NEW INSIGHT: IN-SILICO ANALYSIS OF PHYTOCHEMICALS AS A THERAPEUTIC INTERVENTION AGAINST MENINGIOMA

A DISSERTATION

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CANDIDATE' DECLARATION

I, Rohan, Roll No., 2K21/MSCBIO/35, student of M.Sc. Biotechnology, hereby declare that the dissertation project titled " **New Insight: In-silico analysis of phytochemicals as a therapeutic intervention against meningioma"** which is submitted by me to the Department of Biotechnology, Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the degree of Master of Science, is original and not derived 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 "**New Insight: In-silico analysis of phytochemicals as a therapeutic intervention against meningioma"** which is submitted by **Rohan, 2K21/MSCBIO/35,** 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.

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ABSTRACT

Drug development for conventional delivery targets is the major challenge for therapeutic progress. PI3K signaling has shown a prominent role in progression of meningioma which subsequently makes these receptors a target for efficient treatment approach. Loss or alteration of NF2 (*neurofibromin 2*) with respect to its gene product merlin is crucially implicated in tumor development eventually leads to the meningioma. However, the interactions of meningioma pathophysiology (merlin) to many pathways makes it complicated. Different signalling pathways interacting with merlin are the hippo pathway, PI3K /Akt route and mTORC pathway. We thesis on the inhibitory approach for P13K pathway and phosphorylation of Akt to terminate merlin polyubiquitination and promote its expression and association with PIKE-L thereby activating tumor suppressive action. Our work emphasizes on exploring biological compounds that target the PI3K pathway using the in-silico method.

Here, we implemented 50 phytochemicals from various plant sources against PI3K for molecular docking and assessed as a potential anticancer drug. The docking was performed showing binding energy, drug likeness and affinity of different phytochemicals. The following study demonstrated various phytochemicals (such as Leachianone A, withaferin A, kurarinol and gardenoilic acid B) along with comparing their ADME score, bioavailability radar and score that provides insights on possible therapeutic approach of these biological compounds.

Keywords *- phytochemicals; PIKE-L; PI3K target; AKT pathway; Akt phosphorylation; Molecular Docking; ADME; bioavailability radar; meningioma; NF2.*

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I, Rohan, feel proud to present the dissertation project as a part of the curriculum of M.Sc. Biotechnology. This project could not have been completed without the support and guidance of all the people who assisted in the completion of the project.

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LIST OF ABBREVIATIONS

PIKE-L	Phosphoinositide-3-Kinase Enhancer Long isoform
P13K	Phophoinositide 3-kinase
Akt	Protein Kinase B
ADME	Absorption, Distribution, Metabolism, and Excretion
IMPPAT	Indian Medicinal Plants, Phytochemistry and Therapeutics
NF2	Neurofibromatosis 2
FDA	Food and Drug Administration
PDB	Protein Data Bank
WHO	World Health Organisation
FERM	4.1 protein, ezrin, radixin, moesin domain
SMARCB1	SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1
RTK	Receptor Tyrosine Kinase
VEGF	Vascular Endothelial Growth Factor
mTORC1	mechanistic Target Of Rapamycin Complex 1
CD44	Cluster of Differentiation 44
Rac1	Ras-related C3 botulinum toxin substrate 1
PAK 1	p21-activated kinase 1
PPI	Protein-Protein Interaction
YAP	Yes-associated protein
TAZ	Transcriptional co-activator with PDZ-binding motif
TEAD	Transcriptional Enhancer Factor (TEF)-Associated Domain.
SAV1	Salvador Family WW Domain-Containing Protein 1

MST1/2	Mammalian Sterile 20-like kinases 1 and 2
LATS1/2	Large Tumor Suppressor Kinase 1/2
SMIs	Small Molecular Inhibitors
PKA	Protein Kinase A
SMILE	Simplified Molecular Input Line Entry System
BBB	Blood Brain Barrier

CHAPTER 1
INTRODUCTION

An unnatural increase of brain cells is well recognized as a brain tumor. Cerebral or Brain tumors could be primary (brain-originating), metastatic (tumors that have moved to the brain from other areas of the body), benign (non-cancerous), or malignant (cancerous)[1]. The methods for tackling varied types of tumors have always been either surgery or chemotherapy [2]. Although surgery may not always be an effective alternative due to various challenging conditions patients may confer. In some cases, due to the difficult location of the tumor, it may be impossible to reach and remove it fully, therefore, drugs can aid tumor progression. Drugs can be applied as a combination therapy with surgery too[3]. Other than that, for more precise targeted delivery, we can rely on drug treatments. Hence, drug development perhaps be a substituting therapeutic approach to the treatment of patients with challenging conditions [4]. This thesis will lead us to innovating the drug development strategy for meningioma tumors by using natural compounds obtained from medicinal plants with higher tolerance and minimum or zero side effects.

1.1. Meningioma Tumor

Meningiomas are typical brain tumors formed on the laminate that mask the brain and the spinal cord. According to WHO they are classified as benign, atypical or malignant [5]. Currently, over 97 cases in every 100,000 people for meningioma are reported around the globe, mostly occurring in the women population[6]. Depending on their size and location in the brain, meningiomas can result in symptoms like headaches, seizures, vision issues, and alterations in mood or behavior [7]. These are generally benign i.e. (restricted to a particular location) so treating them from surgery or radiation therapy is applicable.

Over decades of research, we thought that meningiomas are characterised by (NF2) neurofibromin-2 loss. NF2 is a genetic component found on specific site at chromosome 22q encoding merlin protein, which is a tumor suppressor associated with the FERM gene family [8](Brand 4.1). Merlin significantly binds to the actin cytoskeleton with membrane

proteins and tends to possess tumor suppressive potent. Merlin is also reported to conciliate contact-inhibition of proliferation [5].

Loss or mutations in the nf2 gene by radiation causes deletion of nf-2 gene, which is accountable for merlin progression. Merlin-69 kDa protein encoded by NF2 on chromosome 22, in turn shows frequent degradation once nf2 mutation takes place and therefore, a key root inculpated in meningioma tumorigenesis [8].

Studies have depicted that somatic mutations lead to meningioma in 60 percent cases that might be linked to the interactions of SMARCB1 with NF2 [9][10]. Specific mutational pattern is still a matter of research and in most cases frameshift mutation and non-sense mutations were reported for nf2 loss [8]. Patients of vestibular schwannomas are also linked to nf2 loss cases, and have high risk of developing multiple meningioma later.

NF2 deletion and degradation of merlin pathogenesis currently have no clinical insights or drugs in therapeutics due to major interactions of merlin in many signalling pathways. Some pathways associated with merlin are hippo pathway, rapamycin pathway, receptor tyrosine kinase.[11]

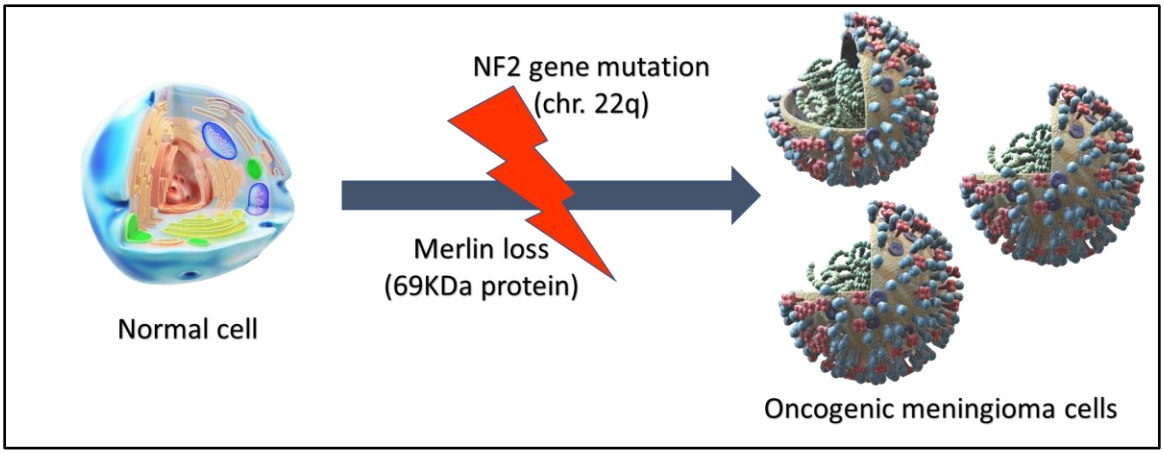

Fig. 1.1 NF 2 mutation and Merlin loss leading to progression of Oncogenic meningioma cells

1.2. Treatment Strategy

Meningioma treatment relies on a varied aggregate of variables, comprising the tumor's mass and location, its rate respective growth, and all-inclusive general health of a patient. The current strategy fighting meningioma includes radiation therapy, radiosurgery (gamma knife) as the tumor can be easily targeted, and surgical removal can also be done in the meningioma[2]. Radiation can also affect the surrounding cells and not applicable at sensitive area like around optical nerve, due to which patient body becomes weak and more prone to develop the tumor again.[12]

Other treatment approaches like immunotherapy, anticancer drugs have shown their overall inefficiency in fundamental treatment of cancer[13][14]. There have been prominent disadvantages that prove their inefficiency. Some of the major factors such as drug resistance, affecting not targeted cells, varied side effects and changes of developing toxicity could be the unwanted consequences.

