen bonds with each of them. Along with lysine 357 (Lys357), it forms a carbon hydrogen bond with the latter.

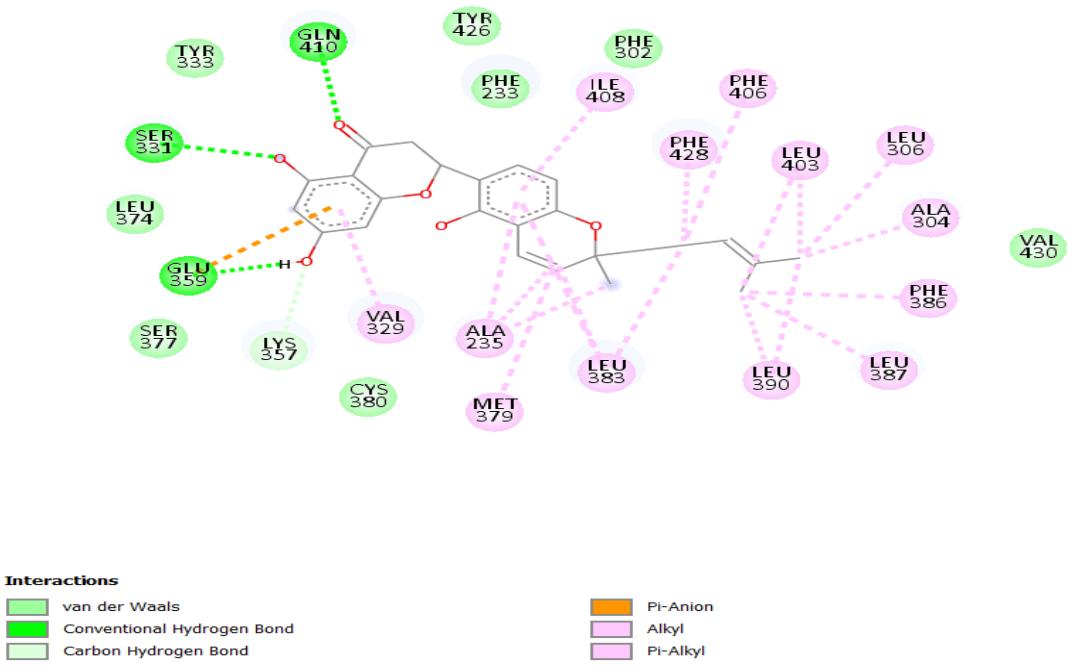


Fig 4.5- Interaction betweenSANGGENON N with 6UYC protein

4.4.3 2D RECEPTOR LIGAND INTERACTIONS OF ISOSATIVAN WITH 6UYC PROTEIN

Isosativan demonstrates the second highest binding efficiency among the compounds, with a binding affinity of -8.54 kcal/mol

Isosativan forms various interaction with the target protein. It forms 9 van der waals interactions: phenylalanine (Phe251), methionine379 (Met379),serine345 (Ser345), Lysine357(Lys357), Tyrosine (Tyr333),Glutamine (Gln410), serine (Ser331), phenylalanine (Phe302), phenylalanine (Phe428). It forms 7 alkyl bonds :Leucine (Leu383), alanine (Ala235), valanine (Val252), isoleucine (Ile408),valanine (Val329), phenylalanine (Phe233),lecuine (Leu374), cysteine (cys343)

Isosativan also form pi-pi bond with Tyrosine (tyr426) as well also form a covalent bond with glutamine (glu359)

