TARGETING SOX2 EXPRESSION IN GLIOBLASTOMA: INSIGHTS FROM COMPUTATIONAL ANALYSIS AND DRUG REPURPOSING

A Dissertation

Submitted in partial fulfillment of the requirement for the degree of

MASTER OF SCIENCE

in

BIOTECHNOLOGY

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May, 2024

ACKNOWLEDGEMENT

At the time of submission of my M.Sc. Dissertation I am grateful to the divine God who has given me the insight, fortitude, and perseverance to complete this endeavor. In addition to work, a lot of other people's support and direction are crucial to this project's success. Thus, I would like to use this opportunity to thank everyone who has contributed to the accomplishment of this project.

I would first want to express my gratitude to my mentor, Prof. Pravir Kumar, Department of Biotechnology, Delhi Technological University, for providing me with the chance to work on a project under his direction. I was able to finish this assignment because of his mysterious oversight, constant encouragement, and knowledgeable direction. I respectfully use this as a chance to thank him.

I want to express my profound appreciation to Ms. Mehar Sahu for her insightful observations and constant guidance. Her analytical comments on the project's problems have been crucial to its successful development.

There are not enough words to express my gratitude to Mrs. Neetu Rani, Ms. Shrutikriti Vashishth, and Ms. Shefali Kardam, Mr. Rahul Tripathi who have supported me in my endeavor and showed me confidence like family.

I would like to thank Mr. Jitender Singh and Mr. C.B. Singh, the technical personnel, for their assistance whenever needed. Finally, I would like to thank my family and friends for their unwavering support over this entire process.

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DECLARATION

I, Anistha 2K22/MSCBIO/09 student of M.Sc. Biotechnology hereby declares that the Dissertation Project entitled **"Targeting SOX2 Expression in Glioblastoma: Insights from Computational Analysis and Drug Repurposing"** 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 Science. This work is original and not copied from any source without paper citation. I have honored the principles of academic integrity and have upheld the normal student code of academic conduct in the completion of this work.

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CERTIFICATE BY THE SUPERVISOR

This is to certify that the Dissertation Project titled **"Targeting SOX2 Expression in Glioblastoma: Insights from Computational Analysis and Drug Repurposing"** which is being submitted by Anistha 2K22/MSCBIO/09, Department of Biotechnology, Delhi Technological University, Delhi in partial fulfillment of the requirement for the award of the degree of Master of Science is a record of the 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

Aim: This study aims to explore the potential of targeting SOX2, a critical transcription factor that contributes to the development of glioblastoma multiform (GBM), an extremely aggressive form of brain cancer. GBM poses a substantial obstacle because of its swift advancement and its resistance to standard therapies. Several transcription factors includingOCT4, NANOG, c-MYC, and SOX2 are crucial for the onset and course of GBM. SOX2 is particularly notable as a potential target for therapeutic intervention because of its vital function in glioblastoma stem cells (GSCs) and its participation in cell proliferation, survival, and self-renewal mechanisms. The study primarily examines the levels of SOX2 expression in GBM by employing the GEPIA2 platform. GEPIA2 stands for Gene Expression Profiling Interactive Analysis 2, which allows for the investigation of gene expression patterns in different cancer subtypes. Using GEPIA2, the analysis of SOX2 expression in GBM can offer valuable information about its potential as a target for therapy and its association with disease advancement and patient results. This research is being conducted to determine if downregulating SOX2 expression could be a viable therapeutic strategy. The computational technique of molecular docking will be utilized to forecast the interaction between SOX2 and potential small molecule inhibitors or modulators.
Additionally, the study seeks to investigate the concept of drug repurposing, which involves assessing the potential of existing drugs that have been approved for other uses to target SOX2 in GBM.

Result: We have found that tumor cells express SOX2 at a higher level than normal cells. We used GEPIA2 to analyze the expression level of SOX2 and predict disease-free survival, and overall survival, and the expression level is compared to other genes and transcription factors (TFs) such as TP53, EGFR, PTEN, c-MYC, SOX2, and more. SOX2 expression level is higher than other TFs. We have identified several potential drugs, including Cosmegen, Niraparib, Penfluridol, Dastinib, Paapverin, etc., that effectively downregulate the expression of SOX2.

Conclusion: SOX2 targeting is a potential treatment for GBM. Drug repurposing and molecular docking can identify drugs that overcome high SOX2 expression levels. These insights suggest a promising direction for cancer treatment research and development.

List of publication

1. Anistha and P. Kumar, "Revolutionizing Glioblastoma Treatment: In Silico Discovery Targets SOX2 Gene through Molecular Docking, Unveiling Potential of Cosmegen and Repurposed Penfluridol," 2024 International Conference on Automation and Computation (AUTOCOM), Dehradun, India, 2024, pp. 197-201, doi: 10.1109/AUTOCOM60220.2024.10486129. keywords: {Drugs;In vivo;Chemotherapy;Surgery;Stem cells;Curing;Radiation therapy;Glioblastoma;CSCs;SOX2;Drug repurposing;Molecular docking;Drug discovery;ArcA;Cosmegen},

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LIST OF ABBREVIATIONS

GBM	Glioblastoma multiform
IDH	Isocitrate Dehydrogenase
CSCs	Cancer Stem Cells
GSCs	Glioma-like Stem Cells
OCT4	Octamer- binding Transcription factor4
SOX2	Sex-determining region Y-box
KLF4	Krupple-like Factor 4
c-MYC	Cellular -Myc
TFs	Transcription Factors
GEPIA2	Gene Expression Profiling Interactive Analysis 2
SPECT	Single-photon emission Computed Tomography
CSF	Cerebrospinal Fluid
fMRI	Function- MRI
PET	Positron Emission Tomography
MRI	Magnetic Resonance Imaging
TCGA	The Cancer Genome Atlas
CNS	Central Nervous System
CT	Computed Tomography
RTK	Receptor Tyrosine Kinase
NF1	Neurofibromin 1
PDGFRA	Platelet-Derived Growth Factor Receptor α
DAXX	Death Domain Associated Protein
ATRX	Alpha- Thalassemia-Linked Mental Retardation
VEGF	Vascular Endothelial Growth Factor
SVZ	Subventricular Zone
NSC	Neural Stem Cells
siRNA	Small interfering RNA
shRNA	Short hairpin RNA

OS	Overall Survival
DFS	Disease-Free Survival
PDT	Photodynamic Treatment
SDT	Sonodynamic Treatment
CaMKIIγ	Calcium/Calmodulin-Dependent
NK1R	Neurokinin 1 Receptor
HBC	Hydrazinobenzoyl Curcumin
CDK4/6	Cyclin-dependent Kinase 4/6
Rb	Retinoblastoma
ArcA	ArcyriaflavinA
NASID	Non-steroidal anti-inflammatory Drug
GTEx	Genotype-Tissue Expression
SMILES	Simplified molecular input line entry system
BBB	Blood-Brain Barrier
LGG	Low-Grade Glioma
TMZ	Temozolomide
ECM	Extracellular material
CAM	Cell adhesion molecule
FAK	Focal adhesion kinase
EMT	Epithelial-mesenchymal transition

1. Introduction

The most prevalent primary brain tumor in adults is glioblastoma multiform (GBM), which accounts for 45.2% of invasive primary brain and central nervous system (CNS) cancer. With a median survival of approximately 15 months, GBM remains an incurable cancer (1). Five years after diagnosis, just 5.5% of patients were still alive. Different genetic mechanisms cause the development of primary and secondary subtypes of GBMs. These subtypes affect people at different ages and have varying outcomes. Although glioblastomas (GBMs) can develop at any stage of life, however at the age of 64 usually become noticeable. The incidence rate is greater in Caucasians than in other ethnic groups, and men are somewhat more vulnerable than women (1.6:1) (2). Lowe-grade astrocytomas, also known as grade II and III gliomas, can progress to glioblastoma, a particular kinds of brain tumor. It can also arise de novo or as a primary glioblastoma. It is also referred to as grade IV astrocytoma and it is the most prevalent type of brain tumor in humans. This tumor is very aggressive and grows rapidly (3). Depending on the existence or lack of certain gene mutations, GBM can be divided into two categories. The first category, which is also the most common, is called GBM with isocitrate dehydrogenase (IDH)-wild type. This type of GBM was previously known as primary GBM and accounted for over 90% of all GBM cases. The second category is called GBM with IDH mutation. About 10% of instances of GBM arise from a lower-grade diffuse glioma (4). Neoplastic cells known as cancer stem cells (CSCs) were first discovered in blood malignancies and then in solid tumors. They are also referred to as tumor-initiating progenitors due to their ability to self-renew and generate new tumors. CSCs have garnered significant attention in research because they play a pivotal role in chemotherapy and radiation therapy resistance, as well as tumor recurrence.GBM has a poor prognosis because of its aggressive nature and lack of response to treatment. Glioma stem-like cells (GSCs) are found in grade IV gliomas (5). The basic transcription factor network that preserves the pluripotency of CSCs is composed of Octabinding Transcription Factor 4, Nanog homeobox (NANOG), Sex-determining region Y-Box (SOX2), Cellular Myc (c-MYC), and Krüppel-like factor 4 (KLF4). To regulate the rate at which their targeted transcripts are expressed, SOX2 and OCT4 co-occupy many enhancers and promoters (6,7). SOX2 is a crucial factor in maintaining the ability of stem cells to self-renew and retain their pluripotency. Its protein and mRNA expression levels are higher in progenitor cells, which are the only brain tissues where SOX2 is significantly present. This suggests that SOX2 could be a potential target for grade IV gliomas (8). GEPIA2 analysis was employed for the detection of expression of SOX2, and to compare its level of expression between the tumor and normal cell. To improve GEPIA2's survival analysis functionality for individual genes, several key changes can be made. These include allowing customization of analysis parameters, integrating multimodal data, adding interactive visualization tools, and utilizing more advanced statistical modeling techniques. A user-friendly interface with cross-platform compatibility and collaborative features for result sharing and project management should be included, along with comprehensive documentation and customer support. These improvements would make GEPIA2 more versatile, user-friendly, and powerful for cancer research. Molecular docking is a computer modeling technique that shows fresh potential in cancer cell targeting through medication design and discovery initiatives (9). To create stable complexes with the least amount of free energy, ligands should be oriented in the best possible way with their target molecules, which could be found out by using molecular docking methods. When compared to other traditional approaches to cancer therapy, this computational drug design process might be considered a more complete strategy that is also more time and

cost-effective (10). The computational scan of a human glioblastoma revealed around 4883 docking sites for SOX2. Using a combination of natural and artificial substances that regulate SOX2 expression through its DNA-binding domain, as well as inhibiting SOX2 expression, can help regulate the structural makeup of glioma cells. This makes it more likely to target SOX2 or identify downstream targetable genes that can control GSCs and ultimately tumors (11). Finding FDA-approved medications with strong binding affinities to SOX2, a transcription factor linked to glioblastoma, raises the possibility of using these medications again to treat glioblastoma.

2. Review of Literature

2.1. Glioblastoma

Gliomas are the generic term for primary brain tumors, which are classified according to the cell considered to be their origin. The pathologists Percival Bailey and Harvey Cushing, who first described gliomas histologically and systematically in 1927, are credited with naming the word "glioblastoma" (12). These include astrocytic tumors (astrocytoma, anaplastic astrocytoma, and glioblastoma), mixed gliomas, oligodendrogliomas, and ependymomas. The majority of malignant primary brain tumors (around 80%) are the most frequent malignancies of the CNS (13). Astrocytomas are a type of brain tumor originating from astrocytes, a glial cell found in the cerebrum and other parts of the central nervous system. The name "astrocytoma" refers to the tumor's origin from astrocytes. These tumors can vary in terms of aggressiveness and malignancy, with glioblastoma multiforme being the most common and malignant type. It is responsible for almost 60% of all adult brain tumors and is a fatal illness with an inferior prognosis, even with the wide range of contemporary therapies available (14). Patients diagnosed with glioma typically have a median survival of 14-15 months. Currently, the acknowledged international standard for glioma diagnosis and nomenclature is the World Health Organization (WHO). Histological criteria are used to classify gliomas into grades I through IV according to their level of aggressiveness. Surgery is an option for treating lesions identified as grade I gliomas since they have limited capacity to proliferate. Grade II to IV gliomas, however, are extremely invasive and aggressive. WHO Grade IV GBM is the most aggressive, invasive, and undifferentiated kind of tumor. According to the WHO classification system, a brain tumor cannot be recognized as GBM unless necrosis is present, which is one of the characteristic features of GBM (15). Malignant gliomas account for 2.5 percent of cancer-related fatalities and rank third among cancer-related causes of death in individuals between the ages of 15 and 34. The Western world has a higher incidence of gliomas than less developed countries. This might be due to differences in diagnosing technique, a lower number of glioma cases being reported, and limited access to care. GBM exhibits a very variable macroscopic appearance, characterized by many areas of bleeding, necrosis, and gelatinous and cystic regions. One characteristic that sets GBM apart from other types of cancer is the tumor’s irregular external appearance. Certain tumor sites seem solid and white, while other areas with tissue necrosis appear fuzzy and yellow. Certain regions of the tumor exhibit obvious cystic degeneration and hemorrhage(6). GBMs can develop in the brain stem, cerebellum, and spinal cord, however, they are nearly exclusively seen in the brain. Sixty-one percent of all primary gliomas are located in four brain lobes: parietal (13%), occipital (3%), temporal (20%), and frontal (25%). Clinical manifestation can cause loss of vision, feeling numbness, extended vulnerability, or altered language depending on the functional role of the damaged brain region.

