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A REVIEW ON THERAPEUTIC APPLICATIONS OF GSK-3 BETA INHIBITORS

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Abstract : Glycogen synthase kinase 3 beta (GSK-3 beta), which is a serine/threonine kinase was initially identified because of its key role in the regulation of glycogen synthesis. But it is now well-established that GSK-3 performs critical functions in many cellular processes, such as apoptosis, tumor growth, cell invasion, and metastasis. Many human disorders, including cancer, have been linked to abnormal GSK-3 activity, underlining its therapeutic promise as a cancer target. [29]. There is conflicting evidence on the effect of GSK-3 inhibition on cancer cell development due to multiple methods through which GSK-3 may influence carcinogenesis. It can act as a tumor promoter as well as a tumor suppressor in different types of cancers [14]. However, it is found that combination of GSK-3 beta inhibitors with chemotherapeutic agents can significantly reduce the resistance of various tumor cells towards the chemotherapy. In the last few years, many GSK-3 inhibitors have been developed, and some are currently being tested in clinical trials [16]. Indazoles are nitrogen-based heterocyclic chemicals that posses many types of biological activities and representatives of this class of pharmacological agents are widely used as antibacterial, anti-inflammatory, anti-HIV, Antiprotozoal and antimalarial agents. Recent studies are showing promising activity of indazole derivatives as anticancer agents.

Index Terms: **Glycogen Synthase Kinase 3 Beta (GSK 3 Beta), Indazole Derivatives, GSK 3 Beta Inhibitors, Cancer, Alzheimer's Disease, Diabetes**

1. INTRODUCTION

1.1. GLYCOGEN SYNTHASE KINASE 3 (GSK-3)

Glycogen synthase kinase 3 (GSK) was found 20 years ago as one of many protein kinases.
GSK-3 has a number of roles in cellular physiology and human health, including:

1.1.1. Multiple Roles of GSK-3 in Cellular Physiology and Human Health

GSK-3 is a serine/threonine kinase (S/T) enzyme. It was discovered in rat skeletal muscle as a kinase that phosphorylated and inactivated Glycogen synthase (GS), the final enzyme in glycogen synthesis. As a result, GSK-3 was discovered to have a critical function in metabolism. GSK-3 has been linked to cancer and ageing (cancer stem cells, cellular senescence, stem cell pluripotency, and differentiation control), immune disorders, metabolic disorders (atherosclerosis, diabetes type II, inflammation, and heart disease), neurological disorders (Alzheimer's, amyotrophic lateral sclerosis (ALS), bipolar disorder, mood disorders, Parkinson's, and Schizophrenia), and others. GSK-3 could be a potential therapeutic target for these and other illnesses. GSK-3 has been linked to malignancies that are resistant to chemotherapy, radiotherapy, and targeted therapy, where GSK-3 inhibition could be beneficial.[14]

1.1.2. Isoforms: GSK-3 alpha and GSK-3 beta

The GSK-3 gene family contains two highly conserved kinases, GSK-3 alpha and GSK-3 beta. The two molecules, on the other hand, serve distinct tasks, and one cannot compensate for the other's absence. Production of GSK-3 alpha, for example, did not reverse embryonic lethality in mice with the GSK-3 beta gene disrupted. GSK-3 alpha and GSK-3 beta are active in non-stimulated cells. Both GSK-3 alpha and GSK-3 beta have strong preferences for primed substrates, which means they prefer substrates that have already been phosphorylated by other kinases [(e.g., casein kinase-1 (CK1), mitogen-activated protein kinases (MAPK) [extracellular regulated Kinase (ERK), p38MAPK, and c-Jun N-terminal kinase (JNK)], 5' adenosine monophosphate-activated protein Kinase (AMPK)] and others. The GSK-3 kinases Phosphorylate greater than 40 proteins including over 12 Transcription factors.[14]