1.3. Drug Repurposing Approach

In the present scenario, there is absence of FDA approved therapy drug for treating meningioma. However, we can use a drug Bevacizumab which is combination therapy and FDA approved for lung cancer in 2004 and glioblastoma in 2009. The Bevacizumab attach to VEGF and thereby inhibiting the VEGF to its cell superficial receptors and further leads to supression of angiogenesis [15]. Although the drug is less efficient, may have certain side effects and non-targeted delivery that accompanied its limitations.

Hence in search of classified drugs and potent treatment we turned towards the natural phytochemicals that are found in plant derived foods like grains, fruits and vegetables that includes phenolic compounds, flavonoids and carotenoids.[16] Several phytochemicals are analyzed to have remarkable anticancer, anti-inflammatory properties and are largely abundant and most importantly less toxic. Phytochemicals block the proliferation mechanics reducing oxidative stress by targeted inhibition and can arrest the cell cycle that ultimately downregulates tumor progression.

Here, we designate 50 flavonoids (phytochemicals) against PI3K/AKT signaling (target protein PI3-K) and evaluate them to develop probable lead agents in treatment of meningioma. Further conformation analysis was done with the help of ADME assay/profiling along with comparative examination of bioavailability score and their binding energy (ΔG).

1.4. Rationale of the Thesis

The primary objective of the specific study is to use molecular docking experiments to find novel phytochemical ligands and assess their capacity to control important molecular pathways implicated in meningioma development. This research holds significant implications for the development of novel curative strategies in controlling meningioma. The rationale for the thesis lies in the need for effective pharmacological interventions for meningioma treatment.

Patients frequently require multiple treatments based on their personalized bodily condition or health status. Since there are lacking FDA-approved drugs for exclusive treatment, we figured that there is an immediate requirement for drug development. Also, every patient is not competent or comfortable for enrolling on the surgical treatment process or chemotherapy due to a number of reasons like a weak immune system, physical health status, age, injuries, diabetic patients, side effects or allergies [17]. Patients with neurodegenerative complications also find it complex because the surgical actions could infer mutational changes and disturb neurological disorders more severely.[18], [19]

Therefore, to deal with difficult situation drug development would be a crucial step and we selected natural compounds to reduce any chances of side effects or toxicity. Also, this approach could lead to a targeted delivery (specific to P13K protein) that is only possible with therapeutic drugs.

Hence, the thesis emphasizes on discovering phytochemicals with satisfactory therapeutic ability to deduce effective drugs for the treatment of meningioma.

CHAPTER 2
LITERATURE REVIEW

2.1. Meningioma tumor in individuals with neurofibromin 2 (NF-2) gene mutations

Meningioma development in citizens with neurofibromatosis type 2 (NF2) is correlated with NF2 gene mutations [5]. The merlin employed as a tumor suppressor protein, which is synthesized by the NF2 gene, controls cell development by connecting the actin cytoskeleton with the plasma membrane proteins, thereby preventing cell division. Despite the fact that NF2 mutations are crucial for meningioma development, therapeutic applications have been constrained by merlin's intricate relationships with several partners and signaling pathways. Our comprehension of how merlin loss leads to meningioma pathogenesis has improved over these years by means of developments in next-generation sequencing in compliance with NF2-deletion-based models.

The neurofibromin 2 (NF2) gene's protein has long been considered to be a requisite for understanding the brain tumors. The moesin-ezrin-radixin-like protein (merlin), which is 69 kDa in size and belongs to the major Band 4.1 FERM gene family, encoded by NF2, which is found on longer arm of chromosome 22 (chr22q).[20]

2.1.1. Type 2 Neurofibromatosis (NF2) genetically influence meningioma

NF2 or neurofibromatosis type 2 provided the very first evidence that meningiomas might be genetically influenced. [21] The inactivation of both the copies of the NF2 gene culminates in the rare tumor condition, noted as NF 2. An estimated 1 in 33,000 people are born with this deformity [22]. Bilateral vestibular schwannomas, which occur in around 60% of NF2 cases, are one of its defining characteristics. But NF2 might manifest clinically in many ways, necessitating the expansion of additional diagnostic standards [23](Table-

2.1). NF2 is also linked to meningiomas, non-vestibular schwannomas, congenital cataracts and ependymomas among other tumor and disease types.[24]

Table 2.1. NF2 clinical diagnostic standards for neurofibromatosis

Diagnosis principle	Additional findings required
Unilateral vestibular schwannoma	Either two; meningioma, cataract, schwannoma, glioma
Bilateral vestibular schwannomas	none
Inheriting history of mutant NF 2	Any two; meningioma, glioma, cataract, schwannoma, neurofibroma
Meningiomas/ the multiple meningioma	Either two; neurofibroma, glioma, schwannoma, cataract

The mutational spectrum of NF2 is broad and primarily non-recurrent. The most frequent modifications are nonsense (39%), point and frameshift (27%) mutations, which cause a severe clinical pattern with a rise in the frequency of multiple and recurrent meningiomas. [25][26], [27] [28]. The significance of analyzing surgical specimens is emphasized by the possibility that mutations can only be found in the tumor tissue.

Around 50% of NF2 individuals develop spinal meningiomas[29][30] and about 20% develop intracranial meningiomas. It is typical to have various meningiomas with multiple stages of development and behavior patterns [31]. While the majority stay constant or expand slowly, others expand rapidly and demand periodic resection [32]. Patients having multiple meningiomas can exhibit many histological subtypes, which suggests early NF2 inactivation prior to subtype commitment. An average of 60% of instances of sporadic meningiomas, indicates NF2 deprivation or inactivation, indicating the significance of this gene across various meningioma subtypes. [33]

However, summarizing majority of studies by researchers on meningioma with respect to next generation sequencing and deeply analyzing the mutational landscape of highly severe (WHO II and III) and low grade meningioma (WHO I)[34], the all-inclusive results suggests that the progression of aggressive meningiomas requires chr22q/NF2 loss.

Even while NF2 alteration and chromosomal losses might be two separate mechanisms that operate in tandem, they are both early stages of tumor progression.[34]

2.2. Tumor suppressor gene- Merlin and interacting pathways

Significantly, merlin is a protein (69 KDa) encoded by NF 2 gene suggested to possess tumor suppressive actions. It is essential in preventing the development and growth of tumors. Merlin function can be lost as a result of NF2 gene mutations or inactivation, which can contribute to the emergence of diseases such neurofibromatosis type 2 (NF2) and specific forms of meningiomas[35]. Merlin affects cell adhesion and signaling pathways in addition to acting as a negative regulator of cell proliferation.

Merlin connects to actin microfilaments, transmembrane sense receptors, and intracellular signaling molecules to control a variety of crucial pathways governing proliferation and survival.[36] The hippo route, the PI3K/AKT/mTORC1 pathway and receptor tyrosine kinases (RTKs) are a few of these. [11][35]

2.2.1. Activated Merlin hindering Contact Resistance mediators

Merlin's tumor suppressor action is linked to its contact resistance or inhibition of proliferation. Merlin surges and dephosphorylates as cells expand in number [37]. A cell-to-cell adhering molecule and sense receptor for hyaluronan- an element of the extracellular outer matrix, CD44 interacts with active, dephosphorylated merlin. This contact blocks the development of cells. A variety of receptor tyrosine kinases (RTKs) involved in growth factor signalling are also connected to CD44. Since merlin generally restricts RTK availability on the cell membrane, merlin knockdown boosts RTK levels in schwannoma cells.[38][34]

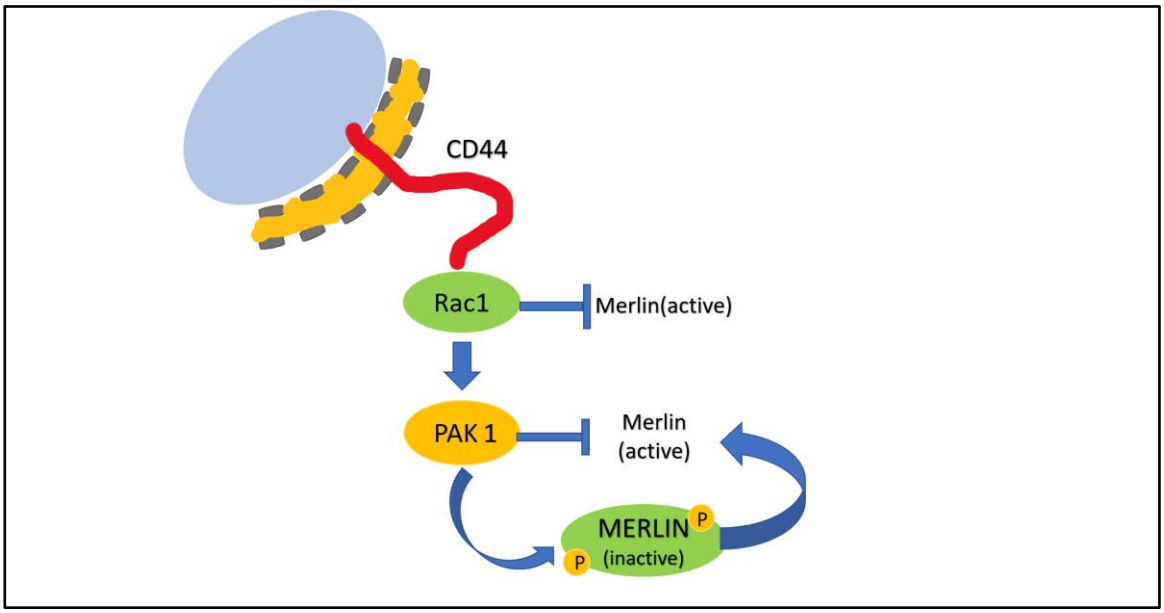

Fig. 2.1. Activated merlin inhibiting PAK1 and Rac1; contact inhibition mediators