The first symptom that most patients experience is headache, but seizures only happen in around 25% of cases (16). Glioblastoma treatment involves a multidisciplinary approach due to its complexity and aggressiveness. Glioblastoma is first treated with surgery to remove the tumor, and then radiation therapy and temozolomide (TMZ) are administered. Temozolomide is a chemotherapeutic drug that works by damaging the DNA of cancer cells. Despite these treatments, GBM remains a challenging disease due to its complexity and heterogenetic nature (17). Despite the available treatments, very few people can survive after developing GBM. Therefore, there is an urgent need for new targeted treatments to address this disease.

2.2. Glioblastoma Imaging

Brain tumors are abnormal growths that arise from uncontrolled cell proliferation in the brain. They lack physiological function and cause abnormal neurological symptoms by enlarging, compressing, and swelling the brain. They can be classified as primary, meaning they start in the brain, or metastatic, meaning they spread to other areas. Gliomas, which include low-grade oligodendrogliomas or astrocytomas and high-grade GBM, are the focus of most research because of their common incidence. To identify, segment, and classify tumors and to aid in treatment planning, neuroimaging modalities such as positron emission PET, MRI, CT, single-photon emission computed tomography (SPECT), and magnetic resonance spectroscopy (MRS) are crucial to the diagnosis. A magnetic resonance imaging (MRI) or computed tomography (CT) scan may be part of the initial diagnostic imaging process (18). Almost all GBMs have asymmetrical masses with a prominent band of increase and an underdeveloped core of necrosis on MRI when enhanced with gadolinium contrast. MRI excels in lesion detection and localization, while CT is superior for calcification assessment. T2 highlights fluid-filled areas, T1 separates healthy tissues, and T1-Gd helps delineate tumor borders. These three unique MRI modalities offer complementary information for the diagnosis. An all-encompassing diagnostic approach is provided by FLAIR pictures, which further distinguish edema from cerebrospinal fluid (CSF). Using blood oxygen level-dependent methods, functional magnetic resonance imaging (fMRI) further identifies expressive cerebral cortex activities (19). Additionally, more sophisticated functional imaging modalities like magnetic resonance spectroscopy and diffusion tensor imaging provide additional vital information on the biochemical makeup and tissue microstructure. This improved comprehension makes a substantial contribution to the development of effective treatment plans and accurate diagnostic evaluation.

Table 1: Summarizing the Neuroimaging techniques for GBM detection

Neuroimaging Technique	Description	Reference
Magnetic Resonance Imaging (MRI)	It gives a thorough representation of the anatomy of the brain, which helps distinguish between tumors and healthy tissue.	(20)
Computed Tomography (CT) Scan	This method produces a finely detailed cross-sectional picture of the brain using X-rays.	(21)
Single-Photon Emission Computed Tomography (SPECT)	Assess blood flow and metabolism in brain tumors.	(22)

Positron Emission Tomography (PET)	Detect metabolic activity of cells. Useful for assessing tumor extent and response to treatment.	(23)
Diffusion Tensor Imaging (DTI)	Measure water molecule diffusion, assisting in surgical planning for tumor removal.	(24)
Functional Magnetic Resonance Imaging (fMRI)	Detect variations in blood flow, which can help locate tumor-affected parts of the brain.	(25)
Magnetic Resonance Spectroscopy (MRS)	Analyses the chemical composition of tissues, providing insight into tumor metabolic activity.	(26)
Perfusion Weighted Imaging (PWI)	Assesses blood flow in the brain, aiding in differentiation between tumor and healthy tissue.	(27)
Dynamic Contrast-Enhanced MRI (DCE-MRI)	Involves contrast agent injection to enhance visualization of tumor vascularity and permeability.	(28)
Diffusion-Weighted Imaging (DWI)	Sensitive to water molecule motion changes, indicating tumor presence.	(29)

2.3. Molecular and genetic mechanism

The complex genetic profile of GBM was revealed by the sequencing of over 600 genes from over 200 human tumor samples through genomic profiling and The Cancer Genome Atlas project (TCGA). This process also identified a set of three core signaling pathways that are frequently activated: the retinoblastoma pathway, the receptor tyrosine kinase/Ras/phosphoinositide 3-kinase signaling pathway, and the tumor protein p53 pathway (30). Most primary and secondary GBMs include changes in these pathways that lead to unchecked cell growth and increased cell survival, as well as the tumor cell's ability to evade senescence, apoptosis, and cell-cycle checkpoints. It has also been established that primary and secondary gliomas differ molecularly or in terms of gene expression patterns. when CSCs are isolated using putative stem cell markers (such as CD133 and ALDH1) that quickly alter in response to biological circumstances. Using CD133 as an example, researchers show how SOX2 expression and cancer stem cells in several tumor cell types are related. It was specifically shown that the CD133+ cell population, rather than the CD133- population, had the ability for brain tumor cells in culture (non-adherent tumorspheres) to self-renew. In brain tumor cells, CD133 has been demonstrated to affect MAPK/ERK signaling (31). Glioma cells exhibit a strong affinity for extracellular matrix (ECM), including the protrusion of a leading process, which precedes the translocation of the cell nucleus during migration. The interaction between glioma cells and ECM is mediated by cell-cell and cell-matrix receptors such as integrins, cell adhesion molecules (CAMs), and cadherins. Glioma cells express various integrin family members, among which beta-1 integrin plays a central role in invasion. Activation of beta-1 integrin triggers signaling cascades, including the activation of tyrosin kinase-like focal adhesion kinase (FAK), which further promotes glioma invasion (32).

2.3.1. Disrupted common pathways in GBM

It is widely recognized that one of the most frequent genetic abnormalities in malignant gliomas is the activation of oncogenic pathways, such as those involving receptor tyrosine kinases (RTKs). Since most GBMs show activation of the RAS–MAPK and expanded PI3 K–AKT–mTOR signaling pathways, these are thought to be common oncogenic changes in these tumors (33). Additionally, it is generally observed that Isocitrate dehydrogenase 1/2 (IDH1/2) mutations exhibit a negative association with Epidermal growth factor receptor (EGFR) gene amplification and monosomy of chromosome 10, changes that are more frequently observed in primary GBMs. While expansion or alteration of the Epidermal growth factor receptor (EGFR) gene characterizes the classical subtype, mutations in neurofibromin 1 (NF1) are primarily identified in the mesenchymal subtype, while mutations in Platelet-derived growth factor alpha (PDGFRA) or IDH1/2 primarily characterize the proneural subtype. Somatic modifications in the death domain-associated protein (DAXX) of the histone H3.3-alpha-thalassemia X-linked mental retardation protein (ATRX) chromatin remodeling process that results in modifications to the chromatin architecture and is important in the pathophysiology of juvenile GBM in around 44% of tumors (34,35).

Table 2: List of pathways disrupted in GBM

Pathway	Description	Reference
RTK/RAS/PI3K Pathway	Dysregulation of RTK signaling leads to activation of downstream pathways promoting cell proliferation, survival, and angiogenesis.	(36)
TP53 Pathway	Mutation in TP53 impairs regulatory functions in cell cycle control, DNA repair, and apoptosis.	(37)
RB Pathway	Mutation in Rb disrupts normal cell cycle progression, leading to uncontrolled cell proliferation.	(38)
TGF-β Signaling Pathway	Dysregulation TGF-β signaling pathway promotes GBM invasion, immune evasion, and epithelial-mesenchymal transition (EMT)	(39)
Hedgehog Signaling Pathway	Dysregulation of the Hedgehog signaling pathway contributes to GBM progression in promoting cell proliferation, survival, and stem cell maintenance.	(40)
Wnt/β-Catenin Pathway.	The Wnt/β-catenin signaling pathway is abnormally activated, which encourages glioma cell proliferation, invasion, and stem cell characteristics.	(41)
Notch Signaling Pathway	Dysregulation of Notch signaling contributes to GBM pathogenesis by promoting cell proliferation, survival, and stem cell properties.	(42)

Angiogenesis Pathways	Aberrant signaling through VEGF and its receptors promotes pathological angiogenesis in GBM.	(43)
EGFR Signaling Pathway	The EGFR signaling pathway is frequently dysregulated through mutation or amplification, promoting cell proliferation and survival.	(44)
DNA damage response and repair pathways	Defects in DNA damage response and repair pathways contribute to genomic stability and therapeutic resistance in GBM.	(33)

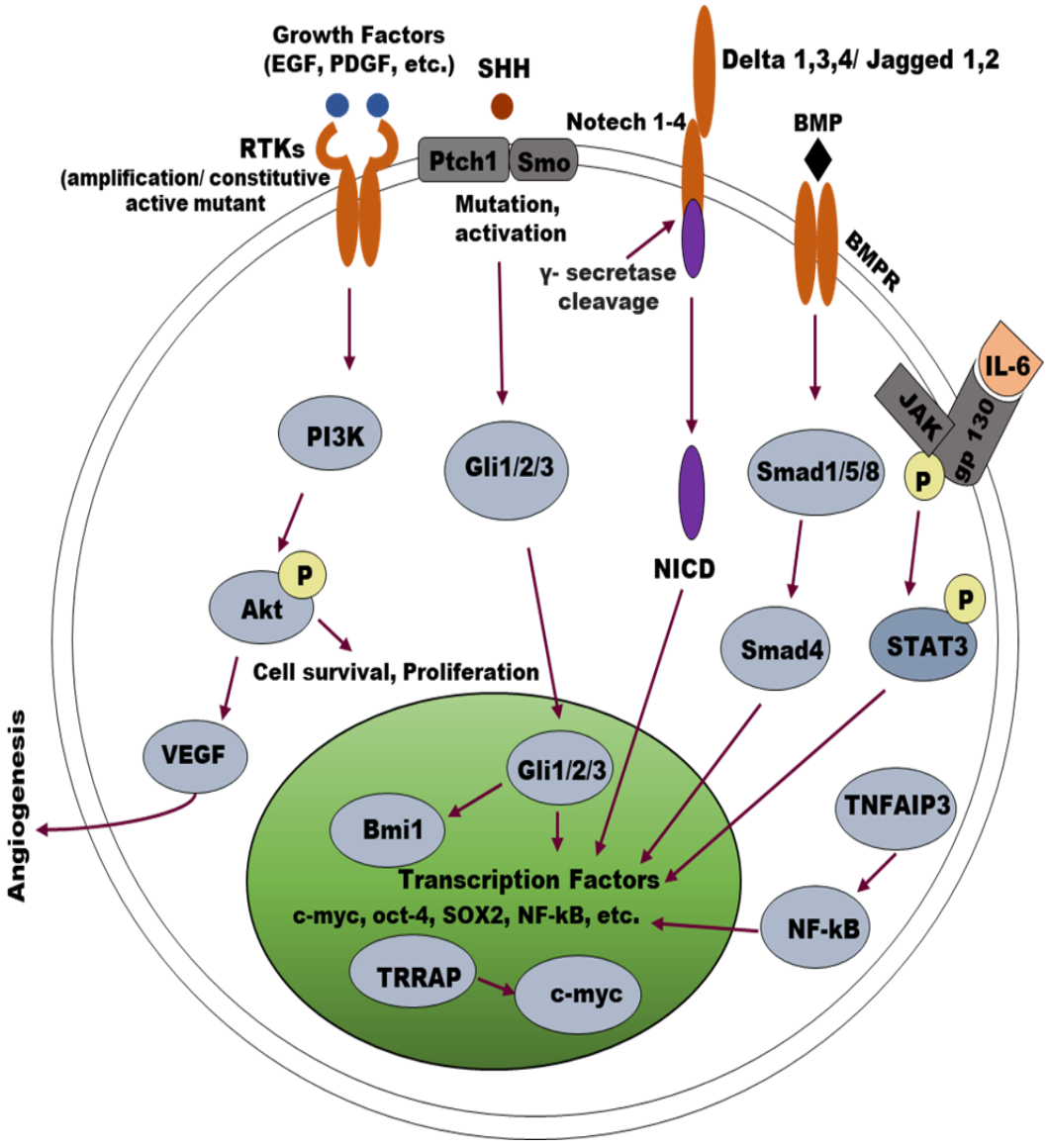

Fig.1. GSCs signaling pathways. Ptch: patched gene; SHH: Sonic hedgehog homolog; BMP: bone morphogenetic proteins; BMPR: BMP receptor; STAT: Signal transducers and transcription activators, Smo: Smoothened gene; TNFAIP: Tumor necrosis factor alpha-induced protein and TRRAP: transformation/transcription domain-associated protein. The activation of these pathways is responsible for the release of various Transcription factors (TFs) such as SOX2, OCT-4, NANOG, etc. that can result in cell proliferation and cell survival.