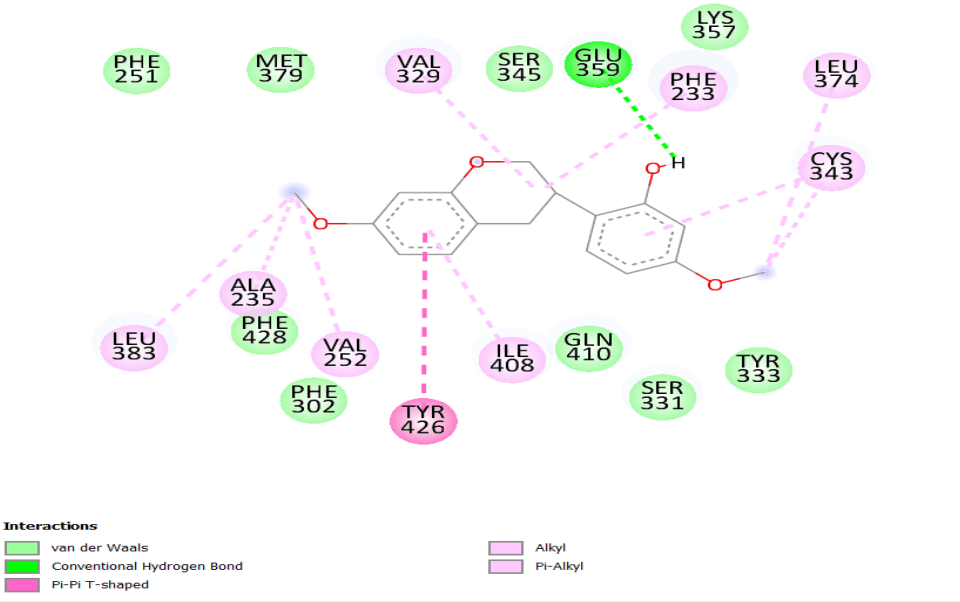


FIG 4.6- Interaction between ISOSATIVAN with 6UYC protein

The bioavailabilty and docking studies indicates that sanggenon has the greater binding affinity for the receptor. After than isosativan has 2nd highest binding affinity

4.5 CHECKING INTERACTIONS WITH PLIP

The software programme plip is used to examine and display protein-ligand interactions[68]. It offers a thorough examination of the non-covalent interactions that take place between proteins and their ligands, including hydrogen bonds, hydrophobic contacts, salt bridges, pi-pi interactions, and others.

PDB format input files containing the three-dimensional (3D) structure of the protein-ligand complex are accepted by PLIP. It examines the interactions between the protein and ligand, identifies the many kinds of interactions, and offers thorough details on the shape and potency of each contact.

In addition to interactive visualisations, such as 2D and 3D renderings of the protein-ligand complex highlighting the individual interactions, the software creates an output file that contains a summary of the interactions.

nderstanding of the molecular interactions between proteins and ligands can be derived by investigating protein-ligand interactions, identifying important interactions that affect binding affinity, and using PLIP[68]. It can be especially helpful in molecular docking investigations and drug discovery.

4.5.1 PLIP INTERACTION OF 6UYC PROTEIN WITH QLV

After uploading the structure or pdb file on PLIP website following interactions were seen such as hydrophobic and Hydrogen bond interactions which helps in camparing the phytochemicals, drugs, molecule etc.

Here the tabular representaion of the data make it more clear in comparing the interaction between a ligand that is self attached with the molecule as well as the natural compounds.

Table 4.3 Hydrophobic interaction of 6UYC with QLV

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
HSD-Z-338	370A	PHE	3.61	1206	1711
HSD-Z-439	302A	PHE	3.69	2858	892
HSD-Z-440	442A	TYR	3.81	2875	2924

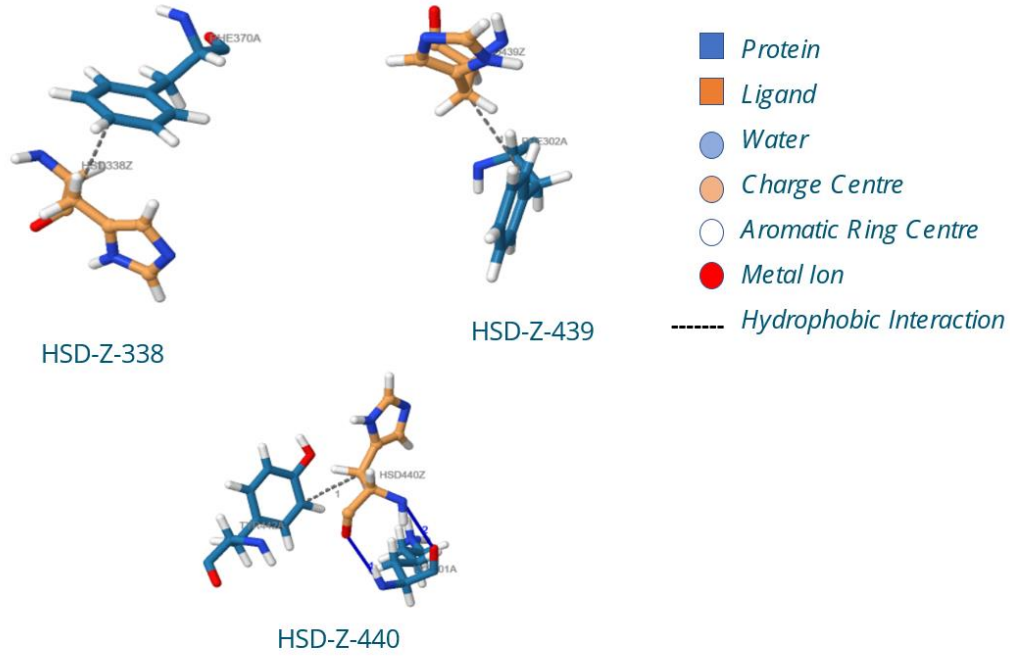


FIG 4.7- Schematic representaion of Hydrophobic interations between 6uyc protein with QLV