2.2.2. Phosphorylation of YAP/TAZ complex Influencing Hippo Pathophysiology

The Hippo cascade constitutes intensive regulation by PPI, i.e., protein protein interaction (Fig.3)[39]. Merlin regulates the Hippo pathway, particularly in meningiomas. Hippo pathway is a conserved signaling route that controls cell over-progression and apoptosis to manage organ size in compliance with suppression of tumor formation [40]. It involves a cascade of kinase (SAV1, MST1/2 and LATS1/2) that phosphorylates complex subunit-YAP, a transcriptional coactivator.[41] Phosphorylation sequesters YAP in the cytoplasm, inactivating the transcription genes related to cell proliferation and cell survival [42]. As suggested by studies, merlin is suggested as a negative regulator, as it phosphorylates the cascade eventually leading to YAP domain phosphorylation and inhibits transcription.[43]

Here, the cascade interacts with P13K signaling which regulates the core elements through AKT [44]. We targeted the interacting pathway (P13K) which may assist the discovery of potent drugs that could readily be able to manage inhibitory actions simultaneously with both the influencing pathways and in turn constitute cytoplasmic degeneration in hippo pathophysiology. Pazopanib, Dobutamine, Dasatinib and Statins are few SMIs (small

molecular inhibitors) that could potentially deactivate YAP/TAZ localisation and block transcription complex (YAP/TAZ-TEAD) formation.[39]

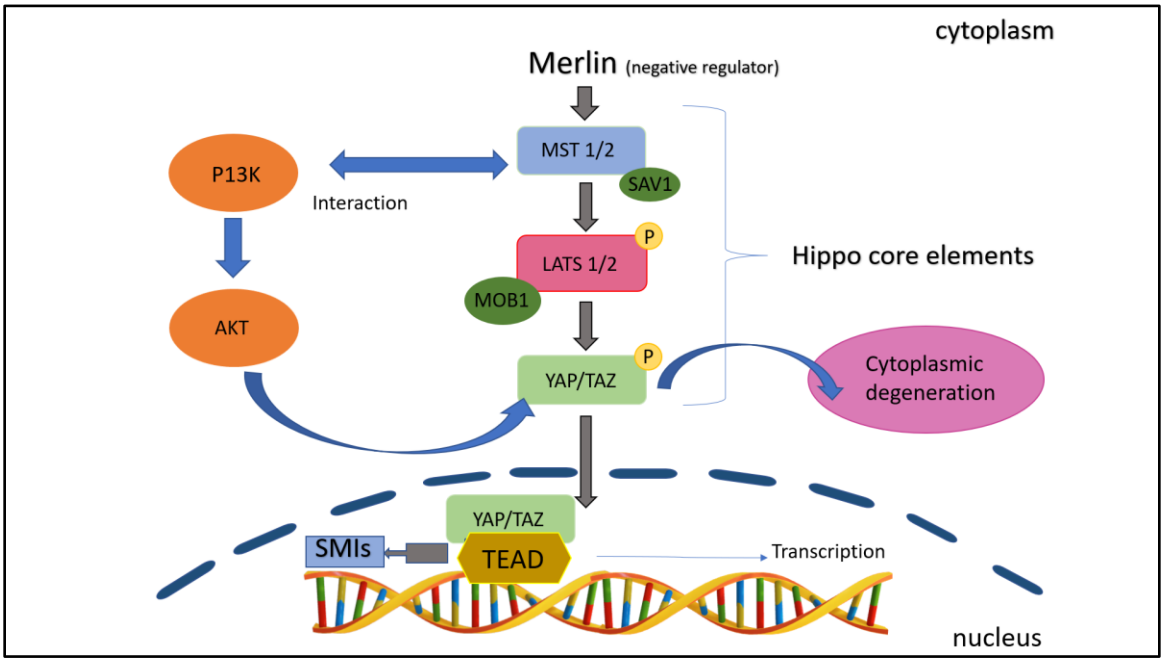

Fig. 2.2. Various interactions of YAP/TAZ complex within Hippo pathway

2.2.3. Role of mTORC 1 in tumorigenesis and relative inhibitors

Merlin regulates mTORC1 in a negative mechanism (Fig. 2.4.). mTORC1 is prominently activated in tumor/meningioma cells and tumors deprived of the merlin protein[45]. Studies showed that initial meningioma cell lines and tumors with merlin deficiency displays prominent activation of mTORC1, and that extrinsic production of wild-type merlin but not variant merlin inhibits mTORC1 route [46]. It's interesting to note that the usual PI3K/Akt and ERK signaling pathways are not required for mTORC1 activation in merlin-deficient cells. The specific non-canonical process through which the depletion of merlin triggers mTORC1 path is currently not fully understood. [34]

Inhibitors of mTORC 1 as a curative approach for a range of Cancer Types

The FDA has currently approved many orally accessible mTORC1 inhibitors, including temisirolimus and everolimus[45]. mTORC1 suppression is a recognized curative approach for a range of cancer types [47]. mTORC1 suppressors have been explored in a variety of (in vitro and in vivo meningioma) models and individuals despite the fact that the correlation of merlin and mTORC1 is still not completely understood. A meningioma cell line's survival and proliferation were considerably reduced by temsirolimus and everolimus treatment in a manner of concentration-dependence, and temisirolimus significantly downregulates tumor burden in xenograft models. [48]

Concurrent use of bevacizumab and everolimus led to an all-inclusive median progression-free cell survival of 22 months in a minor prospective phase 2 trial involving 17 individuals with progressing/resistant symptomatic meningiomas.[49]

2.3. Role of Akt in phosphorylation of merlin

The transformation between merlin's open or closed conformations were previously believed to be mediated by p21-activation kinase 1 (PAK1) or PKA (protein kinase A), as opposed to negative-phosphorylation, conciliated by MYPT1-PP1 [50][51]. Initial research showed that the closed, non-phosphorylated conformation of merlin was necessary for its tumor-suppressing action. However, thorough structural investigations of merlin employing fluorescence energy transfer analysis revealed that the manifestation of phosphomimic and dephosphorylatable S518A and S518D variation or hyperphosphorylation of Serine 518 had modest impact on the conformation of merlin[52]. However, the exact conformational change mechanism is still an interesting area of research for fellow scientists.[52]

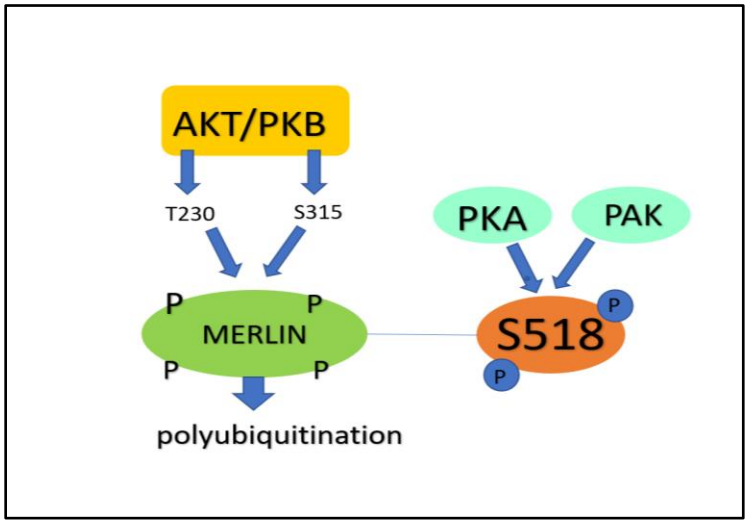

Fig. 2.3. Merlin polyubiquitination by Akt interaction

Merlin exerts growth suppression by a folded configuration which is closely regulated by certain protein kinases phosphorylation, including PKA, AKT and PAK. By interacting with PIKE-L, merlin reduces the activity of PI 3-kinase.

Researchers now demonstrate that merlin serves as a physiological substrate of Akt, and undergoes phosphorylation of both the T230 and S315 residues on merlin [53]. This hyperphosphorylation causes merlin to become polyubiquitinated and degraded by the proteasome by inhibiting its connection with PIKE-L and eliminating its folded shape. This

discovery shows that merlin/PI 3-kinase/PIKE-L negatively feeds back to Akt in tumorogenesis. S518 phosphorylation controls some of Merlin's proliferation-repressive action.[53]

As a result, merlin levels were low in tumors with high levels of phospho-Akt. Our observations thus indicate a unique function for Akt in boosting merlin's phosphorylation and eventual degradation. These findings suggest that PI 3-kinase/Akt pathway inhibitors could assist in recovering merlin activity in tumors, which is important because merlin loss has been associated with schwannomas and meningioma tumors.