2.4. Metastasis of cancerous cells

Cancer cells can spread from the primary tumor to form secondary tumors, known as metastasis. This process has three stages: invasion, intravasation, and extravasation. In the invasion stage, cancer cells break down structural barriers and secrete enzymes. They enter the bloodstream via intravasation and exit it via extravasation, forming secondary tumors (45). The ability to regenerate into a range of malignant cells exists in the cancerous stem cells (CSCs) that propel the growth and dissemination of tumors. In addition to having the ability to repair damaged DNA. CSCs can alter their phenotype to evade the immune system's reaction. Treatments like radiation therapy and chemotherapy are rejected by CSCs because they enter a quiescent phase. Multiple entities have described Glioma stem cells (GSCs). GSCs have been demonstrated to develop into astrocytes, oligodendrocytes, and neurons, even though they do not necessarily need to replicate natural differentiation cascades and frequently have abnormal differentiation patterns with numerous lineage markers (46). Vascular endothelial growth factor (VEGF) is expressed at high levels by GSCs to encourage tumor development. Hypoxia promotes GSC self-renewal and even expands the GSC population. Furthermore, it sustains the development, multiplication, and survival of cancerous cells. GSCs and other types of glioma cells exhibit the Warburg effect. This refers to the preference for aerobic glycolysis over oxidative phosphorylation, which is the more common metabolic pathway in normal cells (47). Tumors that are exposed to high levels of hypoxic conditions exhibit higher rates of metastasis.

2.5. Role of SOX2 in Glioblastoma Pathogenesis

It has been found that SOX2 is expressed in various types of cancer, whether at the protein or RNA level. SOX2 is a member of the SOXB1 group (together with SOX1 and SOX3), which is required for the maintenance of the embryo before implantation. Several studies have identified an overexpression of SOX2 in GBM patient samples. It was first found elevated in 90% of human biopsies studied at the mRNA and protein level. Concerning a putative role of SOX2 controlling cell division modes, recent work showed that the inhibition of the FACT chaperone complex in GSCs promotes their asymmetrical division in a process that involves SOX2 downregulation (48). SOX2 mRNA is shown to be higher in numerous tumors compared to normal tissue, according to data from TCGA. Sox2 is a protein that is expressed extensively in the subventricular zone (SVZ) of growing mouse brains. It is also present in neural stem cells (NSC), neural progenitors, and immature astrocytes. When the brain is damaged, Sox2 becomes re-expressed in astrocytes that are going through cell division. The SOX2 gene is overexpressed in several tumor types (49). Sox2 regulates transcription in a context-dependent manner, and its effect on malignancy varies depending on the type of cancer. Among the important SOX-related proteins, SOX2 has a prominent expression in embryonic stem cells.SOX2, in combination with KLF4, OCT4, and c-Myc, is a crucial transcription factor whose overexpression may promote pluripotency in both mouse and human somatic cells. Two factors - SOX2 and OCT4 - are necessary to produce induced pluripotent stem cells from human cord blood cells (50). Moreover, SOX2 has been linked to several malignancies, such as cancer of the stomach, breast carcinoma, prostate cancer, and neuroendocrine cancers. In malignant gliomas, SOX2 is overproduced, but in healthy cells, it is barely noticeable. SOX2 levels change during tumor progression, and elevated level of SOX2 is associated with a poor prognosis. Higher levels of SOX2 have been linked to increased recurrence rates in sinonasal carcinomas, while rectal cancer patients with elevated SOX2 levels exhibited significantly shorter disease-free survival after chemoradiotherapy (51).

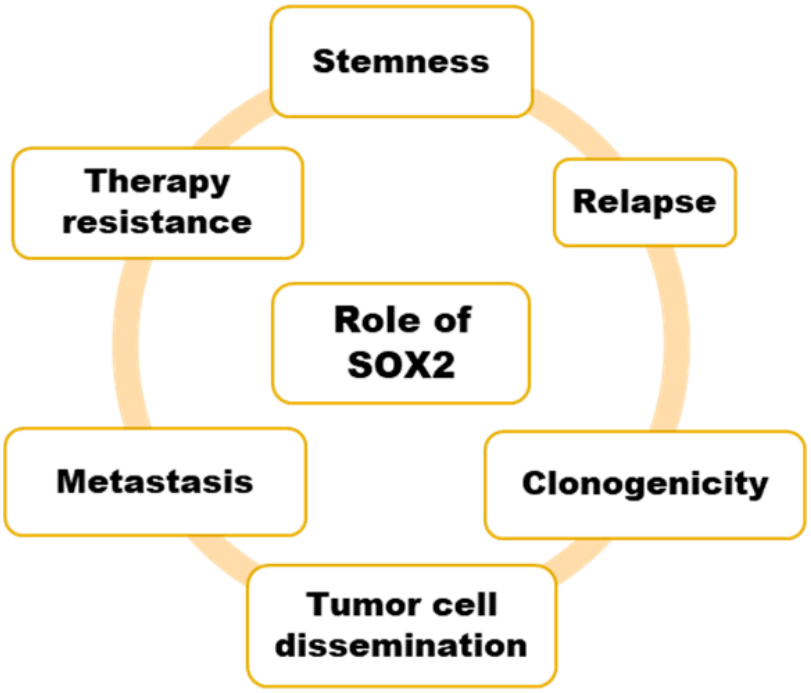

Fig.2. Various roles played by SOX2 in different types of cancers, specifically in glioblastoma multiforme (GBM) and other types of cancer.

2.6. Existing SOX2 Inhibitors and Their Limitations

Various studies have indicated that the SOX2 regulator plays a crucial role in the invasion, metastasis, and migration of cells. Overexpression of NANOG, OCT4, and SOX2, which are pluripotency markers, can lead to a reduction in the differentiation status of cells, ultimately resulting in drug resistance. In some types of cancer, SOX2 has been identified as a useful biomarker for tumor staging and identifying CSC subpopulations. However, addressing signals upstream or downstream of SOX2 could be more beneficial in cancer treatment. There are currently anticancer medications available that target EGFR, such as gefitinib, salinomycin, curcumin, and erlotinib (52). In addition, there are also treatments like SOX2 peptides for immunotherapy and DNA vaccination directed against SOX2. Although RNA interference-based methods have been tested to overcome SOX2 expression, such as short hairpin RNA (shRNA) or small interfering RNA (siRNA), delivery issues and possible immunological reactions limit clinical translation despite preclinical effectiveness. While these medications can help prevent SOX2's downstream self-renewal effects, resistance to these treatments is almost certain and must be addressed (53). As such, it is essential to continue targeting SOX2. Knocking down SOX2 has proven to enhance chemosensitivity and lower the cell's capacity to invade.

2.7. GEPIA2 for expression analysis

The ability to integrate and analyze massive genetic information has allowed bioinformatics tools to transform cancer research in recent years. Gene Expression Profiling Interactive Analysis 2 (GEPIA2) is a technology that is particularly useful in identifying prospective

treatment targets since it may offer insights into gene expression patterns across various cancer types. For gene expression analysis based on tumor and normal samples from the TCGA and GTEx datasets, the GEPIA web server has proven to be an invaluable and often acknowledged resource. To investigate the expression patterns and potential prognostic implications of SOX2 in glioblastoma, the GEPIA2 platform was utilized (9). We are interested in clarifying the role of SOX2 expression in the pathophysiology of glioblastoma and its potential as a therapeutic target by analyzing gene expression data from patient cohorts affected by the disease. Our research could deliver important new information for the creation of effective treatment plans for this debilitating illness. TCGA was utilized in the R environment to perform Cox regression analysis, investigating the correlation between SOX2 expression and patients' disease-free survival (DFS) and overall survival (OS). Furthermore, a relationship between the expression of SOX2 and OCT4 might have implications for the pathogenesis of GBM and how therapy approaches are targeted. Comprehending the molecular interactions among these transcription factors may offer a valuable understanding of the regulatory networks underlying the growth of GBM and the resistance to treatment.

2.8. Natural Anticancer Compounds: Berbamine and Arcyriflavin A

Natural products have been utilized for a long time due to their distinct targeted actions and varied chemical structures. Natural materials exhibit little toxicity and are readily absorbed by the human body (54). Numerous natural chemicals are photosensitizers and sono-sensitizers, such as curcumin, porphyrins, and derivatives of perylene quinone. These molecules are frequently used in fluorescence imaging, diagnostics, photodynamic treatment (PDT), and sonodynamic therapy (SDT). Reactive oxygen species are produced in PDT when excited photosensitizers oxidize biological macromolecules like proteins and nucleic acids, which causes tumor cells to undergo apoptosis (55). It is currently known that well over 700 naturally occurring chemicals have pharmacological properties; several of these substances can target cellular processes or unregulated genes that prevent carcinogenesis. Every cancer patient, or group of patients, has a distinct genetic composition that acts as a cancer operator and can change throughout treatment to activate response mechanisms (56). Several natural substances with well-established molecular targets have shown good therapeutic advantages when taken in combination with specific medications by inhibiting signaling proteins that promote tumor growth. Recent studies have shown that the plant compound Isatin can inhibit neuroblastoma metastasis in both in vivo and in vitro conditions. Tumor cells undergo autophagy and death when exposed to natural substances such as resveratrol, oxyresveratrol, angelicin, gambogic acid, and 18α-glycyrrhetinic acid. Resveratrol is effective against GBM by reducing the TMZ resistance through the downregulation of NF-kB signaling and activating the AMPK pathway while inhibiting mTOR signaling (57). These findings suggest the potential therapeutic roles of these natural compounds in cancer treatment.

The main bioactive ingredient identified from the traditional Chinese herbal remedy Berberis amurensis is Berbamine, a naturally occurring bis-benzylisoquinoline alkaloid. Numerous pharmacological characteristics of berbamine are well-known, including anti-inflammatory, antihypertensive, antioxidant, antiarrhythmic, and antiangiogenic effects. Berbamine's antitumor effects in a variety of tumors have been shown in several recent investigations. Berbamine activates the intrinsic mechanism of apoptosis, which prevents the growth of myeloma, lung cancer, prostate cancer, and liver cancer cells. By preventing angiogenesis, it

also slows the growth of GBM tumors (58). Moreover, paclitaxel and gemcitabine's respective inhibitory effects on the development of gastric and pancreatic cancer were enhanced by berbamine. Additionally, it has been demonstrated that berbamine inhibits the proliferation of cancer stem cells (CSCs) by focusing on calcium/calmodulin-dependent protein kinase II gamma (CaMKIIγ). Berbamine blocks kinase activity by binding selectively to the ATP-binding pocket of CaMKIIγ, which in turn prevents leukemia stem cells and liver CSCs from being able to self-renew. In a more recent discovery, it was shown that co-administration with neurokinin 1 receptor (NK1R) inhibitors, such as SR 140,333, and aprepitant, and CaMKII inhibitors, such as berbamine, hydrazinobenzoylcurcumin (HBC), and KN93, enhanced GSC lethality. Gene silencing with small interfering RNAs (siRNAs) has established the synthetic lethal connection between CaMKIIγ and NK1R in GSCs, proposing a potential combination treatment targeting CaMKIIγ and NK1R to eradicate GSCs. A transcription factor called E2F is released from proliferating cells when cyclin-dependent kinase 4/6 (CDK4/6) binds to cyclin D1 and phosphorylates retinoblastoma (Rb). This process propels the cell cycle forward. Excessive activation of the CDK4/6-cyclin D-Rb-E2F pathway promotes the growth of cancer cells in numerous malignancies, including GBM. Targeting the cell cycle pathway is, therefore, a sensible course of action for treating cancer. Preclinical and clinical studies have extensively employed CDK4/6 inhibitors as anticancer medications, including palbociclib, ribociclib, and abemaciclib. By blocking the CDK4/6-cyclin D-Rb-E2F pathway, they decrease the growth and cause death in a range of tumor cells, including GBM. Therefore, it is imperative to find novel CDK4/6 inhibitors and create potent medication combinations to overcome this resistance (59). The natural substance Arcyriaflavin A (ArcA), which is present in the myxomycetes Arcyria obvelata and Arcyria denudata, inhibits both CDK4 and CaMKII. ArcA caused endometriotic stromal cells, lung cancer, and colon cancer to undergo apoptosis as well as inhibiting the growth of the human cytomegalovirus (60).

2.9. Drug repurposing to treat glioblastoma

Drug repurposing is the process of finding new applications for medications that have already been approved. This approach is considered cost-effective and efficient and is also called "drug rescue," "repositioning," "re-profiling," and "retasking" (61). Recent studies suggest that up to 75% of available medications could potentially be repurposed to treat different diseases. Repurposing drugs is based on two main ideas. This repurposing technique builds models to anticipate undiscovered objectives, biomarkers, or disease processes by using drug-related data, such as drug objectives, chemical configurations, routes, adverse reactions, etc. One benefit of using a single medication is that it can interact with multiple targets, making it easier to find new sites of action for the molecule. The benefit of the target-based strategy comes in its capacity to screen practically all pharmacological molecules with defined chemical configurations. The second idea is that biological processes involved in the pathophysiology of a disease might be linked to targets linked to it, which can lead to the designation of a new indication for a recognized target. Theoretically, a medication targeting these shared components may benefit multiple diseases (62). Drug repurposing based on pathways utilizing data from protein-interaction associations, metabolism, and signaling networks, pathway-based medication repurposing predicts the relationship or resemblance between a medicine and an ailment. For instance, disease-specific pathways are rebuilt utilizing omics data gathered from animals or human patients to act as new targets for repositioned medications. Some computational strategies that are unique and intriguing in the field of drug repositioning have

emerged as a result of the wealth of information and omics data present in pharmaceutical research (63). Drug development may be expedited even further by using these computational tools to create a high-level integration of all available information and data, identify novel signaling pathways, and produce fresh insights into drug mechanisms, interactions, and side effects. The analgesic and antipyretic qualities of aspirin make it a popular non-steroidal anti-inflammatory drug (NSAID). Nevertheless, aspirin has also been shown to have a protective effect against cardiovascular disease because low-dose aspirin taken daily inhibits COX-1, which is again involved in the synthesis of thromboxane A2, a crucial factor in platelet aggregation (64). This results in anti-platelet and anti-thrombosis effects mediated by aspirin. By chance, drugs like metformin, which is used to treat type 2 diabetes, have been shown to have anti-cancer properties. Metformin, a drug used to treat type 2 diabetes, may have a preventive effect on tumor growth. Studies have shown that it reduces glucose levels and increases insulin sensitivity, which is also linked to a lower incidence of cancer among diabetic patients (65).