1.1.3. Differences between GSK-3alpha and GSK-3 beta

GSK-3 alpha and GSK-3 beta are not functionally identical and have different substrate specificities, despite their physical similarity. GSK-3 alpha and GSK-3 beta are 51 and 47 kDa (kilodalton) proteins, respectively. The GSK-3 alpha isoform possesses a glycine-rich extension at its amino terminus. GSK-3 alpha and GSK-3 beta contain 98 percent sequence identity in their kinase domains, but only 36% in their carboxyl termini. GSK-3 alpha and GSK-3 beta have different substrate preferences in the brain and potentially other organs. As a result, GSK-3 isoforms play physiologically significant roles in distinct tissues that may or may not overlap. These data suggest that targeting GSK-3 alpha or GSK-3 beta in specific illnesses is a good idea. GSK-3 beta has been the subject of the majority of biochemical study. However, the development of isoform-specific inhibitors could lead to more targeted and effective treatments.[14]

1.1.4. Substrates of GSK-3 beta

GSK-3 beta regulates more than 40 proteins in a direct manner. Glycogen metabolism, transcription, translation, cytoskeletal control, cell differentiation, proliferation, transformation, and apoptosis are among the many cellular tasks performed by these proteins. GSK-3 beta substrates fall into three categories: metabolic/signalling proteins, structural proteins, and transcription factors. The proteins acetyl CoA carboxylase, amyloid precursor protein, APC(adenomatous polyposis coli) tumor suppressor protein, ATP citrate lyase, Axin, cyclic AMP-dependent protein kinase, cyclin D1, eIF2B(eukaryotic initiation factor 2B), glycogen synthase, insulin receptor substrate-1 (IRS-1), myelin basic protein, NGF(nerve growth factor) receptor, protein phosphatase 1, protein phosphatase inhibitor-2 and pyruvate dehydrogenase belongs to the first group. The structural proteins are dynamin-like protein, microtubule-associated protein 1B (MAP1B), microtubule-associated protein 2 (MAP2), neural cell-adhesion protein (NCAM), neurofilaments, spindle-associated protein Astrin, ninein and Tau. GSK-3 beta targeted transcription factors includes activation protein 1(AP-1), β-catenin, C/EBP alpha (CCAAT enhancer binding protein alpha), CREB (c-AMP response element binding protein), glucocorticoid receptor, HSF-1(heart shock factor 1), Myc(master regulator of cell cycle entry and proliferative mechanism), NFAT(nuclear factor of activated T-cells) and NF-κB(nuclear factor kappa light chain enhancer of activated B cells). [11]

Nitrogen-containing heterocycles are the most popular medications on the market. It is because of their ubiquitous nature that they serve as a major scaffold for a variety of biological substances and pharmaceuticals. As a result, many chemists from all over the world were inspired to explore new methods for synthesizing these heterocycles. Indazole is one of these chemicals with biological, agricultural, and industrial applications. Anti-inflammatory, anti-tumor, anti-HIV, anti-platelet, and serotonin receptor antagonist properties are all present in indazole and its derivatives. These compounds' biological and pharmacological features have a wide variety of applications in the development of new drugs. Many disciplines of heterocyclic chemistry benefit from indazole derivatives, and these reactions are excellent and have a medical approach to their synthesis. Aside from the development of new reactions or better circumstances for existing ones, future developments in this sector are likely to include the application of indazole motifs techniques to target-oriented synthesis. Emil Fisher was the first to define indazole as a "pyrazole ring fused with the benzene ring." Because of its intriguing chemical and biological features, it has been intensively researched. Indazole is a member of the azole family, which includes carbon, hydrogen, and nitrogen atoms. These two-nitrogen heterocyclic organic compounds are also known as benzpyrazole or isoindazolone heterocyclic organic compounds. Indazoles resemble pyridine and pyrrole because they have ten p-electron aromatic heterocyclic complexes, similar to pyrazole.[1]

The basic structure of various medicinal compounds, such as Granisetron, a 5HT3 receptor antagonist used as an anti-emetic in cancer chemotherapy, and Benzydamine, an anti-inflammatory medication, is formed from indazole derivatives. The indazole ring has two nitrogen atoms and can be functionalized at various places with good selectivity. Because of the planarity of the indazole ring, side chain length, and fictionalisations at various points, an enormous variety of Indazole derivatives can be created, resulting in novel compounds with biological and medicinal capabilities.[1]

1.1.5. Advantages

➢ The development of small drug-like compounds with a unique structural framework is an indazole which has great importance for the pharmaceutical industry in order to accelerate drug discovery.