2.3.1. Inhibitors of Akt preventing merlin loss

The Akt signaling inhibitors block the expressive activities of Akt eventually preventing Akt from merlin phosphorylation and supplementary downstream targets.[54] Therefore, potential inhibitors could play a role in regulatory actions associated with cell growth and could be a potent barrier to occlude tumorigenesis.[55]

Numerous Akt inhibitors, including LY2780301[56], capivasertib, AZD5363, triciribine[57], perifosine, natural lignans are small compounds and have been created and investigated in preclinical and clinical settings.[58]

It's crucial to remember that the specific Akt inhibitors and their modes of action can change based on the substance or medication being utilized [58]. Advance studies are being conducted in an attempt to improve the efficacy and security profiles of Akt inhibitors, which are also being developed and used in clinical settings.[59]

2.4. MERLIN SIGNALING- PI3K/AKT pathway: Therapeutic Target

PI3K (phosphoinositide 3-kinase) signaling has always been a significant pathway interacting with merlin protein [60]. The pathway itself functions for cell growth and proliferation in normal cells and merlin has been identified as an inhibitory protein that binds to PIKE-L and inhibits pI3K signaling hence arresting cell cycle. Merlin is a tumor suppressor although in cells with meningioma tumor, downregulation of merlin has been observed due to which the PI3K/AKT activation takes action and further activates mTORC(rapamycin), therefore resulting in progression of tumor cells.

Merlin is known to be a biological substrate of Akt as merlin is phosphorylated by it on both S315 and T230 remnants. Phosphorylation disturbs the conformation of merlin and makes it unable to couple with PIKE-L, leading to merlin polyubiquitination and degradation. [54]

Hence, inhibiting AKT stimulation by controlling the P13k pathway could be considered a potential therapeutic alternative heading towards the cure of meningioma. To accelerate towards this potential approach, we have undergone molecular docking via computational methods and explored the most relevant phytochemicals found naturally and performed docking studies with the target protein PI3K.

PI3K signaling can be managed, thereby controlling Akt activity which in turn becomes unable to perform polyubiquitination against merlin and merlin progression could readily stimulate the tumor suppressive activity.

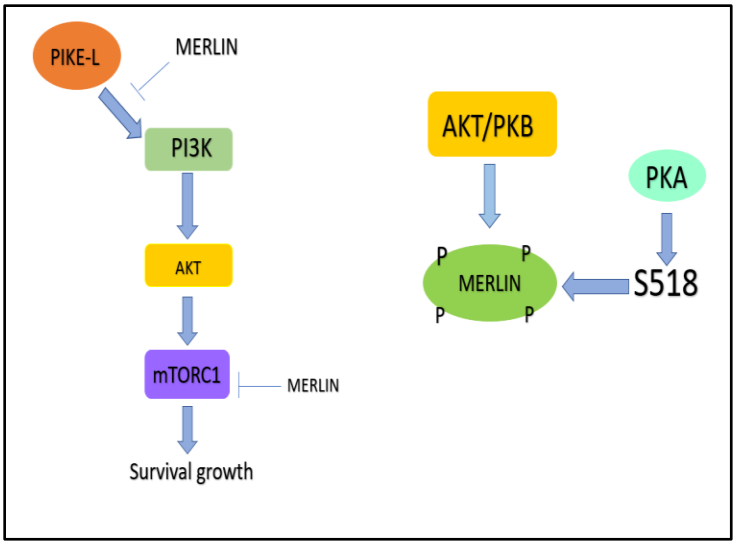

Fig. 2.4. Conventional merlin-PI3K pathway and Akt phosphorylation of merlin.

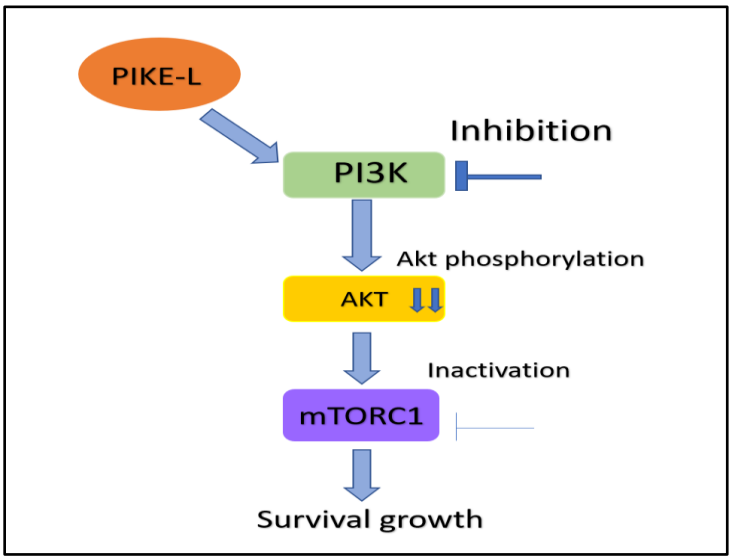

Fig. 2.5. PI3K targeted inhibition as a therapeutic approach.

2.4.1. Structure of P13K target protein

The phosphoinositide 3-kinase (p13k) protein is made up of dual subunits, the 85 kDa subdivision (p 85), and p 110 (110 kDa catalytic subunit) [61], which has four isoforms: alpha, beta, gamma, and lambda, with alpha being the most prevalent subunit.[62]

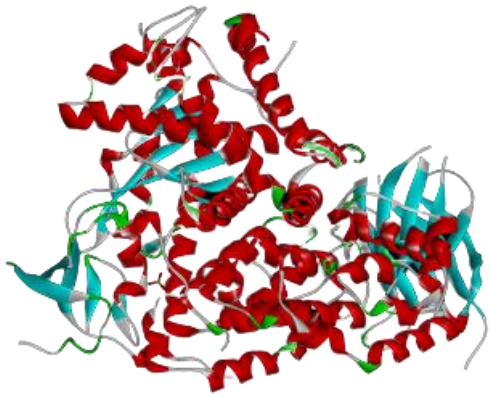

Fig. 2.6. Structure of PI3K from PDB[63]

2.4.2. Impact of P13K Inhibitors in drug repurposing approach

Since the specialized FDA approved drugs for meningioma tumor inhibiting P13K pathways are not commercially available, we intend to take this opportunity to attempt our best and research in the direction of certain drug discovery. However, our experiment could be a potential approach against the tumor as we experimented over natural compounds to discover the new insight for drug development targeting the P13K route inhibition.

Although several inhibitors of this pathway applied for other types of cancer are available.[64] One such inhibitor is Alpelisib, most commonly used against endocrine therapy for breast cancer[64], [65]. Alpelisib is an FDA approved drug for breast cancer listed in 2019[66]. Besides the approval, the drug constitutes various side effects like fatigue, diarrhea, rash, dermatitis and nausea.[66], [67]

CHAPTER 3
METHODOLOGY AND MATERIAL

3.1. Ligand selection and preparation

Fifty biological phytochemical composites of various plant sources were collected via research papers and public data available and downloaded- https://pubchem.ncbi.nlm.nih.gov (SDF, 3D conformer). Additionally, the ligands were turned into sybyl MOL2 format using Discovery studio visualizer software (https://discover.3ds.com/), which makes them competent for molecular docking according to the guiding principles by the docking software.

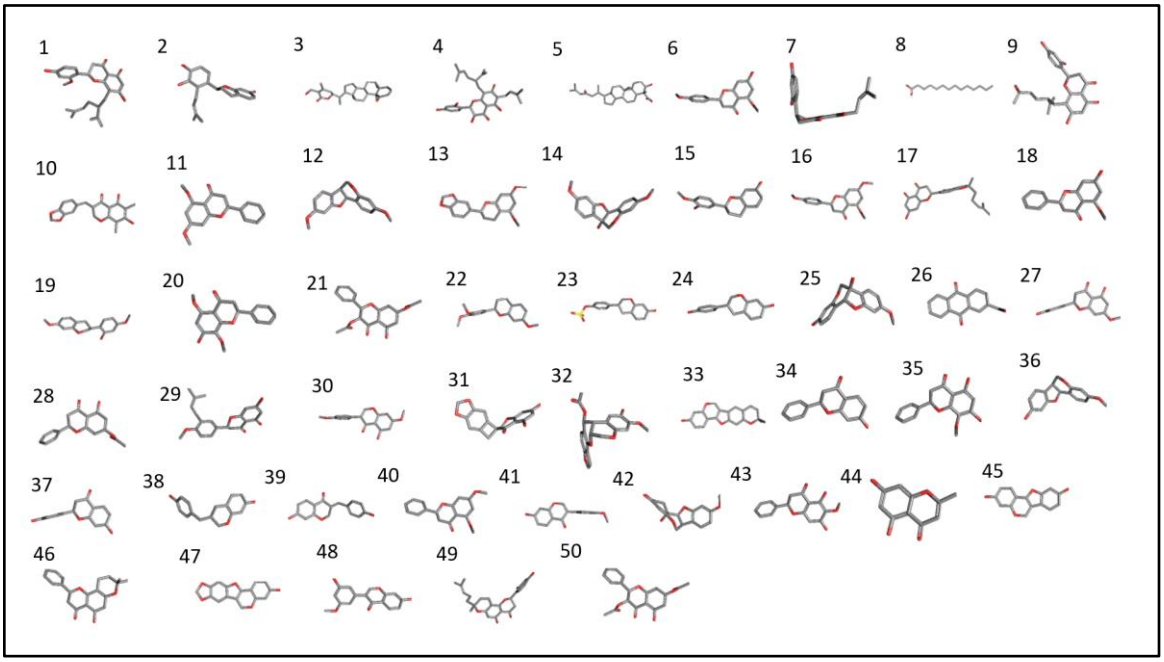

Fig. 3.1. Structure of 50 phytochemicals screening ligands examined

(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.