Table 4.4 :Hydrogen bond interactions of 6UYC protein with QLV

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle
HSD-Z-338	327A	TYR	2.08	2.97	153.39
	384A	VAL	2.29	3.17	146.36
	391A	ARG	3.23	3.88	123.51
	392A	GLN	3.25	4	133.35
HSD-Z-440	301A	LYS	2.18	3.16	166.73
	301A	LYS	2.2	3.02	139.42

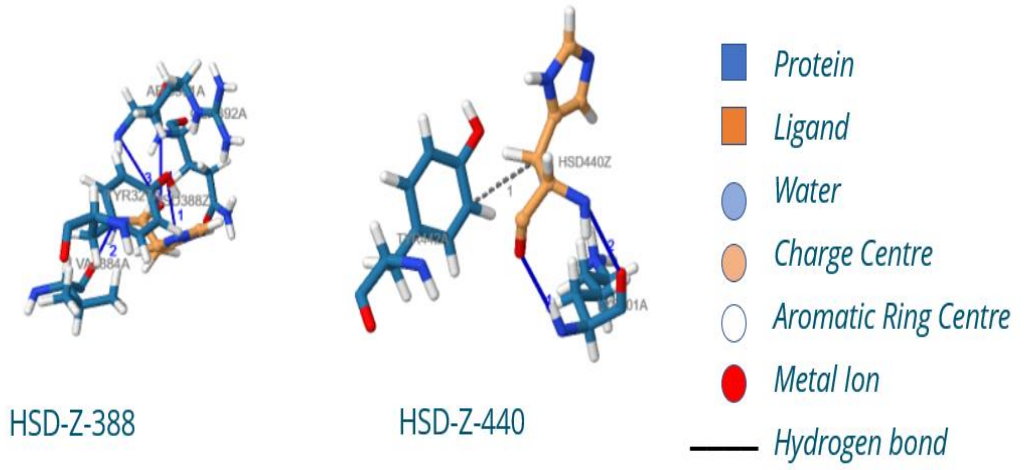


FIG 4.8- Schematic representaion of Hydrogen Bond between 6uyc protein with QLV

4.5.2. PLIP INTERACTION OF 6UYC PROTEIN WITH SANGGENON N

Table 4.5 Hydrophobic interaction of 6UYC with Sanggenon

Index	Residue	AA	Distance	Ligand Atom	Protein Atom
HSD-Z-338	370A	PHE	3.61	706	958
HSD-Z-439	302A	PHE	3.69	1529	535
HSD-Z-440	442A	TYR	3.81	1539	1564

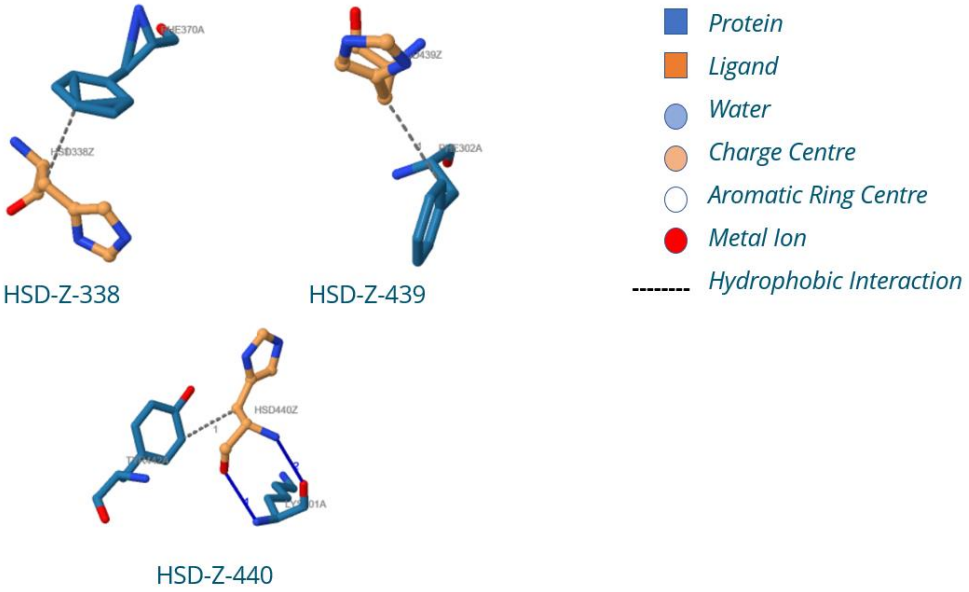


FIG 4.9- Schematic representaion of Hydrophobic interations between 6uyc protein with SANGGENON N