➢ Indazole is an essential heterocyclic moiety in medicine.

➢The indazole nucleus can be found in a variety of alkaloids in nature.

➢Indazole derivatives have an important function in cancer treatment.

➢Indazole derivatives shows antibacterial, antioxidants, anti-inflammatory, antidiabetic, antiviral, antiproliferative, antituberculosis, antispermetogenic, antipsychotic properties. [1]

2. THERAPEUTIC ROLES OF GSK-3 BETA

2.1. GSK-3 BETA IN ALZHEIMER'S DISEASE

Alzheimer's disease affects an estimated 18 million people worldwide, according to the World Health Organization (WHO). The United States, France, Germany, and other countries started substantial initiatives aimed at identifying risk factors, improving caregiving, and doing fundamental research to delay the onset of Alzheimer's disease. Glycogen synthase kinase 3 (GSK-3) is involved in a variety of cellular activities and has been connected to the aetiology of diseases such as diabetes, cancer, and Alzheimer's disease. GSK-3 inhibition has neuroprotective benefits, lowers -amyloid formation, and lowers tau hyperphosphorylation, all of which are linked to Alzheimer's disease. GSK-3 inhibition by selective inhibitors is moderate. With outstanding pharmacokinetic qualities and penetration through the blood-brain barrier, it has a lot of potential for the treatment of Alzheimer's disease. Many inhibitors have been discovered in recent years since GSK-3

plays a major part in Alzheimer's disease and other chronic diseases, many of which are associated to the central nervous system. Some of them have been shown to be effective in cellular and animal models of various CNS diseases. However, some dangers should be avoided in the creation of a GSK-3 inhibitor due to various hazards previously considered when GSK-3 was targeted. If we want a GSK-3 inhibitor to be an effective medicine, high values for IC50 and ATP competition when the compound binds to the enzyme should not be present. A modest inhibition of GSK-3 is required to treat pathological situations since it will be able to reduce aggravated GSK-3 function in diseased tissues while also decreasing activity in healthy tissues, which will be compensated by alternate cellular processes present in humans. GSK-3 inhibitors that are not ATP competitive, such as allosteric modulators, substrate competitive inhibitors, or covalent inhibitors, are emerging as a possible alternative for a safer use in the clinic.[4]

❖ **Compounds in Preclinical and Clinical Trials**

Several GSK-3 inhibitors are now undergoing preclinical or clinical testing. GSK-3 inhibitors are then mentioned with the therapeutic indication of Alzheimer's disease. The University of Sao Paulo is in phase II with lithium carbonate against GSK-3 for Alzheimer's disease and cognitive impairment, while Wayne State University is in phase IV with lithium carbonate against bipolar disorder. The National Institute of Neurological Disorders and Stroke submitted Lithium Against AD, which is in phase II, however there has been no update since March 2008. Noscira has two drugs in pre-clinical trials: NP-12 (TDZD) and NP-103. A phase II clinical trial for Alzheimer's disease is now underway using NP-12 (NP031112, Tideglusib). Crystal Genomics' NP-103 and CG-301338, as well as Takeda's GSK-3 beta inhibitor, are now in preclinical testing. The development status of Cambrex's XD-4241, GlaxoSmithKline's SB-415286, Amphora's GSK-3 beta inhibitor, Sanofi-Aventis' SAR-502250, Cephalon's CEP-16805, and Lundbeck's GSK-3 beta inhibitor is unknown. The success or failure of these medications in preclinical and clinical trials will either encourage or discourage further research.[4]