3.2. Protein Preparation

Target protein 3-Dimensional structure of PI3K (phosphoinositide 3-kinase) was selected and downloaded via. (RCSB) protein data bank website (http://www.rcsb.org/pdb/home/home.do) accompanied by PDB ID 3QJZ. [68]

Applying the discovery studio (Biovia DS Visualizer 2021) program, any unwanted ligands or H2O molecules were eliminated, retaining only the target protein of interest and subsidiary polar hydrogen atoms were appended to the protein. Once the heteroatoms, water and additional inhibitor removal was achieved, the resultant protein was preserved in PDBQT format. Performed energy minimization of protein to relax the structure and optimize any dynamic steric hindrances. Energy minimization is crucial to obtain stable protein conformation. The protein acquired was suitable for docking examination and the saved structure was retrieved for the test.

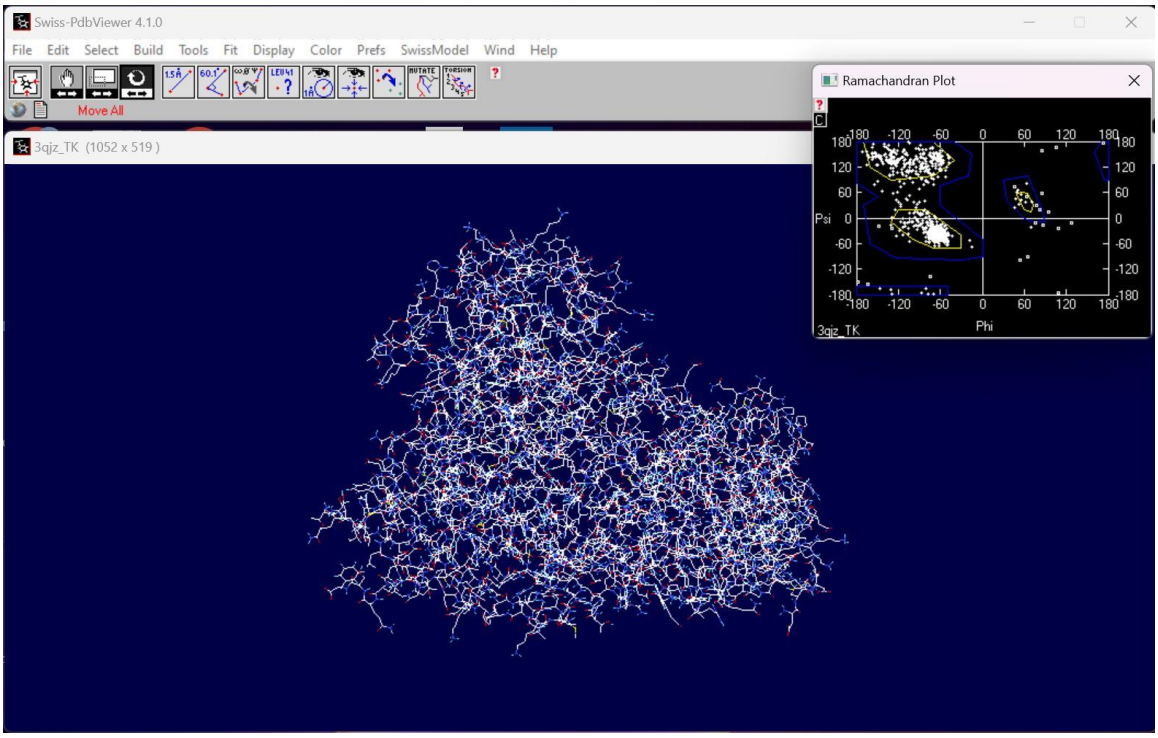

Fig. 3.2. Energy minimization assisted by Swiss PDB Viewer tool

3.3. Docking Analysis

Soon after the preparation of protein and ligands, the molecular docking was implemented using the publicly available software SwissDock (http://www.swissdock.ch/docking/).

The SwissDock is a computational docking tool which is widely used by researchers for virtual screening and ligand-protein or protein protein interactions processes and predictions. The specialized prepared protein pdb file was uploaded on the target gene site.[69]

The ligands were also uploaded at the ligand site on SwissDock. But a very crucial step before uploading the ligand is to remodel the downloaded sdf ligand file into sybl mol2 configuration otherwise further process could be hampered.

After carefully uploading both ligand and the target protein, the identifying title was provided at the naming section along with the email address and docking was initiated. We have performed the process multiple times for all the ligands because we can upload one ligand at the time at SwissDock for the assessment. Results were collected from the link provided at the email address after job termination.

Docking calculations were performed after collecting the final results on personal mail ID, by gathering information. The 3D structure was downloaded and assessed under UCSFchimerax 1.16 software (https://www.cgl.ucsf.edu/chimera/). The ADME analysis including binding affinity, inhibition constant and binding residue was conducted for detailed profiling of the results.

3.4. Lipinski's Rule of Five (RO 5)

To assess a compound's drug likeness—a significant step in the drug invention process that helps evaluate whether a given chemical is suitable to be orally active—Lipinski's RO5 is utilized. Bioinformatics (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp) and computational biology was utilized in this investigation to screen ligands for the RO5 [70]. This analysis was done on bioactive substances that had enough binding energies to become a candidate for therapeutic approach.

The characters assessed were the molecular weight of flavonoids, LogP values (Lipophilicity), variable number of hydrogen bond donors and H bond acceptors. Adhering to these guidelines or rules provided us with the first line of refinement from a bunch of compounds to prioritize higher chances of effective drug generation.

3.5. ADME Assay/ Analysis

Applying Swiss ADME (http://www.swissadme.ch/index.php) one can find out or evaluate the pharmacokinetics parameters which includes Absorption, Distribution, Metabolism and Excretion [71]. This is one of the crucial methods for drug analysis and development[72]. The medicine's pharmacokinetics might have shortcomings or problems that could affect the therapeutic effectiveness and safety of the treatment[73]. ADME profiling aids in identifying these potential problems or issues. Predictive modeling tools, in vitro experiments, and animal studies are several experimental and computational methods used to assess the ADME characteristics of drug candidates.[74] [75]

To perform ADME profiling, we used the SwissADME tool where we uploaded the canonical or SMILE structures of our compounds for assessment and retrieved the resultant data regarding the compounds. The data was then analyzed for further refinement. Thereafter, an informative table of satisfying compounds were curated leading to potential therapeutic drugs.[72], [75]

3.6. Bioactive score and bioavailability radar

Bioactivity score and bioavailability radar both were obtained from Swiss ADME (http://www.swissadme.ch/index.php) and its values show if the drug is orally bioavailable.[76] kinase inhibitors (KI), G-protein coupled receptors (GPCR), enzyme inhibitors (EI), ion channel modulators (ICM) and nuclear receptor ligands (NRL) are some of the properties examined.[77]

Several other parameters like solubility, lead likeness and synthetic accessibility were also taken into account. For this test, the canonical SMILE structures of phytochemicals from PubChem were obtained. [16] The substances meeting these requirements were used as lead substances and put through additional processes. [77]

CHAPTER 4
RESULTS

4.1. Evaluation of Molecular Docking outcomes

Loss of the nf2 gene plays a pivotal part in cancer development and progression.[78] This is becoming necessary towards making a drug that will inhibit p13K signaling so that merlin degradation will not occur. For this analysis 50 phytochemicals were taken and then their binding affinity between ligands and receptors were compared using binding energy.

Out of 50 phytochemicals, which are BBB permeable, 10 phytochemicals with more binding energy were listed. After docking, molecular weight, binding energy, and no. of hydrogen acceptor and donor were noticed and profiled. The binding energy of the 10 best phytochemicals falls under the range of -7.45 to -9.41. From these results, we attempted to provide a new insight into the availability of phytochemicals that can better interact and target the involving pathways and further opens up a new window for the possible treatment approach in tumor research.