Table 3: Recent tools and software used in drug development and drug repurposing.

Category	Tools/Software	Function	Links/Reference
Molecular Modeling and Simulation	Schrodinger Suite	Molecular docking, Molecular dynamics (MD) simulations	https://www.schrodinger.com/platform/ (66)
	Molecular Operating Environment (MOE)	Computational chemistry, molecular modeling	https://www.chemcomp.com/Products.htm (67)
	GROMACS	MD simulations	https://www.gromacs.org/ (68)
	NAMD	Scalable MD simulations	https://www.ks.uiuc.edu/Research/namd/ (69)
	CHARMM-GUI	Interface for molecular simulation	https://www.charmm-gui.org/ (70)
Virtual Screening	AutoDock Vina	Molecular docking, virtual screening	https://github.com/ccsb-scripps/AutoDock-Vina (71)
	Gold	Predicting binding of small molecules to protein targets	https://www.ccdc.cam.ac.uk/solutions/software/gold/ (72)
	Zinc Database	Database of compounds for virtual screening	https://zinc.docking.org/ (73)

	PyRx	Virtual screening software for computational drug discovery	https://pyrx.sourceforge.io/downloads (74)
	SwissDock	Virtual screening software for molecular docking	https://www.expasy.org/resources/swissdock (75)
	UCSF DOCK	The suite of programs for molecular docking	https://dock.compbio.ucsf.edu/ (76)
Drug Design	BIOVIA Discovery Studio	Simulating small molecules and macromolecules	https://discover.3ds.com/discovery-studio-visualizer-download (77)
	OpenEye Toolkit	Molecular modeling, cheminformatics	https://www.eyesopen.com/modeling-development-platform (78)
	ChemDraw	Chemical structure drawing	https://revvitysignals.com/products/research/chemdraw , http://www.cambridgesoft.com/ (79)
Bioinformatics and Cheminformatics	BLAST	Sequence comparison to a database	https://blast.ncbi.nlm.nih.gov/Blast.cgi (80)
	KNIME	Data analytics, reporting, integration	https://www.knime.com/ (81)
	Clustal Omega	Multiple sequence alignment	https://www.ebi.ac.uk/jdispatcher/msa/clustalo (82)
	RDKit	Cheminformatics data processing	https://www.rdkit.org/ (83)
Drug Repurposing Tools	DrugBank	Comprehensive drug data resource	https://go.drugbank.com/ (84)
	LINCS	Relationship between gene	https://lincsproject.org/

		expression and drug action	(85)
	Repurposing Hub	Database of drugs with known and potential uses in new indications	https://www.broadinstitute.org/drug-repurposing-hub (86)
Pharmacokinetics and Toxicology	ADMET Predictor	Predicts absorption, distribution, metabolism, excretion, and toxicity	https://www.simulations-plus.com/software/admetpredictor/ (87)
	Derek Nexus	Predicts toxicity based on structure-activity relationship	https://optibrium.com/project/derek-nexus/ (88)
	pkCSM	Predicts pharmacokinetic and toxicity properties using graph-based signature	https://biosig.lab.uq.edu.au/pkcsm/ (89)
	SwissADME	Free tool to evaluate pharmacokinetics, drug-likeness, and BBB	http://www.swissadme.ch/ (90)

2.10. Molecular Docking as a Tool for Drug Discovery

Selecting the appropriate lead molecule is crucial to the overall success of the drug development process. Structures-based approaches enable the selection of datasets of compounds based on the morphological and physical compatibility of ligands to a certain receptor. These approaches depend on knowledge acquired through the understanding of the 3D configuration of an interesting receptor (91). Thus, molecular docking is one of the most well-liked and effective structure-based in-silico techniques for predicting the interactions between molecules and biological targets. To complete this procedure, ligand molecular orientation within a receptor is often predicted first, and then complementarity between them is estimated using a scoring function (92). The three most popular computer modeling techniques—molecular docking, MD simulation, and ADMET modeling—have been essential in making it simple to identify potential candidates for in vivo and in vitro experiments. Although molecular docking-based computational screening finds the hit compounds with the best binding affinities and the appropriate binding mode, it is frequently hindered by inadequate or inaccurate receptor flexibility modeling. Because proteins are active groups, their conformations are essential for biomolecular recognition of ligands; therefore, in a simulation setting, their flexibilities provide a more realistic representation of the biological system (93).

Virtual screening based on the physicochemical properties and molecular descriptors of active ligands is very helpful in identifying hits and leads through library enrichment for screening. This approach is commonly used to reduce and enrich the ligand library for molecular docking. Recent studies have indicated that ligand shape-matching performs equally well as, if not better than, docking.

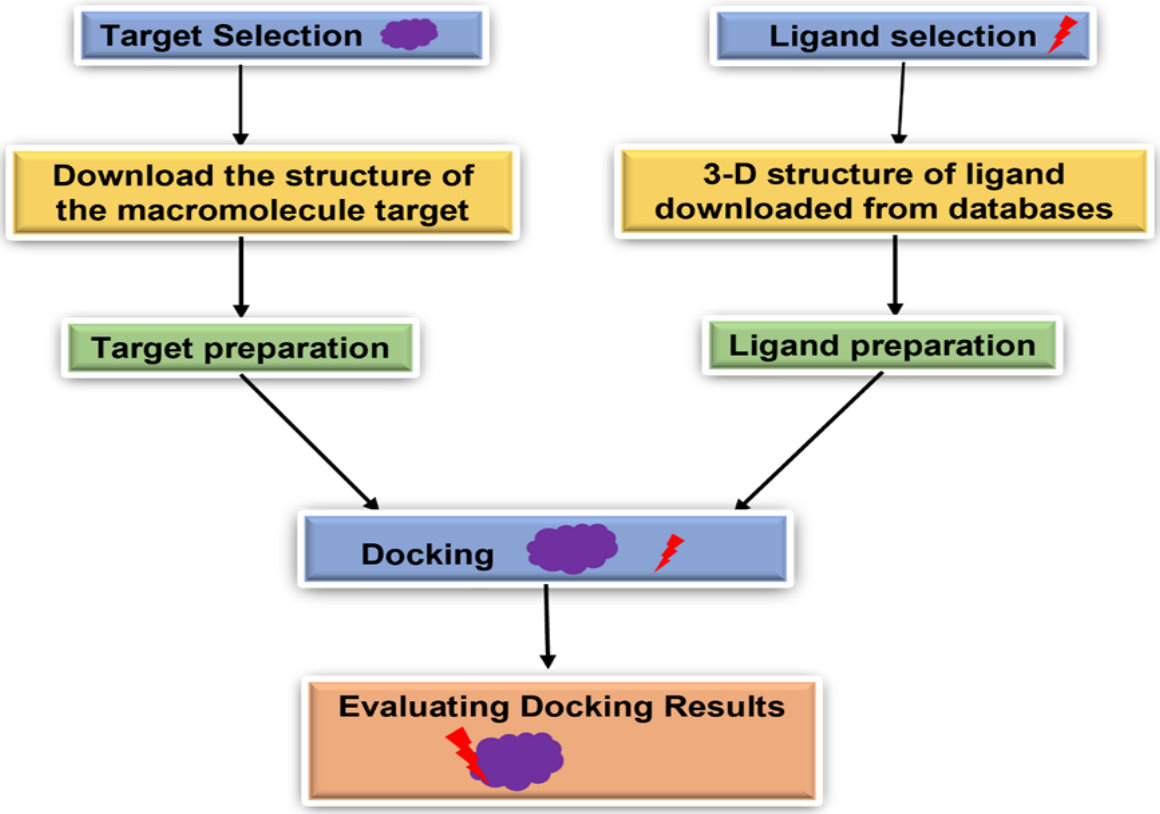

Fig.3. Molecular Docking Workflow, which indicates key steps.

A search strategy to examine the state variables and a scoring system to order the different potential binding modes are needed for all docking techniques. Search techniques can be broadly classified as systematic or stochastic while scoring systems might be empirical, force field-based, or knowledge-based. Systematic search techniques are deterministic and sample the search space at predetermined intervals.

3. Methodology

3.1. Selection of datasets- Identification of SOX2 expression

Here I took SOX2 to check its expression in various tissue and glioma cells. The expression level of SOX2 was analyzed by using GEPIA2 (http://gepia.cancer-pku.cn/). GEPIA2 provides valuable insight into the gene expression patterns based on data from The Cancer Genome Atlas (TCGA) and the Genotype-Tissue Expression (GTEx) projects. For the expression analysis of SOX2 first I visited the GEPIA2 platform and entered the gene of interest, selected the cancer (GBM), dataset source (TCGA or GTEx), and expression pattern. After the completion of the analysis, GEPIA2 generates interactive plots displaying the expression level of SOX2, across different tissue and cancer types.

3.2. Comparision of expression profiles and statistical analysis

I used the comparative feature of GEPIA2 to compare the expression profiles of SOX2 across various types of cancers. ANOVA tests and t-tests are used to determine the significance of the difference in SOX2 expression between normal and tumor tissue. This analysis helped me identify the differential expression pattern of SOX2 and its association with physiological and pathological states. After analyzing the expression of SOX2, I used molecular docking to downregulate the gene. This will help us overcome the increased expression level.

3.3. FDA-approved medication selection (using SwissADME)

When developing pharmaceutical compounds, it is essential to consider how they are absorbed, distributed, metabolized, and excreted, which is also known as ADME. Certain factors need to be considered before choosing a medication, such as lead likeness, BBB permeability, and Lipinski. Only drugs that meet these standard requirements are chosen for molecular docking. To assess the criteria for small ligand molecules, we use an online web-based server called SwissADME (http://www.swissadme.ch/). The structure can be entered in different forms, including SMILES, which represents a molecule's chemical structure. We can share, compare, and find chemical data based on canonical SMILESAfter applying BBB, Lipinski, and Leadkines filters, only 37 out of the initial 81 compounds passed the ADMET analysis.

3.4. Protein and ligand preparation

3.4.1. Receptor preparation

The protein structure was downloaded from the PDB database using (https://www.rcsb.org/) with PDB ID 2LE4. The structural issue was identified by utilizing visualization tools like PyMOL. The heteroatoms and water molecules were removed from the targeted gene or protein since they can interfere with the docking calculation. A hydrogen bond was added to the protein structure and the binding site of the protein was identified.

3.4.2. Active site prediction

To understand how a protein works and explore potential treatments, it's important to identify its active binding sites. There are several computational techniques and tools available to

predict these binding sites. One such method is FTsite (http://ftsite.bu.edu), which is a detection technique specifically designed to identify possible locations where a ligand can bind to the protein.

3.4.3. Ligand Preparation

The drug smiles downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov/) were used for various parameter analyses on swissADME. The 3D SDF file can also be downloaded from PubChem. Open Babel is a free and open-source software package that makes it easier to communicate chemical information in various languages, including popular cheminformatics formats such as SMILES, InChI, MOL, and MOL2. The ligands can be converted from SMILES strings into MOL2 forms. The 3D SDF files can be transformed into MOL2 as SwissDOCK only accepts the MOL2 format of the targeted ligand.

3.5. Protein-ligand docking studies

SwissDOCK is a helpful tool for molecular docking that predicts protein-ligand interactions. The Group for Molecular Modeling at the Swiss Institute of Bioinformatics has created a web-based tool called SwissDock (http://www.swissdock.ch/docking) that allows you to dock ligands and proteins. Once the docking simulation is complete, you can view the predicted binding energy, binding mechanism, and details of the ligand-protein interaction. To use SwissDock, simply enter the ligand in a mol2.file and the targeted protein in pdb format. Then, submit the docking job to initiate the simulation. SwissDock uses molecular docking calculations to predict the interaction between the provided ligand and protein.

3.6. Analyse the structure of the protein-ligand complex

Various molecular visualization software like PyMOL, Chimera, and VMD can be used to analyze the protein-ligand complex graphically. This analysis helps in determining the orientation of the ligand's binding site, and the overall binding mode, and identifying any possible steric conflicts. BIOVIA, a Dassault portfolio, is utilized to discover chemical and biological materials. The findings are then visualized in Chimera file format obtained from SwissDOCK. UCSF Chimera software is used to visualize the structural connection between the protein and drugs. Chimerax files are converted into pdb format, and Discovery Studio is used to create the 2D and 3D confirmations.