2.2. GSK-3 BETA IN DIABETES

Diabetes is caused by a malfunction of the insulin signalling pathway. The biochemical mechanism by which insulin increases glycogen production in mammalian skeletal muscle was elucidated by Dent et al. (1990). Due to its negative regulation of multiple components of the insulin signalling pathway, type 2 diabetes was the first illness condition to be linked to GSK-3 beta (Embi et al.,1980). 3-phosphoinositide-dependent protein kinase stimulates AKT, which inactivates GSK-3 beta in this pathway. GSK-3 beta inactivation causes glycogen synthase to be dephosphorylated and activated, which aids glycogen production. (Cohen and colleagues, 1997). Non-selective GSK-3 beta inhibitors, as described by Sung and colleagues in 1998, may be useful as medicines for the treatment of insulin resistance in type 2 diabetes (Sung Et al., 1998). Inhibition of GSK-3 beta increases insulin action and glucose metabolism in human skeletal muscle, according to later research (Nikoulina et al., 2002). GSK-3 beta inhibitors are likely to have a comparable effect on plasma glucose reduction as insulin, making GSK-3 beta an appealing target for the treatment of type 2 diabetes (Dokken et al., 2005). Treatment with GSK-3 beta inhibitors resulted in improved glucose clearance, which was attributed to a twofold increase in hepatic glycogen production. In Zucker diabetic fatty (fa/fa) rats, this outcome was observed in oral glucose tolerance tests and euglycemic-insulinemic clamp experiments (Cline et al., 2002). Non-selective GSK-3 beta inhibition improved insulin action in the prediabetic obese Zucker rat's insulin-resistant skeletal muscle, in part by alleviating the negative effects of GSK-3 beta activity on post-insulin receptor insulin signalling (Qu et al., 2006). GSK-3 beta has also been implicated as a negative regulator of the insulin signalling pathway in other signalling pathways. Protein tyrosine phosphatase 1B (PTP1B), for example, activates GSK-3 beta and acts as a negative regulator of insulin signal transduction. This effect was highlighted when Hong and Lee reported in 1997 that lowering PTP1B improves insulin sensitivity and boosts insulin-dependent metabolic signalling in diabetic animal models (Hong and Lee, 1997). However, as the design and development of modulators for negative regulators has progressed, this method has taken a back seat.

2.3. GSK-3 BETA IN SARS-COV2

The possibility of Glycogen Synthase Kinase-3 (GSK-3) inhibitors for the treatment of SARS-CoV2 is highlighted in Christopher E. Rudd's incisive study. The GSK-3-mediated phosphorylation of critical serine residues in SARS-CoV2 Nucleocapsid proteins, which are required for viral replication, is described in the manuscript. These findings, along with preclinical evidence confirming GSK-3's role in modulating innate and adaptive immune responses, support the author's notion that GSK-3 inhibitors could be examined as a viable COVID-19 infection treatment. In models of herpes (MHV-68) and lymphocytic choriomeningitis (LCMV-C13) viral infections, GSK-3 small-molecule inhibitors and GSK-3 siRNA reduced PD-1 expression, boosted CD8 + T cell activity, and improved viral clearance. Increased T cell function produced by GSK-3 inhibition resulted in anti-tumor efficacy comparable to that seen in animal models of metastatic melanoma and lymphoma treated with anti-PD-1 monoclonal antibodies. Studies using animal models of haemorrhagic shock suggest that inhibiting GSK-3 beta reduces hepatic and renal failure by upregulating anti-inflammatory IL-10 and downregulating IL-12p40 and IL-6, a cytokine implicated in the cytokine release syndrome seen in patients with severe SARS-CoV2. By regulating the NF-kB-induced inflammatory response, GSK-3 beta inhibition reduces the systemic inflammatory response (SIR) in models of sepsis and ischaemia/reperfusion damage. These findings could have implications for SIR and the common diffuse intravascular vascular coagulopathy seen with SARS-CoV2 infection. In a model of lipopolysaccharide (LPS)-mediated inflammation, GSK-3 beta suppression also reduced mRNA production of IL-1, IL-6, and inducible NO synthase (iNOS).[6]

2.4. GSK-3 BETA IN CANCER

Cancer is the second highest cause of death in the United States and one of the most common causes of death worldwide. Prostate cancer is the leading cancer type with projected new cases and the second in estimated cancer deaths in the United States in 2020, according to cancer statistics released by the American Cancer Society in 2020. Despite ongoing efforts to create anticancer drugs, present cancer therapy options are restricted due to associated adverse effects and the development of drug resistance. As a result, finding new and effective treatments for various tumours is a constant focus of medical study. The molecular foundation of cancer evolution has been studied in the last two decades, allowing for the identification of a variety of important cellular components involved in carcinogenesis. Protein kinases are among these biological components that, when altered or overexpressed, can cause cancer. Protein kinases regulate practically every cellular function, including metabolism, transcription, cell division, motility, survival, signalling, and programmed cell death. They catalyse