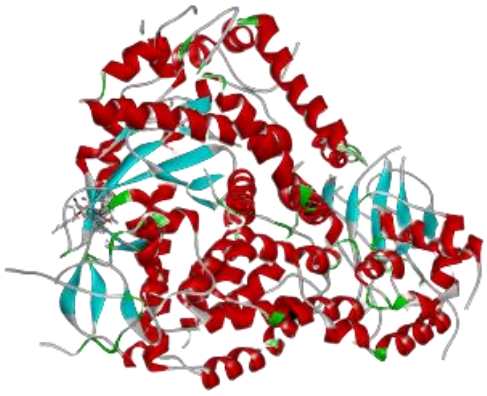

Fig. 4.1. Leachianone A 3D docking structure interaction (Most potent phytochemical assessed)

TABLE 4.1. Compared Phytochemicals against target protein

Phytochemicals	Mol. Wtg.	Binding energy (ΔG) (kcal/mol)	Hydrogen acceptor	Hydrogen donor
Leachianone A	438.52	-8.06	6	3
Kazinol U	326.39	-7.85	3	3
Withaferin A	470.61	-7.92	6	2
Kushenol M	508.61	-7.85	7	5
Gardenolic acid B	486.69	-7.98	4	3
Tsugafolin	300.31	-7.62	5	1
Cudraflavanone B	356.37	-7.47	6	4
Myristic acid	228.38	-7.45	1	1
Kurarinol	456.53	-9.41	7	4
Alpelisib*	270.28	-7.13	4	1

*Control

A list of flavonoids along with the most potent phytochemical assessed. Top ten phytochemicals and Lechianone A with -8.06 kcal/mol, constitutes greater binding energies compared to the control drug.

Leachianone A forms hexadic Van der Waals interactions and three conventional hydrogen bonds; LYS 214, ASN 217 and GLU 302. Two alkyl bonds were observed at LEU 297 and ILE 220.

Two pi-donor hydrogen bonds were observed at ILE 303 and ILE 125 and one pi-pi stacked interaction at PHE 221.

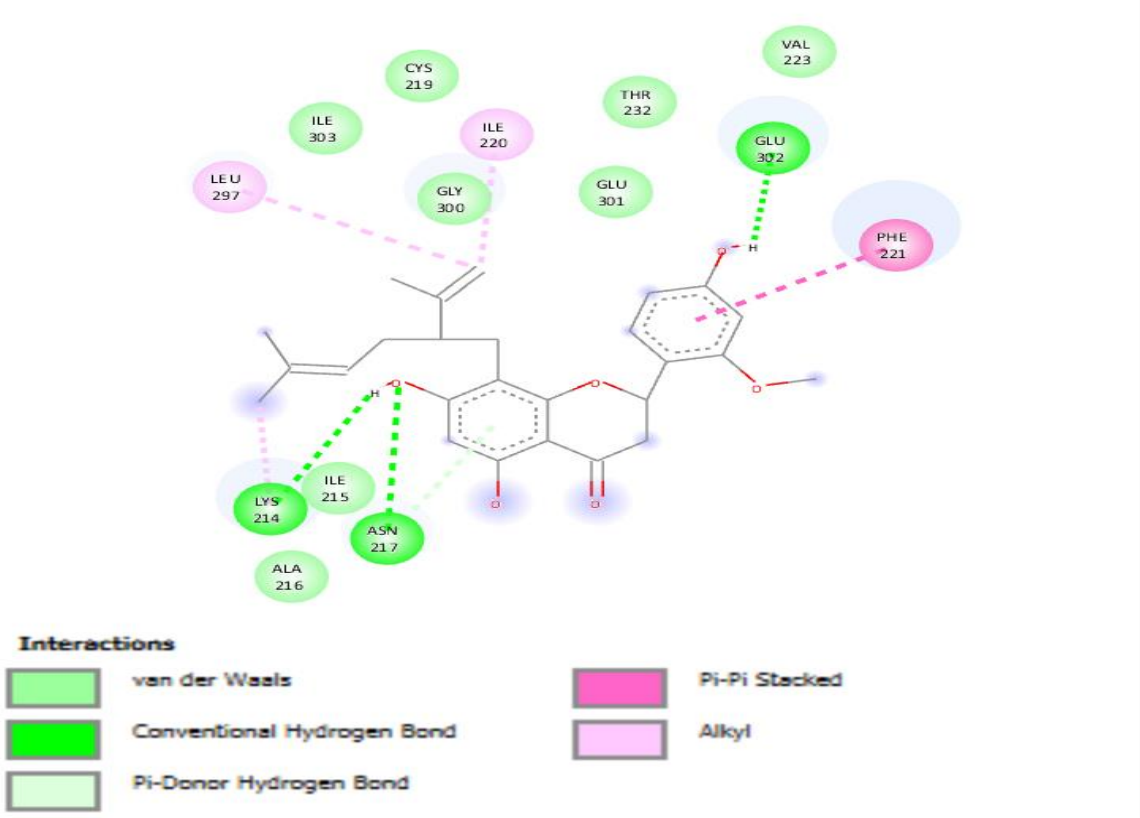

Fig. 4.2. Representation of 2D Interlinkage of Leachianone A with protein-P13K

4.2. Pharmacokinetic screening of phytochemicals

Ten phytochemicals were investigated for Lipinski rule and profiling ADME, then bioavailability radar structure and B-score were also obtained. Bioactive score comes out to be 0.55 for all except Gardenolic acid B.

This in-silico work provides the insight to measure or compare the drug likeness of the compound. All of the above-mentioned phytochemicals are water soluble, have a low bioactive score, and are non-toxic, making it simple to use them in a wet lab experiment. [79]The ADME and test provide the pertinent information regarding the safety of the chemical or biomolecule.[76], [80]

In terms of pharmacodynamics, the medicine created from these molecules can either be administered intravenously (direct injection) or consumed inside nanocapsules or

nanoshells, in which the molecule or molecules are enclosed in non-toxic nanomaterials.[81]

Also, we can use the stimulation techniques to confirm the credibility and safety assurance of the discovered medicine. This could be performed using GROMACS software (http://www.mdtutorials.com/gmx/).[82] This software creates an artificial cell line environment within the computer system which further tells us about the interaction of molecules and other susceptible chemical reactions.

TABLE 4.2. Using Swiss ADME, In-Silico pharmacokinetics of ligands

Phytochemicals	Binding energy	BBB test	Bioavailability score	Mol. refractivity	LOGP
Leachianone A	-8.06	P	0.55	125.34	3.38
Kazinol U	-7.85	P	0.55	94.87	2.54
Withaferin A	-7.92	P	0.55	127.49	3.39
Kushenol M	-7.85	P	0.55	145.76	3.86
Gardenolic acid B	-7.98	P	0.56	138.28	3.68
Tsugafolin	-7.62	P	0.55	80.51	2.45
Cudraflavanone B	-7.47	P	0.55	97.31	2.64
Myristic acid	-7.45	P	0.55	71.18	3.12
Kurarinol	-9.41	P	0.55	127.02	2.9
Alpelisib*	-7.13	P	0.55	74.02	2.13

*Control

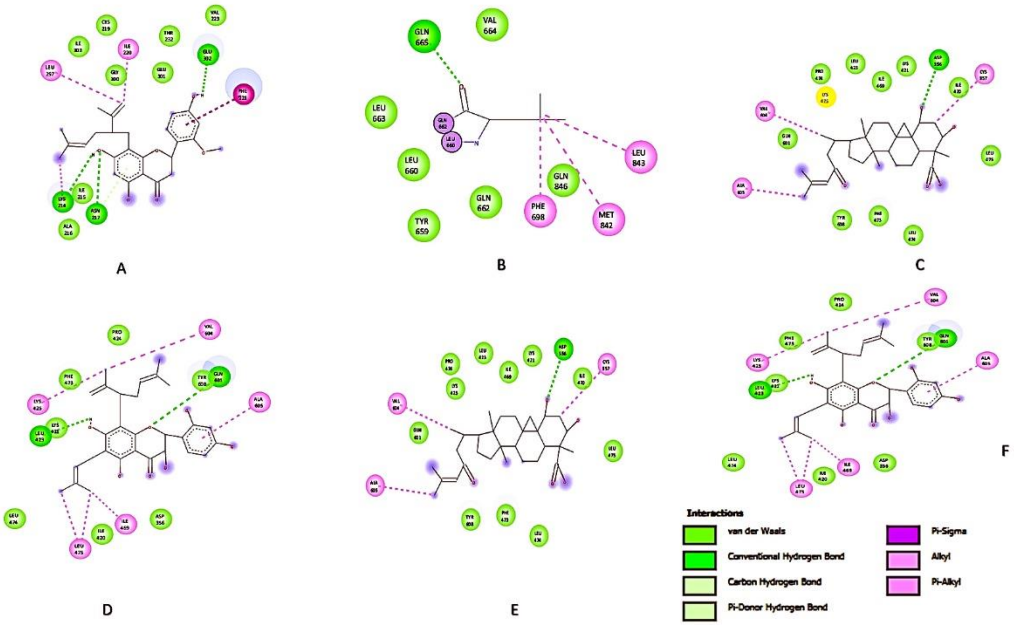

Fig. 4.3.1. 2D Interactions of phytochemicals with Target Protein; A) Leachianone A, B) Kazinol U, C) Withaferin A, D) Kushenol M, E) Gardenolic acid B, F) Tsugafolin