4. Results

4.1. Expression analysis of SOX2- GEPIA2 reveals SOX2 as a potential glioblastoma target

In this study, I employed GEPIA2 to analyze the expression patterns of the SOX2 gene across normal cells and tumor cells. The results revealed distinct expression profiles of SOX2 in various tissue types, shedding light on its potential roles in both physiological and pathological conditions. Visual representations such as boxplots were generated to illustrate the differential expression of SOX2. Boxplots depicted the SOX2 expression levels in normal and tumor cells providing a clear visualization. A notable observation was the heterogeneous expression of SOX2 across different tissue types, with some exhibiting significantly higher and lower expression levels compared to others. For instance, tissue such as lung adenocarcinoma (LUAD), low-grade glioma (LGG), and GBM displayed elevated SOX2 expression in tumor cells compared to their normal counterparts, suggesting a potential oncogenic role of Sox2 in GBM. Fig.3.

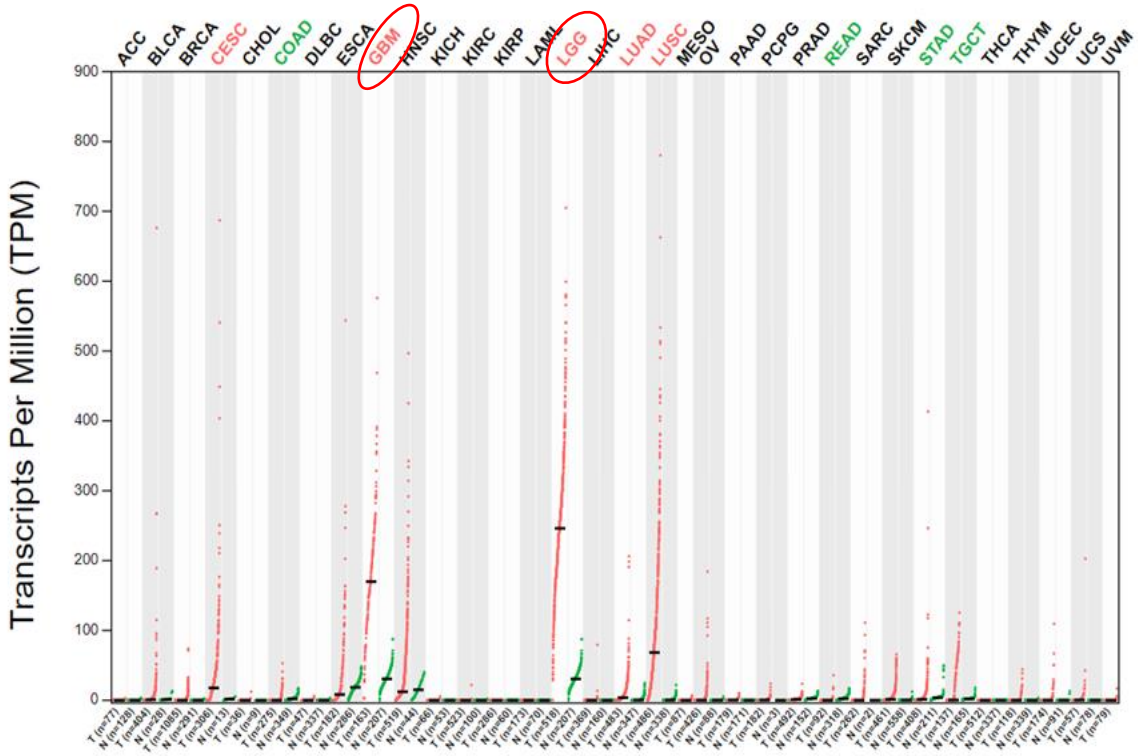

Fig. 4. Demonstrate the expression of SOX2 in different types of cancer and its expression is higher in GBM and LGG(Low-grade glioma) by using GEPIA2. The red line demonstrates the expression of genes in diseased cells and the green lines depict the expression of genes in normal cells.

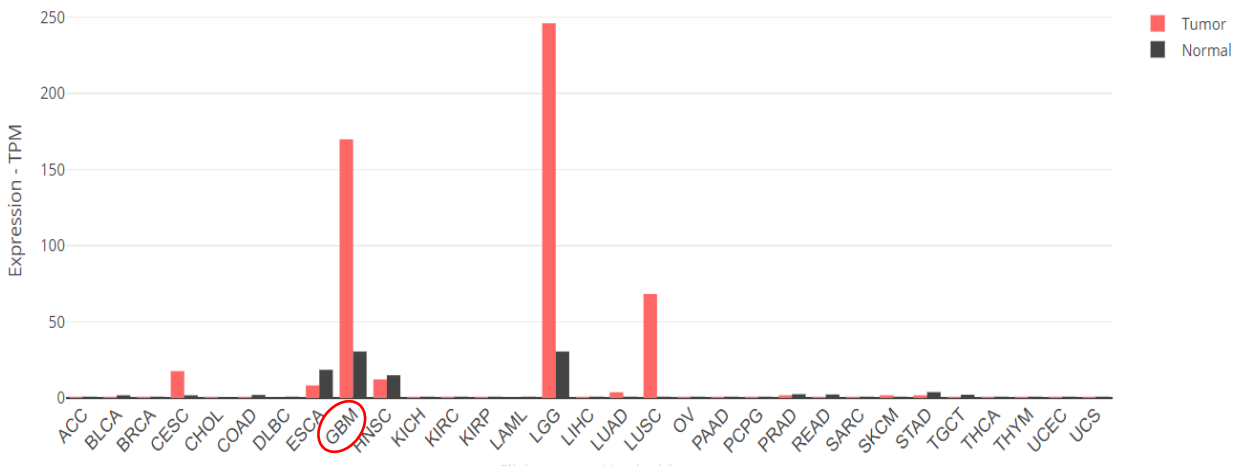

Fig.5. The GEPIA platform displays a bar plot for each tumor sample and its associated normal tissues. This plot indicates the expression of SOX2 in GBM. The bar height represents the median expression of normal tissue or a specific tumor type. The red bar plot represents the presence of the gene in the tumor cell, while the black line bar plot depicts the expression of the gene in normal cells.

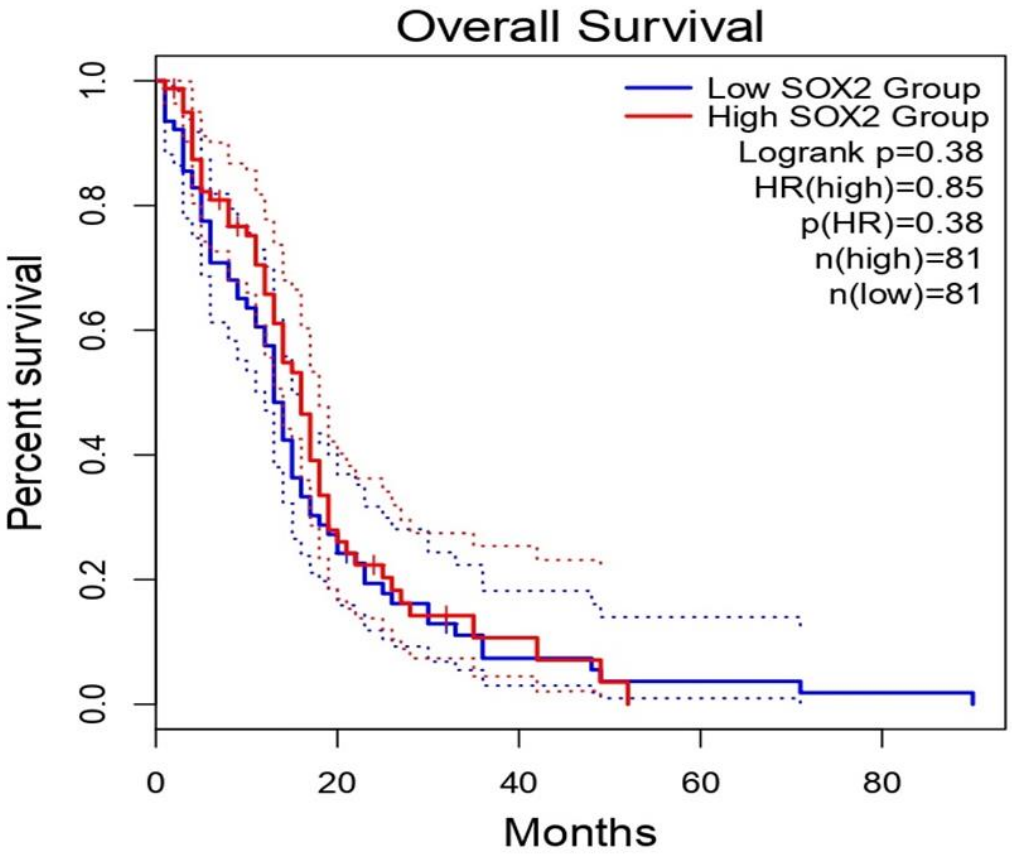

Fig.6. Effect of SOX2 concentration on overall survival. SOX2 expression and overall survival of Glioblastoma multiform patients were analyzed Using the Kaplan Meier plotter database.

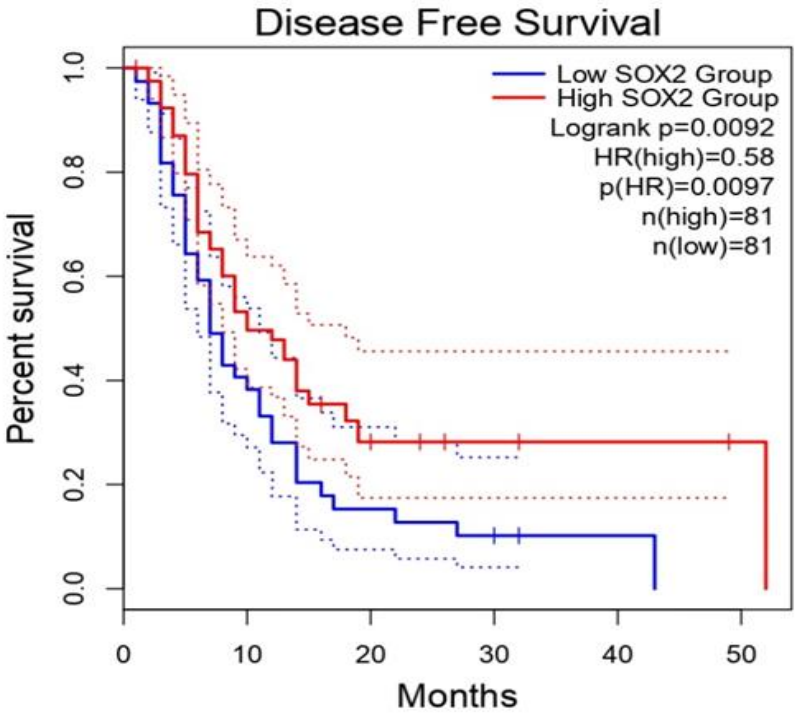

Fig.7. SOX2 expression in a diseased-free condition.

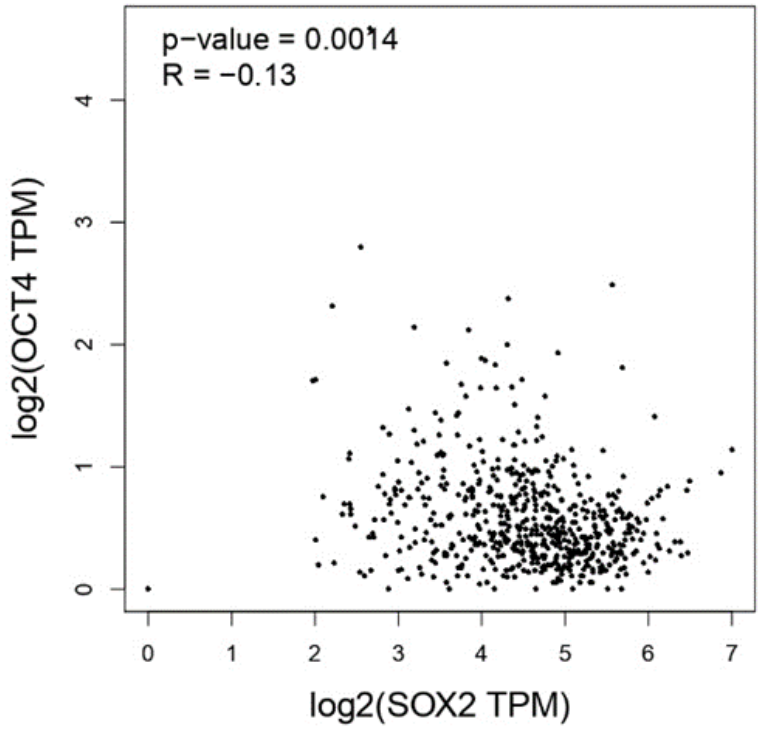

Fig.8. Correlation between SOX2 and OCT4. p-value indicates selected significant thresholds, R-value indicates the correlation coefficient.