the reaction of adding a phosphate group to a nucleophilic amino acid in the presence of a Mg2+ ion to transfer a gama phosphate group from an ATP molecule to substrate proteins. Tyrosine kinases (TKs), serine/threonine kinases (STKs), dual specificity kinases, which phosphorylate both serine/threonine and tyrosine amino acids, and histidine kinases are the four main types. Kinases and phosphatases are in charge of the reversible protein phosphorylation process, which can be disrupted and result in a variety of diseases. Uncontrolled cell proliferation, which is prevalent in cancer, is caused by impaired kinase activity. This enzyme family has become one of the most important drug targets in the world due to its involvement in a variety of diseases, including cancer..[2]

❖ Roles of GSK-3 beta in cancer: There is conflicting evidence on the effect of GSK-3 inhibition on cancer cell development due to multiple methods through which GSK-3 may influence carcinogenesis.

- GSK-3 as a Tumor-Promoter: Despite years of research, GSK-3 performs a multitude of roles in cancer, all of which are complex and disputed. Because of its aberrant expression, GSK-3 may increase cell proliferation while simultaneously acting as a tumour promoter. In a range of tumour types, including colon, liver, ovarian, and pancreatic malignancies, GSK-3 is overexpressed in the body. When GSK-3beta expression was repressed, pancreatic cancer development and angiogenesis were reduced. GSK-3beta knocked-down cells have decreased amounts of Bcl-2 and vascular endothelial Growth factor (VEGF). GSK-3 inhibitors may be effective in the treatment of tumours where GSK-3 overexpression, which acts as a tumour promoter, is present.[14]
- GSK-3 as a Tumor-Suppressor: GSK-3 has anti-tumors effects as well. By phosphorylating beta-catenin and causing beta-catenin to be destroyed by Ubiquitin/proteasome, GSK-3 suppresses the Wnt/beta-catenin pathway. Overexpression of constitutively active GSK-3 beta mutants improved chemosensitivity, cell cycle arrest, and tumorigenicity in breast cancers in multiple investigations. In breast cancer, medications that inhibit GSK-3 triggered EMT and invasion. GSK-3 inhibition boosted beta-catenin stability, which raised c-Myc, cyclin-B1, and survivin expression, increasing proliferation and carcinogenesis, according to these studies. GSK-3 may have a delicate balance between tumour suppressor and tumour inducer roles, based on these findings.[14]

❖ **Signalling Pathways Associated with GSK 3 Beta:**

GSK-3 could be a cancer target due to its roles. Multiple signalling pathways, including the NF-kB protein, which is typically deregulated in cancer and contributes to cancer progression, trigger many pro-inflammatory genes. GSK-3 also participates in the EGFR/PI3K/AKT/GSK-3/mTORC1, NF-kB, and WNT/-catenin pathways. All three of these pathways are typically dysregulated in human cancer and tumour formation. In multiple studies, GSK-3 inhibitors have been proven to reduce the course of various cancers. Various pharmaceutical companies have invented and developed multiple GSK-3 inhibitors since the first finding of GSK-3's biochemical activity and the link between GSK-3 and many prevalent human disease states. [15]

❖ **Roles of GSK-3 beta in mitochondrial functions:**

The importance of mitochondria in cell death regulation makes GSK-3's mitochondrial function an especially appealing subject of research. In hepatoma cells, for example, pharmacological suppression of the PI-3K signalling pathway can increase the impact of chemotherapy by reactivating GSK-3 and facilitating mitochondrial translocation of Bax and subsequent apoptosis. They defined this conceptual framework as follows: The mitochondrial effects of the Gold(III)-dithiocarbamato complex AUL12, a new generation gold-based chemotherapy aimed to improve platinum-based drug selectivity, bioavailability, and efficacy while reducing toxic side effects. Because AUL12 raises intracellular ROS levels, we decided to target the elevated ROS levels that are characteristic of tumour cells. They reasoned that because cancer cells are forced to induce anti-oxidant defences in order to establish a novel homeostatic state, a further increase in ROS levels would overwhelm their remaining anti-oxidant capabilities, triggering PTP opening and cell death in a selective manner, without causing significant damage to non-transformed cells. Following suppression of the RC complex I, which induces GSK-3 Tyr-phosphorylation and activation, they discovered that AUL12 causes a rapid burst of mitochondrial superoxide levels. The mitochondrial GSK-3 phosphorylates CyP-D, which enables PTP opening, whereas the cytosolic GSK-3 interacts with Bax and causes it to translocate to the mitochondria, where it contributes to PTP induction and tumour cell death. AUL12 was found to be significantly less harmful in non-transformed cells and after in vivo injection. These findings show that inhibiting specific signalling pathways maintained by mitochondria in tumour cells can shut down critical mechanisms that protect neoplasms from the toxicity of many anti-neoplastic strategies, and pave the way for the development of a new class of chemotherapeutic compounds that make cancer cells more susceptible to chemotherapy.[17]