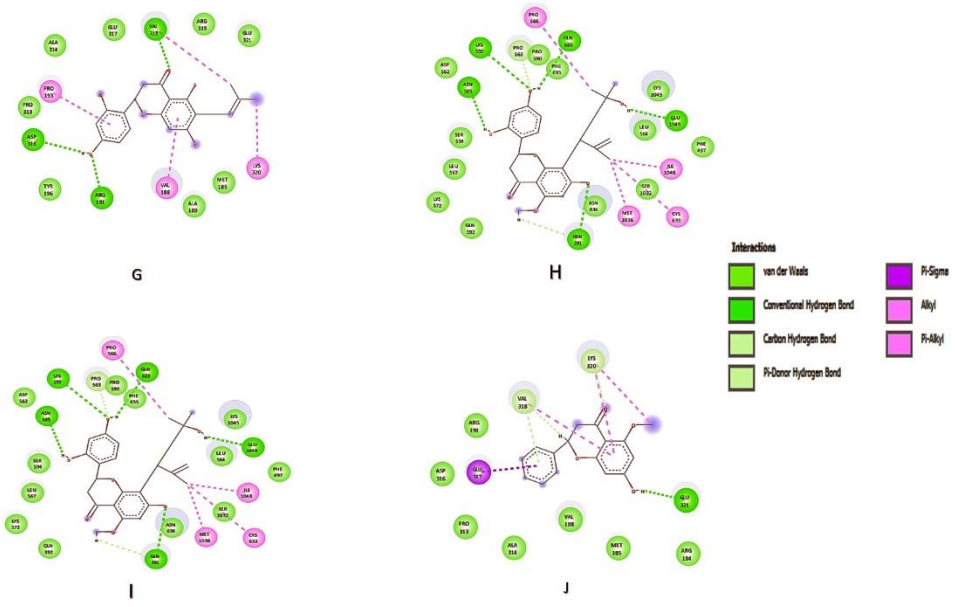

Fig. 4.3.2. 2D Interactions of phytochemicals with Target Protein; G) Cudraflavanone B, H) Myristic acid, I) Kurarinol, J) Alpinetin

4.3. Bioavailability Radar Examination

For the purpose of discovering lead compounds, bioavailability testing was implemented on the natural flavanoids retrieved out of the source IMPPAT database. Ten of the 50 examined compounds—Leachianone A, Kazinol U, Withaferin A, Kushenol M, Gardenolic acid B, Tsugafolin, Cudraflavanone B, Myristic acid, Kurarinol, Alpinetin—showed no lead likeness violations. To further evaluate the effectiveness of the binding, simulation can be applied to these molecules.

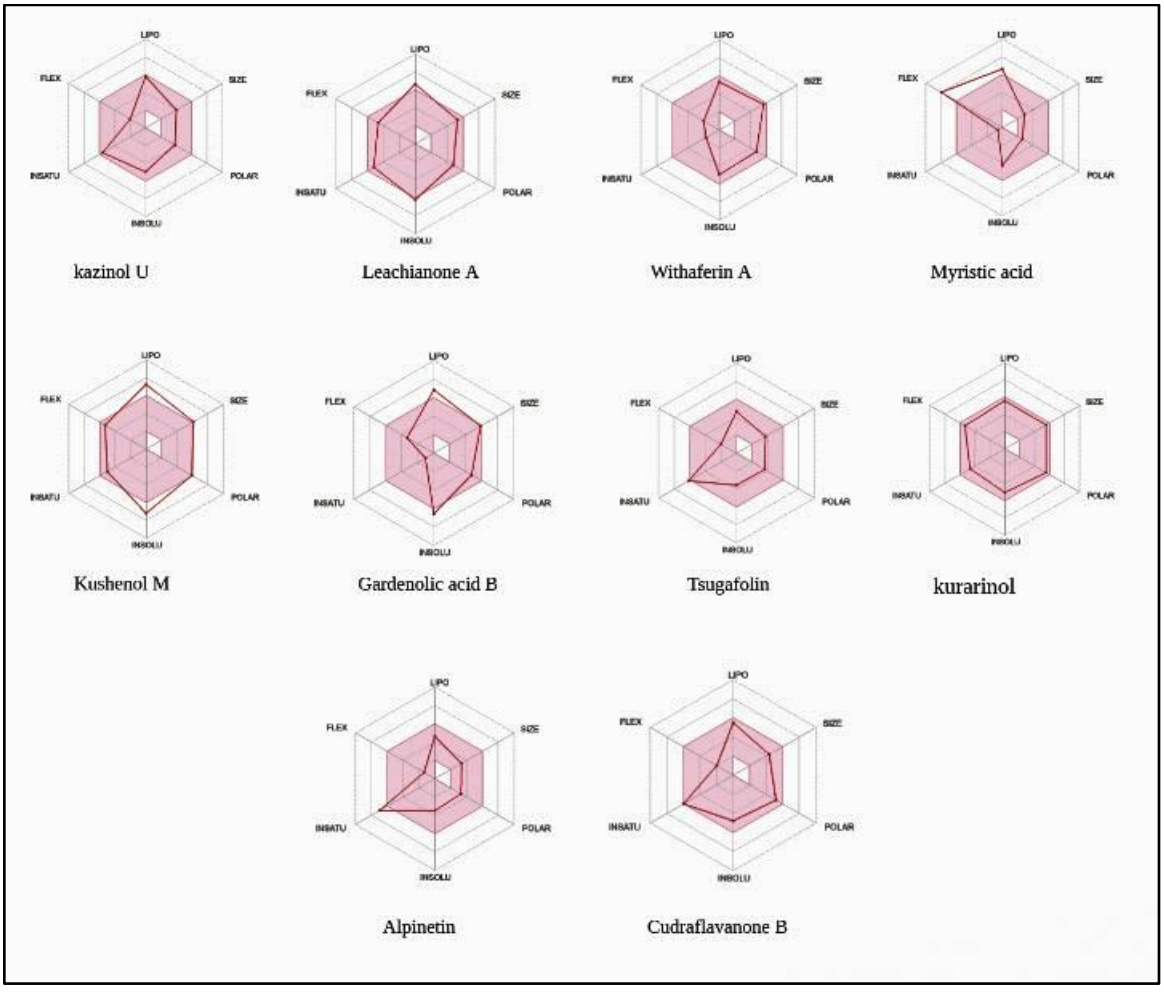

Fig. 4.4. Radar Plot of ligands- Natural compound bioavailability parameter

CHAPTER 5
DISCUSSION

The literacture data from Section 2 states the prominent correlation between neurofibromin 2 gene mutation and meningioma tumor development. Meningioma tumor has always been an interesting investing approach for the researchers due to its complexity of occurrence in varied range of population and also because of a number of unknown causes responsible for its progression. The study reveals vital and interesting facts about meningioma and provides a preliminary glimpse of their causative agents and their potential treatments.

The studies depict that the neurofibromin 2 gene mutation on chr. 22q shows satisfactory reasons to become a causative agent for meningioma progression.[5] NF 2 is a gene which encodes for merlin protein, which is a tumor suppressor located at the 69KDa site[8]. Merlin loss/ NF 2 loss has been observed in patients with meningioma. Although, even after diagnosing the importance of merlin in meningioma, there are absence of FDA-approved drug for the medicinal therapy or remedy of tumor. This is because merlin is a TSG complex interconnected to actin cytoskeleton and constitute a number of complicated pathways and therefore it is difficult to develop a targeted drug with effective therapeutic properties[36]. The pathways interacting with merlin are the Hippo pathway, mTORC1/ P13K/ AKT pathways, and RKTs (receptor tyrosine kinase)/ contact inhibition signaling.[11]

For uncovering potential therapy in suppression of the tumor, we have undergone a circumstantial analysis of merlin pathophysiology and interactions. The P13K pathways is concluded to be the most significant and important interaction of merlin functioning. The pathway functions for proliferation but merlin in normal patients regulates the following proliferation by inhibiting P13K activation, coupling with PIKE-L[83]. Merlin also interacts with mTORC 1 performing inhibition, to block the uncontrolled progression of cells[83]. Although patients with meningioma show merlin loss and hence the merlin becomes incompetent to regulate growth, which in turn leads to tumor.

Second phenomena to understand about merlin is that the protein also interacts with AKT subsequently and AKT in tumor patients disturbs merlin function and phosphorylate merlin at S315 and 130 remnants, which leads to merlin polyubiquitination. [54]

Hence, to tackle the stumbling situation, inhibiting P13k and controlling AKT is one such therapeutic approach that could take the experiment further[84]. The phytochemicals selections and Insilco molecular docking were performed to examine possible therapeutic natural compounds for the inhibition of the P13K pathway and in turn, restore progression of merlin. This thesis attempts to lead us to specific natural compounds that could become potential therapeutic drugs after intense research in dry and wet lab validity tests.

Analysis of studies demonstrated that targeting the P13K pathway can not only affect the AKT and its subsequent activation domains but also have an intense influence on the Hippo pathway whose interaction with merlin is well discussed in Section 2 Literature review.[44]

The P13K targeted inhibition could influence cytoplasmic degeneration in Hippo pathway and the discovered drug with the P13K target can also regulate Hippo activation and proliferation of cells[42]. Therefore, the target drug development approach is a multi-purpose attempt to discover an efficient tumor-suppressive drug.