Table4.6 Hydrogen bond interactions of 6UYC protein with Sanggenon

Index	Residue	AA	Distance H-A	Distance D-A	Donor Angle
HSD-Z-338	384A	VAL	2.3	3.17	146.75
	391A	ARG	3.21	3.88	126.69
	392A	GLN	3.28	4	131.39
HSD-Z-440	301A	LYS	2.18	3.16	169.27
	301A	LYS	2.16	3.02	145.92

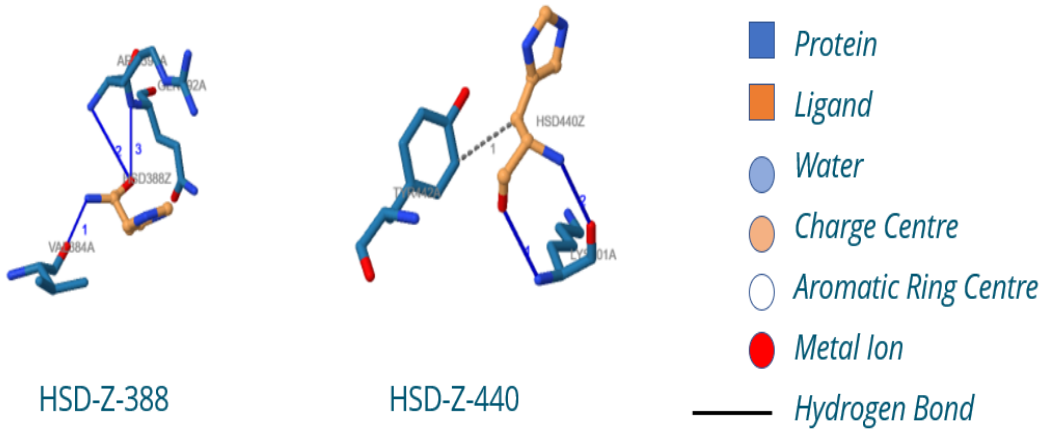


FIG 4.10 - Schematic representaion of Hydrogen Bond between 6uyc protein with SANGGENON N

After comparing the interaction of control vs experimental the result came out to be : all the interaction were same when comapared in both hdrogen as well as hydrophobic interaction so we can conclude that sanggenon binds to the exact place where the 6UYC inhibitor was bind.

CHAPTER-5
DISCUSSION

Meningiomas particularly brain tumors derives from the meninges of the brain. The management of meningiomas, including surgical techniques, radiation treatment, as well as molecular docking an new and promising approach , is covered in this article along with the present state of knowledge, treatment outcomes, and future directions.This articles typically focuses on NF2 loss and how it corelated with merlin and hippo signalling pathway . A considerable majority of meningiomas have loss of the NF2 gene, which is a significant genetic change. Meningiomas develop and progress because of the loss or inactivation of the NF2 gene, which functions as a tumour suppressor.. Merlin protein function is lost in meningiomas due to deletion or inactivation of the NF2 gene. Meningiomas proliferate and develop out of control as a result of its lack of function. Merlin has a crucial role in regulating signalling pathways, cell adhesion, and proliferation in the context of tumour suppression. As a result, increased cell proliferation and tumour developmentoccurs. There are many pathways which are associated with nf2 loss i.e PI3K , Contact inhibition and hippo pathway. Hippo pathway is itself a vast pathway which is operated by a huge numbers of genes but our study focuses on how nf2 or merlin loss effects it. In the context of tumour development, especially meningiomas, the Hippo pathway and NF2 depletion are intertwined. The Hippo pathway is a signalling mechanism that controls how quickly cells divide and grow into organs. Loss of NF2, and more specifically, loss of the Merlin protein, is essential for controlling the Hippo pathway.The transcriptional co-activators (YAP) and (TAZ) are ultimately controlled by a sequence of protein interactions and phosphorylation processes that regulate the Hippo pathway. YAP and TAZ are phosphorylated and trapped in the cytoplasm when the Hippo pathway is activated, leading to their deactivation and destruction. As a result, the target genes involved in cell development and proliferation aren't activated when they move into