GSK-3 beta translocation into mitochondria in response to stress implies that it receives signals and challenges from the cytoplasm. The mitochondrial pool of GSK-3 beta appears to interact with mitochondrial proteins such as PI3K-Akt, HK II, PKC, respiratory chain components, and mPTP subunits, according to accumulating evidence. GSK-3 beta influences cell fates through changing mitochondrial biology, which has a large spectrum of substrates. Inactivation of GSK-3 beta improves mitochondrial biogenesis, increases mitochondrial dynamics, decreases mitochondrial permeability, and reduces mitochondrial death. Inactivation of GSK-3 beta could be a potential technique for clinical medication development. Natural goods are a fantastic resource for researching potential medicines. The varied effects of GSK-3 beta, on the other hand, are still debatable. More research is encouraged. [7]

❖ **GSK-3 & Carbohydrate metabolism in cancer:**

GSK-3 was found as an inhibitor of glycogen synthase, which is the rate-limiting kinase in glycogen production, as previously stated. Glycogen, the body's carbohydrate storage form, is primarily found in the liver and muscle, although it can also be found in other cell types. It's worth noting that glycogen expression is substantially lower in poorly differentiated cancer cells, which are the most aggressive and have the highest rate of proliferation. Rapidly dividing cancer cells are expected to demand a steady and large supply of glucose, with little need for glycogen production or storage GSK-3 may contribute to cancer cell proliferation by limiting glycogen production, allowing cancer cells to fully utilise glucose for energy and macromolecular synthesis. Given that cancer cells' energy metabolism is mostly based on glucose, cancer cells should be more susceptible to changes in glucose metabolism than normal cells. GSK-3 inhibition may affect glucose metabolism in cancer cells by upregulating glycogen synthesis, resulting in changes in catabolic (anaerobic glycolysis) and anabolic (nucleotide synthesis) processes in the cancer cell, which could lead to decreased cancer cell proliferation and survival, though this hypothesis needs to be investigated further. [12]

2.4.1. Lung cancer

In lung cancer cells, wingless integration suppresses GSK-3 beta, resulting in an increase in free beta catenin and up-regulation of E-cadherin. In 2003, Ohira et al. reported on this phenomena. Their findings show that WNT/b-catenin signalling induces E-cadherin expression in lung cancer cells, which is an evolutionarily conserved mechanism. Because of its effects on E-cadherin, loss of WNT7a expression may be essential in lung cancer formation or progression (Ohira et al., 2003). Tian et al. (2006) investigated the putative function of GSK-3 beta in lung cancer and found that cigarette smoke components inhibited GSK-3 beta in vitro in a similar way to lithium or SB216763 Inhibition of GSK-3 beta by cigarette smoke or GSK-3 beta inhibitors such as lithium and SB216763 increased involucrin expression in cultured swine tracheobronchial epithelial cells, most likely through negative control of AP-1 activity, resulting in squamous differentiation. These findings shed information on the potential significance of GSK-3 beta in the development of lung cancer.[9]