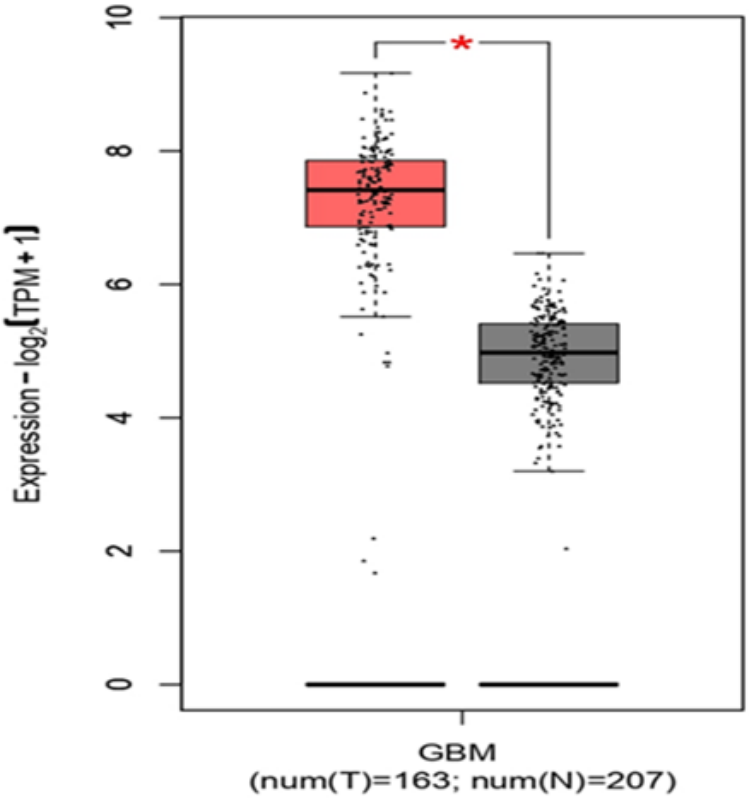

Fig.9. Examined SOX2 expression comparison between normal and tumor cells. SOX2 expression has been altered in cancer by comparing the levels of SOX2 expression in normal cells.

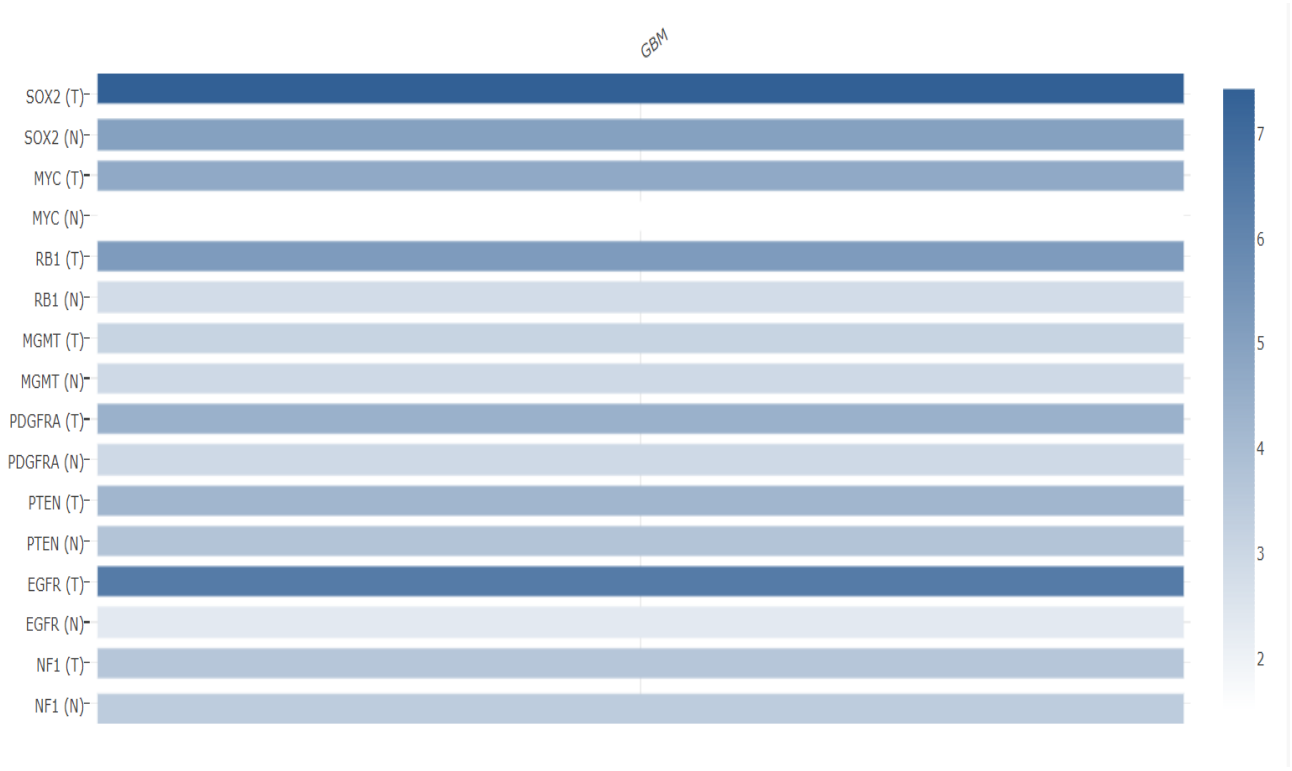

Fig.10. The color intensity is used to compare the expression levels of various genes in normal and tumor cells. A darker color signifies higher gene expression in the given sample. For instance, the expression of SOX2 is higher in tumor cells than in normal cells and other genes.

This analysis reveals the higher expression level of SOX2 in tumor cells The observed difference in SOX2 expression profiles underscores the importance of tissue context in modulating SOX2 expression and function. Additionally, the identification of tissue-specific expression patterns highlights the potential roles of SOX2 in tissue development, homeostasis, and disease pathogenesis.

The elevated expression of SOX2 in certain tumor types, such as GBM suggests its involvement in cancer progression and highlights its potential as a therapeutic target in specific malignancies.

4.2. Molecular docking results

Most GBM cases were found to have overexpressed the transcription factor SOX2. Downregulation of SOX2 exerts antimetastatic, antiproliferative as well as pro-apoptotic effects on GSCs. Knockdown of SOX2 eliminates Akt phosphorylation and decreases PI3K expression. Transcription factor SOX2 (PDB ID https://doi.org/10.2210/pdb2LE4/pdb) has 81 amino acid residues that make up the high-mobility group box (HMG) domain, which allows it to bind with DNA.

4.2.1.Predicted active site of SOX2

The active site of SOX2 has been identified using FTsite prediction, which revealed that SOX2 has three active sites for interaction. These sites are numbered 1, 2, and 3, and are denoted by the colors pink, green, and blue, respectively. The amino acid sequences at these sites are as follows: Site 1 (pink) spans from amino acid 1 to 21, Site 2 (green) spans from amino acid 46 to 56, and Site 3 (blue) spans from amino acid 58 to 71.

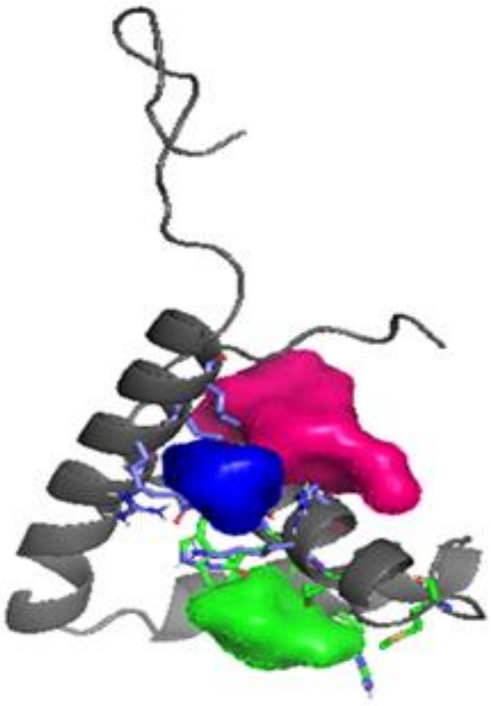

Fig. 11. Three potential active sites of SOX2 protein.

4.2.2.Interaction between SOX2 and drugs

After completing the docking process, we investigated 20 molecules through molecular modeling. The Berbamine docking score was -8.03, and the ArcA score was -6.9. The table below shows the docking score of drugs with SOX2, along with their binding energies and interactions.

Table 1: Tabular representation of reference drugs and finding drugs with SOX2 representing the full fitness and estimated ΔG.

S.No.	Drugs	Cluster	Element	Full Fitness (Kcal/mol)	Estimated ΔG (kcal/mol)
Reference Drug1	Berbamine	0	0	-842.15	-8.03
Reference Drug 2	ArcyriaflavinA1	0	0	-976.46	-6.95
1	Cosmegen	6	0	-660.48	-10.8
2	Niraparib	1	3	-857.12	-9.42
3	Penfluridol	6	0	-671.39	-8.5
4	Dasatinib	8	4	-969.6	-8.33
5	Papaverine	0	0	-1093.5	-7.9
6	Bisoxatin	0	0	-1093.5	-7.9
7	Seratrodast	0	0	-991.8	-7.8
8	Caroverine	0	0	-927.99	-7.7
9	Citalopram	0	0	-927.99	-7.6
10	Quercetin	0	0	-1093.5	-7.6
11	Testolactone	0	0	-1093.5	-7.6
12	Zaleplon	1	0	-948.4	-7.43
13	Dibazepin	12	3	-920.84	-7.43
14	Ethylmorphine	0	3	-925.79	-7.39
15	Loxapine	0	0	-913.8	-7.37
16	Methyltestosterone	0	0	-958.34	-7.36
17	Lorazepam	3	3	-912.77	-7.21
18	Quinine	3	0	-918.26	-7.15
19	Nylidrin	7	0	-965.88	-7.14
20	Etonogastre	1	14	-937.58	-7.12

According to our research, the drugs Cosmegen, Niraparib, Penfluridol, and Dasatinib have higher binding efficiency compared to the reference drugs Berbamine and ArcA. Among these four, Cosmegen and Niraparib have the highest binding efficiency with -10.8 and -9.42 respectively. Additionally, drugs like Papaverin, Bisoxatin, Seratrodast, and Citalopram, as well as all the drugs mentioned in the table above, have higher binding efficiency than ArcA. Therefore, this study suggests that these drugs can either be used in combination with Berbamine or alone to improve the disease condition.

4.2.3.Visualization of Interactions

In this study, we observed the 2D and 3D confirmation of six drugs, Cosmegen, Niraparib, Penfluridol, Dasatinib, Papaverine, and reference drugs (ArcA and Berbamine) after binding with SOX2. For structural visualization and identifying the interacting residue, UCSF Chimera was used. The top drugs that showed high binding efficiency were visualized using UCSF Chimera. You can also use BIOVIA for visualization. The structural visualization of these drugs is provided below.

Table 2: Tabular representation of binding energies and the interaction of reference and finding drugs with SOX2.

Compounds	Binding Energy (KJ/mol)	Interacting residue
Arcyriflavin (Reference)	-6.95	Arg3, Lys5, Arg6, Arg16, Arg20
Berbamine (Reference)	-8.03	Arg16, Arg19, Arg20
Cosmegen	-10.8	Arg3, Val4, Lys5, Arg6, Arg16, Arg19, Arg20
Niraparib	-9.42	Arg16, Arg6, Arg20, Arg59, Leu60, Leu63
Penfluridol	-8.5	Lys5, Arg6, Arg16, Arg19, Arg20
Dasatinib	-8.3	Arg3, Lys5, Arg6, Arg16, Arg20, Ala23, Leu60
Papaverine	-7.9	Arg3, Lys5, Arg6, Arg16, Arg19, Arg20, Ala23, Leu60

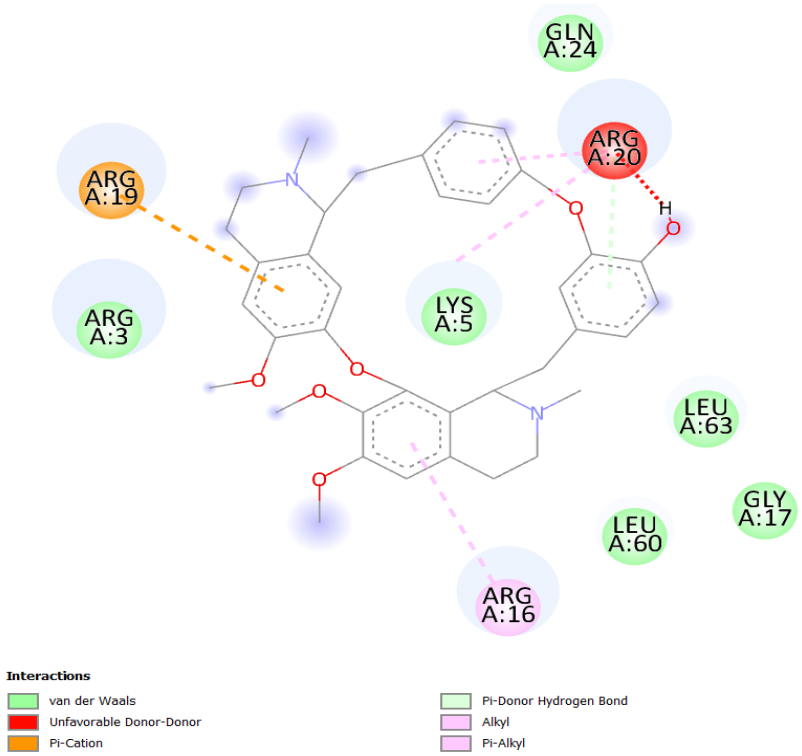

Fig.12. 2D presentation of the binding interaction between Berbamine and SOX2. Binding interactions encompass various types of intermolecular forces, including Van der Waals forces, pi-alkyl, alkyl, pi-donor hydrogen bonds, and unfavorable donor-donor and pi-cation-like interactions.