the nucleus. For experimental purpose TEAD complex that binds to YAP is searched and targeted so that it inhibits the YAP/TEAD complex anf further cell proliferation would stop . In order to find possible phytochemicals that might interact with the target protein 6UYC in the Hippo pathway, the strategy uses molecular docking experiments. Based on bioavailability tests, the top 10 phytochemicals were chosen after initial screening of 50 phytochemicals. Sanggenon and Isosativan among them had greater protein 6UYC binding affinity. Flavonoids for eg. Sanggenon and Isosativan have been utilised in the past to make medicines. The following stage was contrasting how protein 6UYC interacted with both its inhibitor and with Sanggenon and Isosativan independently. By examining the complexes' 2D architecture, a comparison was made. The interactions between the protein and ligands were also further examined and confirmed using the PLIP software. Sanggenon N may be a potential substitute for the inhibitor, according to the findings, which showed that Sanggenon and Isosativan bind to the same site as the inhibitor. It's crucial to remember that additional wet lab tests are required to verify these results and demonstrate the efficacy of Sanggenon N in the setting of meningioma. In general, this method combines in silico screening of phytochemicals with computational methods like molecular docking and interaction analysis to find prospective therapeutic candidates. The outcomes of these computational analyses serve as a foundation for more experimental research and the prospective creation of a medication for the treatment of meningiomas.

CHAPTER-6
CONCLUSION

The in-depth investigation focuses on the association between meningioma, a specific type of brain tumour, and the nf2 gene and Merlin protein. The Hippo pathway, which is associated with nf2 in meningiomas, was studied in detail in this work. As no FDA approved drug and medications includes combination of cancerous drug . these comination are related to greater side effects and more failure or reoccurance rate. Since natural compounds have long been used in traditional medicine and human diets, they are frequently more readily accepted by the body than synthetic medications. As well as they posses lesser sideeffect and higher target selectivity. Sanggenon N which is extracted from the root bark of white mulberry plant , satisfied all the screening parameters. It showed more binding affinity than 6UYC with its inhibitor. Sanggenon N can be potent and it is vaible replacement of inhibitor as well as to deactive the YAP/TEAD complex. In order to confirm their safety and efficacy through wet lab differebt tests and subsequent clinical trials, even though they appear promising in silico and may have medicinal potential. These actions are essential to make sure that any possible medication candidates made from natural substances are thoroughly examined and satisfy the criteria for human use.

CHAPTER-7

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APPENDIX: A SUPPLEMENTARY INFORMATION

Protein 6UYC (FASTA FORMAT)

>6UYC_1|Chains A, B|Transcriptional enhancer factor TEF-4|Homo sapiens (9606)

GSAWQARGLGTARLQLVEFSAFVEPPDAVDSYQRHLFVHISQHCPSPG
APPLESVDVRQIYDKFPEKKGGLRELYDRGPPHAFFLVKFWADLNWGP
SGEEAGAGGSISSGGFYGVSSQYESLEHMTLTCSSKVCSFGKQVVEKV
ETERAQLEDGRFVYRLLRSPMCEYLVNFLHKLRQLPERYMMNSVLEN
FTILQVVTNRDTQELLLCTAYVFEVSTSERGAQHHIYRLVRDGNS

APPENDIX B: LIST OF PUBLICATIONS

- Simran, Rohan & Das A *, New Insight ; Insilico study of phytochemicals as a Therapeutic Approach in Meningioma.

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CANDIDATE' DECLARATION

I, Simran Singh, Roll No., 2K21/MSCBIO/63, student of M.Sc. Biotechnology, hereby declare that the project Dissertation titled **"Exploring Natural Compounds Targeting The Hippo Pathway For Potential Treatment Of Meningioma"** which is submitted by me to the Department of Biotechnology, Delhi Technological University, Delhi in partial fulfillment of the requirement for the award of the degree of Master of Technology/Bachelor of Technology, is original and not copied from any source without proper citation. This work has not previously formed the basis for the award of any Degree, Diploma Associateship, Fellowship or other similar title or recognition.

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CERTIFICATE

I hereby certify that the Project Dissertation titled **"Exploring Natural Compounds Targeting The Hippo Pathway For Potential Treatment Of Meningioma"** which is submitted by **Simran Singh, 2K21/MSCBIO/63,** Department of Biotechnology, Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the degree of Master of Science, is a 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.

PLACE: Delhi

DATE:

02/06/2023

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