2.4.2. Colon cancer

Shakoori Et al. (2005) found that pharmacological inhibitors inhibiting GSK-3 beta activity and RNA interference inhibiting GSK-3 beta expression caused apoptosis and decreased proliferation in colon cancer cells. This observation shows that GSK-3 beta plays a function in tumour cell survival and proliferation. Others discovered that prostaglandin E2 trans-activated the b-catenin/TCF-dependent activation of TCF-4 in colon cancer cells by inhibiting GSK-3 beta (Liao Et al., 2004). The activation of TNF-related apoptosis-inducing ligand (TRAIL) by wortmannin was fully abolished when GSK-3, a downstream target of active AKT, was inhibited. Wang et al. reported on this (2002). Inhibition of PI 3-kinase caused the production of TRAIL in colon cancer cell lines, according to their findings. The research also paved the door for a better understanding of the PI 3-kinase/AKT/GSK-3 Pathway's role in intestinal cell homeostasis. Kang and colleagues showed in 2008 that inhibiting GSK-3 beta in human tumour cells regulates Cdc25A ubiquitin-mediated proteolysis during the early stages of the cell cycle. GSK-3 beta inactivation was closely linked with Cdc25A overproduction during the G1 phase of the cell cycle. The PI-3K/AKT pathway inhibits both GSK-3 beta and CHK1, which promotes cell cycle progression by increasing Cdc25A levels.[9]

2.4.3. Prostate cancer

In prostate cancer cells, the activity of Glycogen Synthase Kinase-3 beta is essential for androgen-stimulated gene expression. The crosstalk between the PI3K/AKT and androgen pathways is mediated by B-catenin. The numerous roles of PI3K/PK in cell cycle progression were described by Liang and Slingerland (2003). GSK-3 beta is phosphorylated and inactivated by the PI3K/AKT signal, resulting in higher nuclear levels of b-catenin. As a result, elevated b-catenin stimulates prostate cell growth and survival via increasing androgen receptor activity. GSK-3 beta inhibition makes prostate cancer cells more susceptible to TRAIL-induced apoptosis. Caspases-8 activity is required, while NF-kB activation is not required. This shows that TRAIL resistance in prostate cancer cells may be caused by a mechanism involving GSK-3 beta activation.[9]

2.4.4. Renal cancer

Each year, 64,000 new cases of renal cell carcinoma (RCC) are diagnosed in the United States, with 14,000 deaths due to RCC. Systemic therapy for metastatic RCC has significantly improved in the last decade, moving away from immunotherapeutic interferon alpha and toward a variety of targeted therapeutics, such as anti-angiogenic drugs targeting vascular endothelial growth factor and its receptors, mTOR inhibitors, and receptor inhibitors, which are needed to improve treatment outcomes for patients with metastatic RCC. Glycogen synthase kinase-3 (GSK-3) is a serine/threonine kinase that has a role in a variety of diseases, including cancer9-ING-41, a maleimide-based ATP-competitive small molecule GSK-3 beta inhibitor, has been demonstrated to be effective in advanced cancer patients. Treatment with 9-ING-41 alone caused cell cycle arrest and death in kidney cancer cell lines, and autophagy inhibitors improved 9-ING-41's anticancer effects when used in combination. On kidney cancer cell lines, 9-ING-41 treatment boosted the cytotoxic effects of cytokine-activated immune cells and potentiated the anticancer effects of targeted therapies. These findings supported the inclusion of patients with renal cancer in 9-ING-41 investigations, both as a single agent and in conjunction with already available treatments.[18]

2.4.5. Giloblastoma multiforme (GBM)

GSK-3 beta expression and activity in GBM cell lines were shown to be greater than in normal brain tissue. In 57 human tumour specimens, the active form of GSK-3 beta (pGSK3y216) was linked to poor progression-free survival and overall survival (OS), and multivariate analysis demonstrated that GSK-3 beta activation was an independent predictor of poor outcome. Multiple pathways in the pathogenesis of GBM have been linked to GSK-3 beta. When c-Myc is active, GSK-3 beta inhibition can cause glioma cell cytotoxicity. According to a study by Koru et al., GSK-3 inhibition may selectively target a subpopulation of GBM with stem cell-like traits In PDX models of human GBM, Ugolkov et al. found that combining the GSK-3 beta inhibitor 9-ING-41 with lomustine, one of the conventional therapy for recurrent GBM, increased anticancer efficacy. In staged orthotopic GBM12 and GBM6 PDX models with minimal response to single agent lomustine, the effect of 9-ING-41 was demonstrated. Importantly, the combination treatment resulted in histologically proven cures and a considerable increase in overall survival.[19]