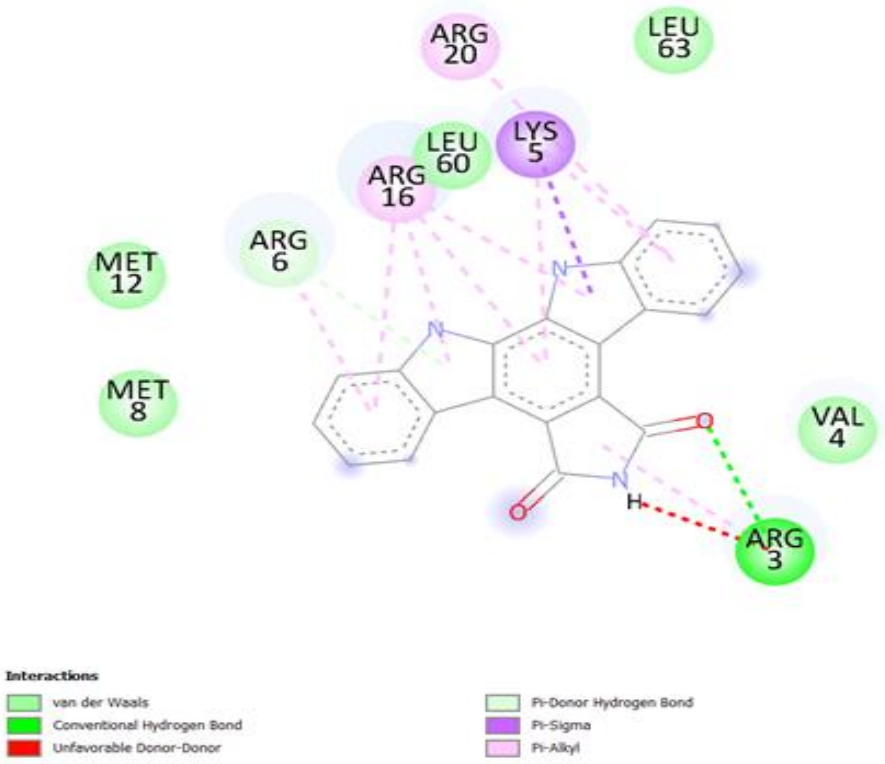

Fig.13. 2D presentation of the binding interaction between ArcA and SOX2. Binding interactions include a range of intermolecular forces, including Van der Waals forces, conventional hydrogen bonds, pi-alkyl, pi-Sigma, and pi-DONOR hydrogen bonds, as well as unfavorable donor-donor and pi-cation-like interactions.

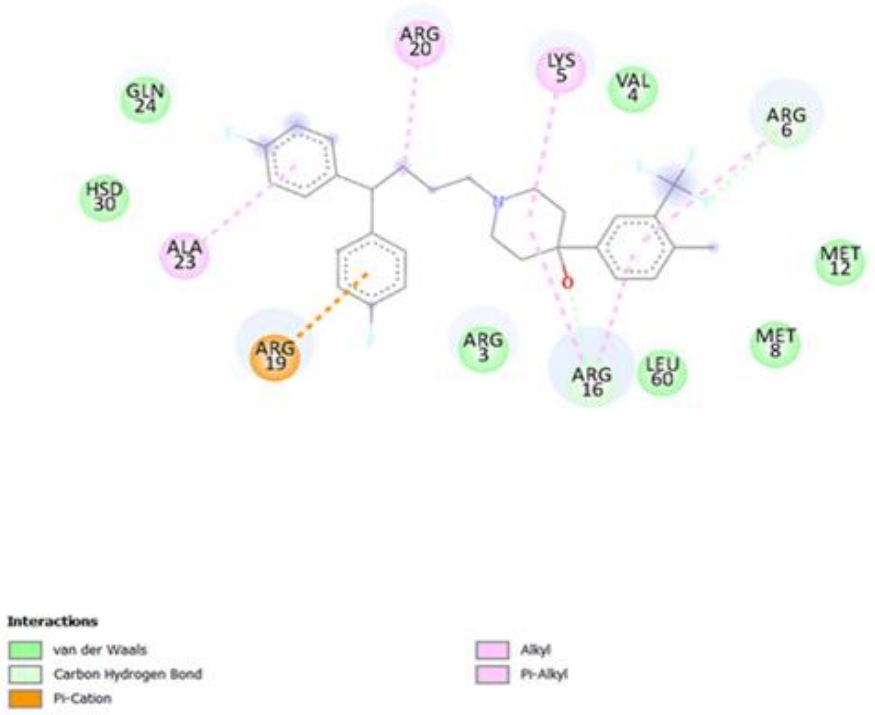

Fig.14. 2D presentation of Interaction between and Cosmegen SOX2. Binding interactions encompass various types of intermolecular forces, such as Van der Waals forces, pi-alkyl, pi-cation, and conventional hydrogen bonds.

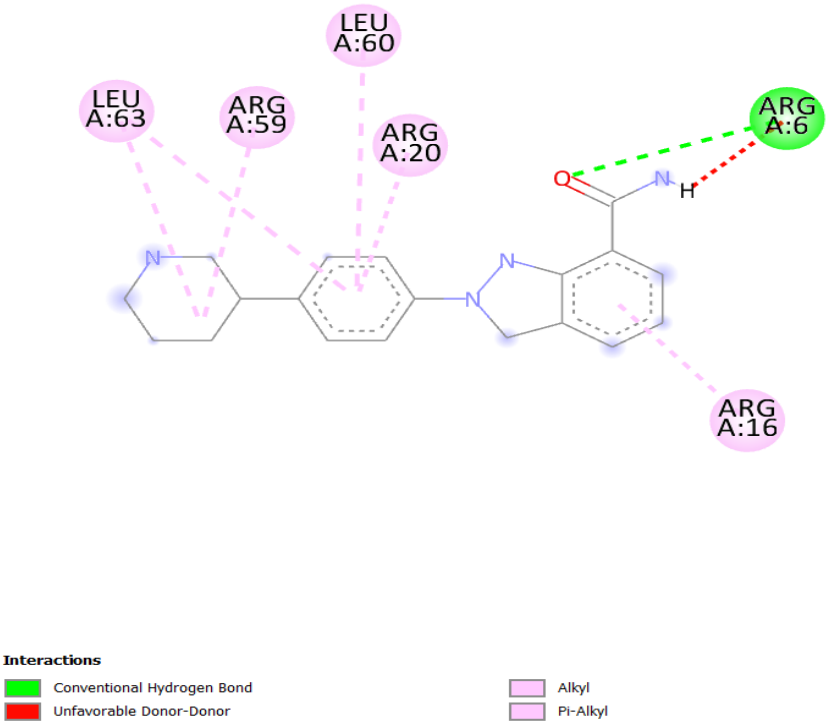

Fig.15. 2D binding interaction between Niraparib and SOX2. Binding interactions involve various types of intermolecular forces, including pi-alkyl, alkyl, conventional Hydrogen bonds, and unfavorable donor-donor.

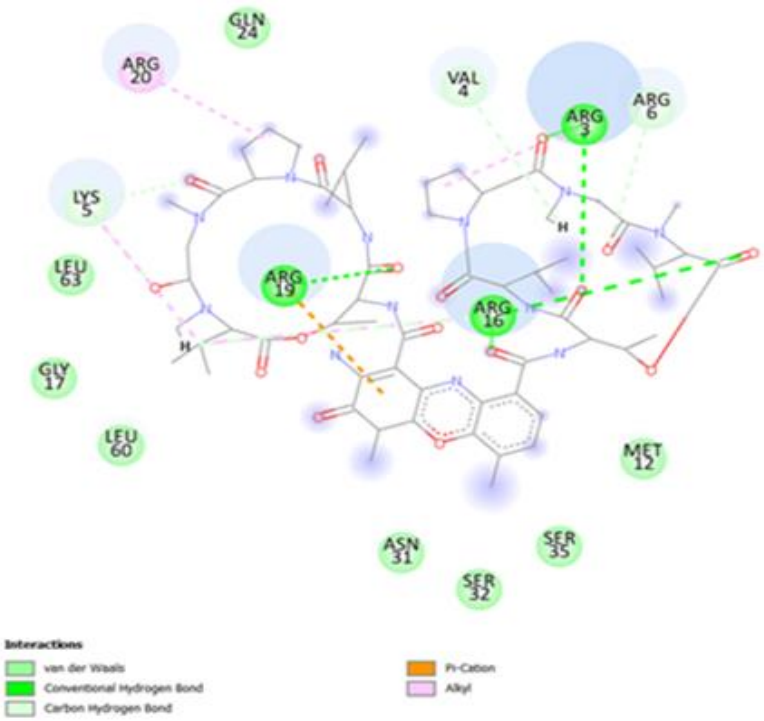

Fig. 16. 2D presentation of SOX2 and Penfluridol. Several intermolecular forces, including van der Waals, alkyl, conventional hydrogen bonds, and carbon-hydrogen bond interaction, are involved in binding.

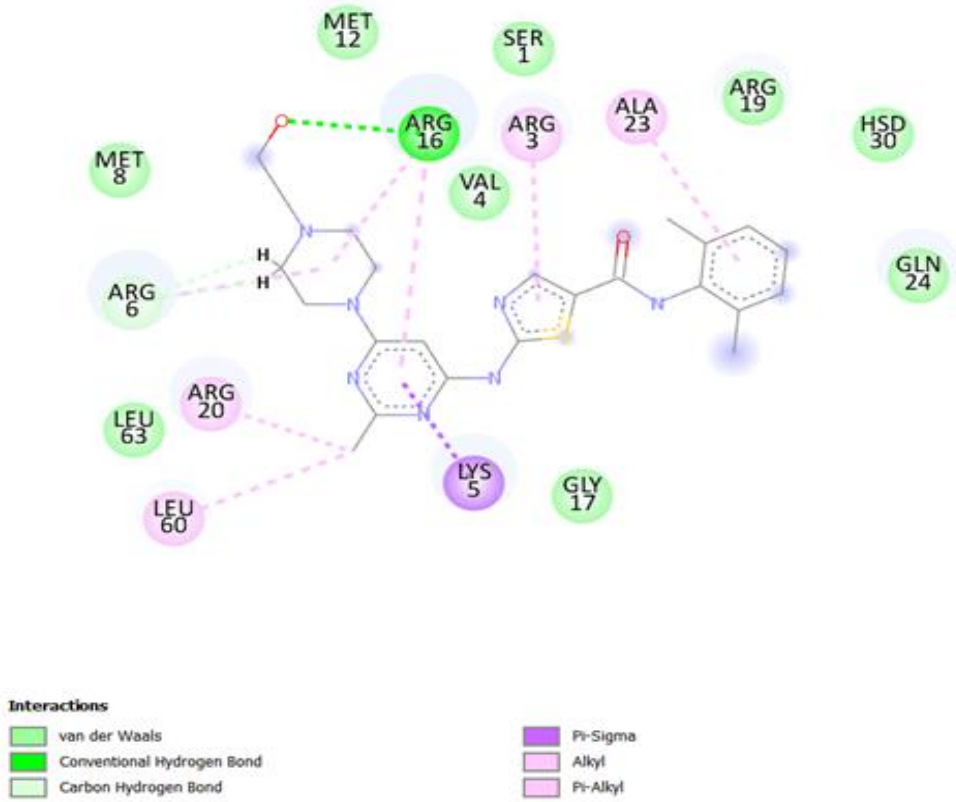

Fig. 17. 2D presentation of interaction between Dasatinib and SOX2. Binding involves many intermolecular forces, including typical hydrogen bond interactions, pi-alkyl, pi-sigma, carbon-hydrogen bonds, and Van der Waals forces.