Plants contain natural substances known as phytochemicals, which have traditional therapeutic properties without severe side effects or hypertoxicity. Due to their minimal risk relative to synthetic medications, these phytochemicals can be used to find prospective therapeutics with inhibitory effects on the target site.

The IMPPAT presented a list of natural compounds, which were refined using information obtained by ADME profiling to produce lead compounds that could potentially serve as substitutes or as inhibitors.

Molecular docking facilitates the binding affinity for the ligand phytochemicals and presented the most potent compounds such as Leachianone A, withaferin A, kurarinol and gardenolic acid B with greater binding affinity compared to the control. The bioavailability testing was also performed for the reliability and examination of the pharmacokinetics of

the selected compounds. Bioavailability radar was also plotted to check the oral intake and pharmacogenetic effects of the drugs.

Out of the ten best compounds, Leachianone A has been found to be the most potent phytochemical after intense examination and could lead us to an effective drug development for therapeutic purposes.

However further investigation and wet lab experimentations need to be performed before any clinical trials. The In-silico study could provide leading chemicals along the line but in-hand testing is equally crucial for validating step before approval of drugs for the patient's use.

CHAPTER 6
CONCLUSION

The computational molecular docking analysis is executed to inspect the potential phytochemicals activity to downregulate tumor progression through rectification of PI3K signaling. We found specific phytochemicals (such as withaferin A, leachianone A, kurarinol and gardenoilic acid B) which commands over drug likeness, therapeutic potential and minimum toxicity. This explains that the biological compounds have the capacity to bind with protein and suppression of the target that regulate cell proliferation and merlin degradation.

This elucidates that these phytochemicals can be an expressive catalyst for tumor suppressor merlin. However, further investigation is required to provide the pharmacodynamics of these phytochemicals. Also, the bioavailability score, Swiss ADME analysis and bioavailability radar scans could help in providing further insights in extended study of these compounds.

CHAPTER 7
FUTURE PROSPECT

The scores of ligand-binding types and linking affinities are computed using molecular docking techniques. It is challenging to estimate trustworthy ligand-binding relationships and mechanisms. The creation of the ligand and detection of targets for the already-existing candidate ligands are the two crucial computerized docking processes in the drug development sector.

In order to avoid the surgical procedure, we can immediately approach medications after doing docking and validating the results through wet lab analysis. Also, by using ADME/T assessment we could determine multiple features of the following compounds that can support wet lab experiments [71]. The repurposing of the phytochemicals discovered in our research could accelerate the diagnosis and treatment approach in meningioma. Also, virtual screening practices provide cost-effectivity because wet lab experiments are more expensive.

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APPENDICES

APPENDIX A: SUPPLEMENTARY INFORMATION

TABLE S1: Bioavailability examination parameters of all screened compounds from IMPPAT Database

Molecule	Binding Energy	Mol. Wtg.	Lipinski Violations	Bioavailability Score	Lead violations
4',7-Isoflavandiol	-6.7	324.4	0	0.11	1
EQUOL	-6.83	242.3	1	0.17	1
6alpha-Hydroxymedicarpin	-6.84	286.3	0	0.55	2
2-hydroxymethyl-anthraquinone	-6.86	410.48	2	0.55	2
Sakuranetin	-6.93	286.3	3	0.55	3
Pinocembrin 7-acetate	-6.95	298.3	1	0.55	1
4'-O-Methyllicoflavanone	-7.06	354.4	3	0.55	1
7-O-Methylbiochanin A	-7.17	298.3	1	0.56	1
Scillascillin	-7.18	312.3	1	0.11	1
12-Deoxo-12alpha-acetoxyelliptone	-7.19	396.4	1	0.55	0
Anhydrotuberosin	-7.19	320.3	0	0.55	0

Methylophiopogonanone A	-7.23	342.34	0	0.55	0
Chrysin dimethyl ether	-7.24	379.41	0	0.55	1
Homopterocarpin	-7.26	284.31	0	0.56	3
3-Hydroxy-5,7-dimethoxy-3',4'-methylenedioxyflavan	-7.27	330.3	2	0.56	1
(-)-Variabilin	-7.34	300.3	1	0.17	2
7,3'-Dihydroxy-4'-methoxyflavan	-7.34	272.3	1	0.11	1
Naringenin trimethyl ether	-7.37	314.3	1	0.11	1
Sanggenon N	-7.45	422.5	0	0.56	2
Alpinetin	-7.47	270.3	0	0.56	2
Kazinol U	-7.85	326.39	0	0.55	0
5-Hydroxy-7-methoxy-3-(4-hydroxybenzylidene) chroman-4-one	-8.03	287.63	3	0.55	2
Leachianone A	-8.06	438.52	1	0.55	1
2H-1-Benzopyran-7-yloxy	-6.53	240.3	1	0.55	2

5-Hydroxy-7,8-dimethoxyflavanone	-6.73	300.3	0	0.55	0
Isomedicarpin	-6.74	270.3	1	0.55	0
Liquiritigenin	-6.82	256.25	0	0.55	3
7-Hydroxy-3-(4-hydroxybenzyl) chroman	-6.9	321.42	0	0.55	3
7,4'-Dihydroxyhomoisoflavanone	-7.0	270.3	1	0.56	1
Dihydrobonducellin	-7.01	284.3	1	0.56	3
5,7-Dimethoxyflavanone	-7.09	284.3	1	0.56	1
Calycosin	-7.16	284.26	2	0.55	2
Sanggenol L	-7.23	422.5	1	0.55	2
5,7,3'Trihydroxy-4 'methoxy -8-prenylflavanone	-7.26	238.61	0	0.55	2
Isosativan	-7.27	286.3	2	0.55	3
5-Deoxycajanin	-7.30	284.3	0	0.55	3
1,11b-Dihydro-11b-hydroxymedicarpin	-6.64	288.3	0	0.55	0
Dihydrooroxylin A	-6.72	286.3	0	0.17	0
Noreugenin	-6.72	192.2	0	0.55	0
Anhydroglycinol	-6.74	254.2	1	0.55	1
Dihydroobovatin	-6.85	324.4	1	0.55	2

3-Hydroxy-8,9-methylenedioxypterocarpene= Dehydromaackiain	-6.96	420.43	1	0.11	2
7,3'-Dihydroxy-5'-methoxyisoflavone	-7.05	284.3	1	0.55	2
Kazinol A	-7.28	394.5	0	0.55	3
7-Hydroxy-5,8-dimethoxyflavanone	-7.30	300.3	0	0.55	3
3,7-O-Diacetylpinobanksin	-7.34	356.3	0	0.55	3
3',4',7-Trimethoxyflavan	-7.4	300.4	2	0.55	1
Cudraflavanone B	-7.47	356.37	2	0.56	0
Tsugafolin	-7.62	300.31	1	0.55	1
Kushenol M	-7.85	508.61	1	0.55	1
Kurarinol	-9.41	456.5	1	0.55	2

APPENDIX B: LIST OF PUBLICATIONS

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

  Accepted in: IEEE-BHTC, IEEE Bangalore Humanitarian Technology Conference - B-HTC 2023
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Dear Author:

We are pleased to inform you that paper submitted by your team with
Paper ID: 58
Title: **New Insight; Insilico study of phytochemicals as a Therapeutic Approach in Meningioma**
has been accepted (Minor revision required) for presentation between 24-26th March 2023 at JSS Hospital Mysore. Exact schedule will be sent shortly. At least one of the authors must register and physically present the paper to be considered for publication.

Please fill the registration form after paying the registration fee. Registration fee details are available here: https://www.bhtc-2023.ieeebangalore.org/registration.php
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3. References are not in IEEE Format."
4. Resolution of the Images should be increased.
5. Further cell line studies/animal studies is suggested for pharmacodynamics and pharmacokinetic studies

Reviewer 2:
1. Abstract should be 150 to 250 words.
2. Cite all the reference papers.
3. Research paper should have at least five sections Introduction, Related work or literature survey, Methodology, Re Discussion, Conclusion and Future scope
4. With the suggested method expected some results and comparison with different technology.

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in **IEEE Bangalore Humanitarian Technology Conference (IEEE B-HTC 2023)** organized by JSS Academy of Higher Education and Research, JSS Hospital, Mysuru, during 24th and 25th March 2023

Dr. Sudarshan Patil Kulkarni
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Professor, Dept. of ECE,
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CANDIDATE' DECLARATION

I, Rohan, Roll No., 2K21/MSCBIO/35, student of M.Sc. Biotechnology, hereby declare that the dissertation project titled " **New Insight: In-silico analysis of phytochemicals as a therapeutic intervention against meningioma"** which is submitted by me to the Department of Biotechnology, Delhi Technological University, Delhi in partial fulfilment of the requirement for the award of the degree of Master of Science, is original and not derived 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 "**New Insight: In-silico analysis of phytochemicals as a therapeutic intervention against meningioma**" which is submitted by **Rohan, 2K21/MSCBIO/35,** 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.

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PROF. PRAVIR KUMAR
HEAD OF DEPARTMENT
Department of Biotechnology
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