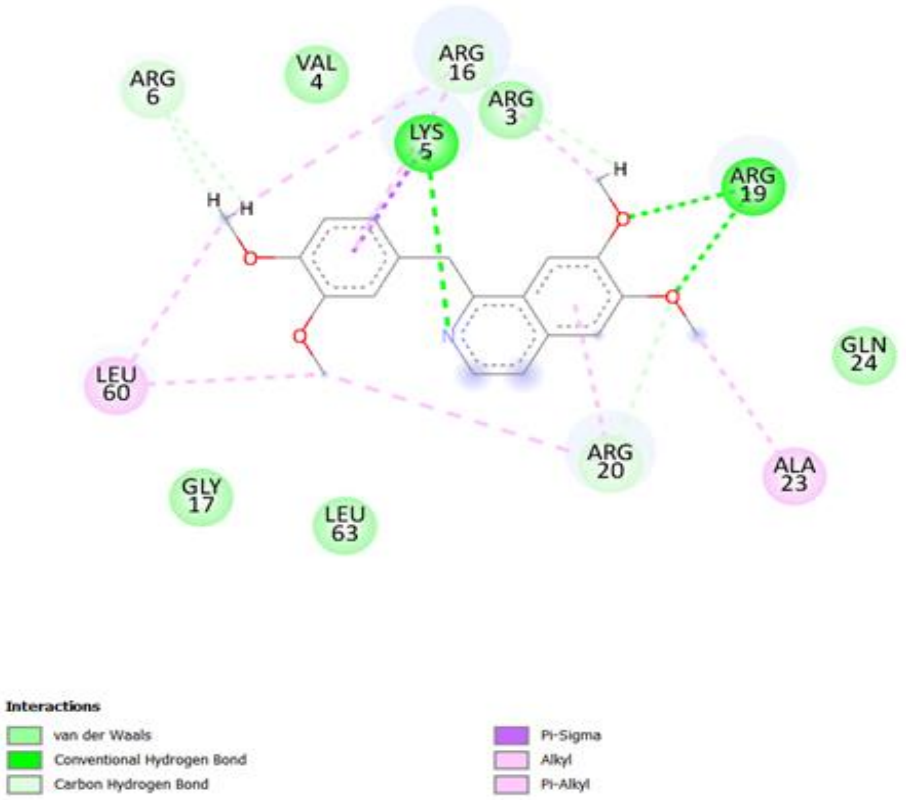

Fig. 18. 2D presentation of interaction between Pepaverine and SOX2. Several intermolecular forces, including Van der Waals forces, alkyl, pi-alkyl, pi-Sigma, carbon-hydrogen bonds, and typical hydrogen bonds.

5. Conclusion and Discussion

GBM is a highly aggressive type of brain cancer that spreads rapidly to other parts of the CNS. Comprehensive research is needed to understand the molecular processes and signaling networks underlying this cancer. Unfortunately, both the overall patient survival rate and the number of therapeutic options are quite low. CSCs play an important role in cell growth, and metastasis, and provide resistance to treatments like radiation therapy and TMZ. The retention of CSC characteristics in gliomas and medulloblastomas has been associated with high expression of SOX2, a transcription factor involved in stem cell maintenance. GSCs are essential for the growth of glioma cells and for the development of treatment resistance. Interestingly, glioblastoma stem cells show significant levels of SOX2, but glioma CSCs that have had SOX2 knockdown lose their ability to proliferate and retain stem cell characteristics. Inhibiting SOX2 can cause cells that initiate GBM tumors to cease proliferating and become less tumorigenic. Downregulation of SOX2 has been shown to aid glioblastoma therapy. Berbamine and ArcA function together to suppress malignancy in GSCs in both in vitro and in vivo environments. Notably, GEPIA2 analysis underscores SOX2 as a prime therapeutic target specifically for glioblastoma. Strategic downregulation of SOX2 expression can disrupt the stemness properties inherent in GBM cells, stymieing tumor growth and potentially enhancing treatment efficacy. The concurrent administration of ArcA and Berbamine effectively halts the progression of GSCs. Using computer-aided software, we can repurpose some drugs for treatment. Molecular docking helps identify the most advantageous orientation and conformation of ligands by predicting the interaction between tiny molecules (ligands) and specific proteins. It is also used for drug development. This approach can expedite the development of effective treatments by leveraging existing safety and pharmacokinetic data. Molecular docking of SOX2 is valuable for understanding its biological functions and identifying potential targets to overcome its expression. By utilizing certain FDA-approved medications, the growth of CSCs can be controlled. There are other drugs available that have a higher ability to control malignancy, such as Cosmegen, Dasatinib, Niraparib, Penfluridol, and Papaverine, but more research is still required to demonstrate how they can be used to improve treatment. Targeting SOX2 faces several significant challenges, including the tumor's cellular and genetic heterogeneity, as well as effective drug delivery across the BBB. Advancements in genomics and bioinformatics could enable more precise identification of GBM. Personalized treatment plans targeting SOX2 could improve efficacy and reduce resistance.

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List of Publication

1. Anistha and P. Kumar, "Revolutionizing Glioblastoma Treatment: In Silico Discovery Targets SOX2 Gene through Molecular Docking, Unveiling Potential of Cosmegen and Repurposed Penfluridol," 2024 International Conference on Automation and Computation (AUTOCOM), Dehradun, India, 2024, pp. 197-201, doi: 10.1109/AUTOCOM60220.2024.10486129. keywords: {Drugs;In vivo;Chemotherapy;Surgery;Stem cells;Curing;Radiation therapy;Glioblastoma;CSCs;SOX2;Drug repurposing;Molecular docking;Drug discovery;ArcA;Cosmegen},

Certificate of Presentation

Presented to

Anistha

In Research Article Entitled Revolutionizing Glioblastoma Treatment: In Silico Discovery Targets SOX2 Gene through Molecular Docking, Unveiling Potential of Cosmegen and Repurposed Penfluridol

In the **International Conference on Automation & Computation (AUTOCOM – 2024)** organized by **Department of Computer Science & Engineering** , Graphic Era Hill University Uttarakhand, India from 14-16 March , 2024.

Prof. D. Bordoloi

Prof. R. Gowri

Revolutionizing Glioblastoma Treatment: In Silico Discovery Targets SOX2 Gene through Molecular Docking, Unveiling Potential of Cosmegen and Repurposed Penfluridol

Publisher: IEEE

Cite This PDF

Anistha ; Pravir Kumar **All Authors**

Abstract:
The most severe type of brain tumor resulting from astrocyte malignancy is called a glioblastoma (GBM). Despite numerous developments, the only available treatments are still radiotherapy and chemotherapy, followed by surgery, with a 14–15-month overall survival rate. These treatments have limitations when it comes to improving survival and curing. New treatments targeting GBM based on molecular pathways and pathophysiology are required. As SOX2 interacts with various substrates, it can be utilized as a target here and maybe a desirable target for novel compounds. Through this investigation, we have attempted to categorize different compounds according to their expression and binding efficiency, that can inhibit SOX2 through various pathways. Our investigation revealed that with the help of molecular docking Cosmegen, Penfluridol, and other compounds can inhibit the functioning of SOX2, further resulting in decreased capacity of CSCs (cancer stem cells) to proliferate.

Published in: 2024 International Conference on Automation and Computation (AUTOCOM)

Date of Conference: 14-16 March 2024

DOI: 10.1109/AUTOCOM60220.2024.10486129

Date Added to IEEE *Xplore*: 03 April 2024

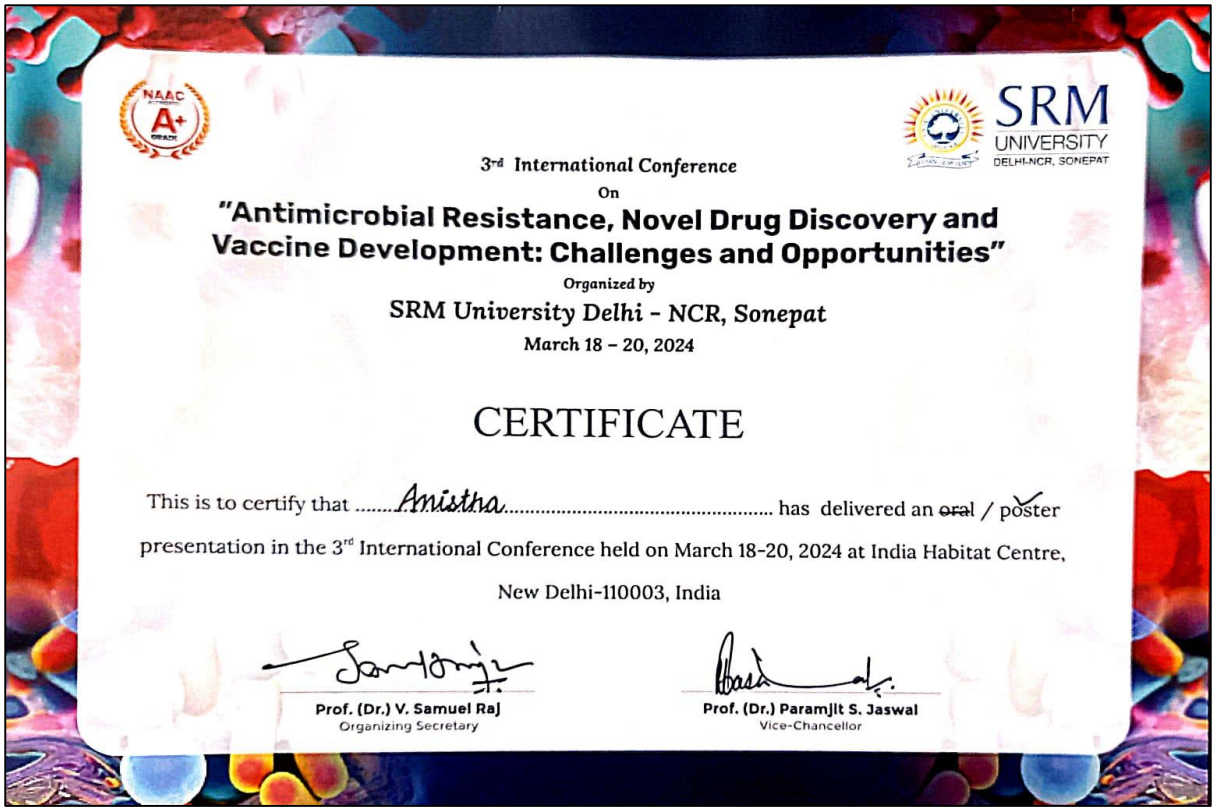
Publisher: IEEE

Conference Location: Dehradun, India

ISBN Information:

I. Introduction

Glioblastoma multiform (GBM) is an aggressive, malignant primary brain tumor with a 15-month median survival rate



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Translational Neuroscience: Bridging Gap between Bench to Bedside

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This is to certify that Prof./Dr./Ms./Mr. Anistha

of Delhi Technological University has Participate as ***Delegate*** in the Two Days National Symposium on ***"Recent Advances in Neurochemistry and Neurosciences"*** held from 25th April 2024 to 26th April 2024 at Convention Centre, Jamia Hamdard, New Delhi. He/She has also presented in Young Investigator/Poster Session.

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Summary

ANISTHA

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EDUCATION

AUG 2022- MAY 2024

MSC. BIOTECHNOLOGY, DELHI TECHNOLOGICAL UNIVERSITY

Covered key topics including molecular biology, genetic engineering, bioinformatics, and bioprocessing. Developed proficiency in experimental design, data analysis, and scientific communication through research projects and coursework.

JUL 2019- MAY 2022

BSC. LIFE SCIENCES, DELHI UNIVERSITY

A comprehensive undergraduate program providing a solid foundation in various disciplines within life sciences. We covered fundamental concepts in biology, chemistry, genetics, physiology, and ecology, among others.

AUG-2017-JUN 2019

DIPLOMA IN ANIMAL HUSBANDRY AND DAIRYING, NATIONAL DAIRY RESEARCH INSTITUTE

Diploma in Animal Husbandry and Dairying graduate with a strong foundation in animal care, management, and dairy production.

SKILLS

- Skilled in livestock handling, nutrition management, breeding techniques, and veterinary care.
- Effective communication skills to collaborate with interdisciplinary teams, present findings, and write technical reports or research papers
- Understanding of protein structure prediction, molecular modeling, and docking techniques. Familiarity with software tools like PyMOL, MODELLER, and Swiss-PdbViewer.
- Ability to work effectively in multidisciplinary teams

ACTIVITIES

Internships: -

1. **One Month (1 May 2019- 31 May 2019)**

Worked as an intern at ''The Kurukshetra-Karnal Co-operative Milk Producers'' Union Limited.

Description: - Monitoring and maintaining quality standards throughout the production process. This includes conducting tests to assess milk quality, such as fat content, protein content, and bacterial counts, and ensuring compliance with regulatory requirements. Learn how to maintain accurate records and documentation related to production activities, quality control tests, inventory management, and any incidents or deviations encountered during the internship.

2. **4 Months (10 Feb 2020- 10 Jun 2020)**

Work as an at VentAllOut, Delhi

Description: - Work as a content writer with a proven track record of creating engaging and informative content across various platforms. Skilled in researching, writing, editing, and proofreading content tailored to the target audience. Managed content calendars, prioritized tasks, and met deadlines consistently in a fast-paced environment, while maintaining quality and attention to detail.

3. **45 Days (15 June – 31 July)**

Work as an intern at '' ESIC Model Hospital in BasaiDarapur, Delhi''

Description: - Working as an intern in a hospital's microbiology, biochemistry, and histopathology labs offers a valuable learning experience. Learn how to perform various diagnostic tests such as culture and sensitivity tests, Gram staining, and biochemical tests. In the histopathology lab learn about specimen processing, embedding, sectioning, and staining.

PUBLICATION

1) Anistha and P. Kumar, "Revolutionizing Glioblastoma Treatment: In Silico Discovery Targets SOX2 Gene through Molecular Docking, Unveiling Potential of Cosmegen and Repurposed Penfluridol," 2024 International Conference on Automation and Computation (AUTOCOM), Dehradun, India, 2024, pp. 197-201, doi: 10.1109/AUTOCOM60220.2024.10486129. keywords: {Drugs;In vivo;Chemotherapy;Surgery;Stem cells;Curing;Radiation therapy;Glioblastoma;CSCs;SOX2;Drug repurposing;Molecular docking;Drug discovery;ArcA;Cosmegen},