2.4.6. Neuroblastoma

Neuroblastoma is a rare sympathetic nervous system cancer that affects predominantly infants and young children under the age of five. Its distinct appearance and tumour biology provide difficulties in developing successful treatment regimens, particularly in patients identified as high risk (>MYCN expression). The suppression of the GSK-3 signalling pathway in cancer has been a focus of research in recent years. In recent years, studies investigating GSK-3 inhibitors in cancer treatment have mostly focused on three compounds: Tideglusib, AR-A011418, and LY2090314. The data show that inhibiting GSK-3 with LY2090314 suppresses NB growth. In comparison to Tideglusib,

low doses of LY2090314 greatly inhibited NB cellular development. This research shows that LY2090314 has the potential to be a future treatment for NB.[20]

3. GSK 3 BETA INHIBITORS

With the growing interest in targeting GSK-3 for anti-cancer and anti-inflammatory therapy, as well as the treatment of neurological illnesses, the number of inhibitors accessible has expanded.[8]

3.1. LITHIUM

The most prevalent usage of lithium is to treat bipolar disorder. It was previously discovered to be a selective inhibitor of GSK-3, which considerably benefited study into the signalling pathways of this enzyme. GSK-3 dysregulation and lithium inhibition may have a role in mental disease and treatment, according to this discovery. Its biological mechanism of action is unknown. In the brain, lithium has several effects, one of which is the reduction of GSK-3-induced tau phosphorylation. At therapeutic doses, it reversibly reduced tau phosphorylation and had no effect on neuronal structure, even at high concentrations. It also promotes neuroprotection and lowers neuronal mortality induced by fibrillary b-amyloid, which appears to be mostly related to GSK-3 inhibition. Future study into the effects of mood-stabilizing medications, as well as the molecular mechanisms behind affective disorders, will be influenced by these discoveries. [15]

3.2. VALPROIC ACID

Valproate, a mood stabiliser also used to treat bipolar disorder and epilepsy, has been shown to inhibit the GSK-3 enzyme in this way. Valproic acid decreases GSK-3 activity in vivo, suggesting that lowering GSK-3 beta activity could help with behavioural issues in addition to Alzheimer's disease. It operates by inhibiting histone deacetylase directly, which is a distinct method. This finding could explain valproic acid's effectiveness in the treatment of bipolar disorder and point to a mechanism for valproic acid-induced birth defects. To better understand how mood-stabilizing drugs function, the involvement of GSK-3 in this pathological process, and the clinical value of GSK-3 inhibitors, more research is needed. It is extremely useful in a variety of scenarios. [5]

3.3. ATP Competitive and ATP Non-competitive Inhibitors

The remaining small molecule GSK-3 inhibitors can be divided into two groups: ATP competitive and non-competitive. ATP competitive inhibitors are inhibitors that compete with ATP for binding to GSK-3 beta.Several ATP competitive GSK-3 inhibitors from different Structural classes

1. Lithium Chloride
2. Maleimide Derivatives.
3. Staurosporine and Organometallic Inhibitors.
4. Indole Derivatives.
5. Paullone Derivatives
6. Pyrazolamide Derivatives
7. Pyrimidine and Furopyrimidine Derivatives
8. Oxadiazole Derivatives
9. Thiazole Derivatives

Hymenialdisine has been demonstrated to have immunosuppressive properties, as well as inhibiting GSK-3, according to subsequent studies. Because it has been discovered to inhibit other kinases in addition to GSK-3, such as cyclin-dependent kinase and casein kinase 1, it is likely that competition with ATP binding sites is the mechanism of action.

Paullones are a different type of competitive inhibitor with anti-tumor potential. Alsterpaullone has recently been discovered to cause apoptosis by inducing caspase-9 activation via mitochondrial membrane rupture. The potential of mitochondrial membranes is referred to as mitochondrial membrane potential.

GSK-3 inhibitors such as indurubins and maelimides have also been developed, while much of the research so far has focused on their potential applications in diabetes and neurological disease.

Thiadiazolidones (TDZD) are the first ATP-independent GSK-3 inhibitors. They are likewise specific to GSK-3 and do not inhibit other kinases, and early research has shown that they are effective anti-inflammatory medicines, but there is limited evidence that they could have an anti-cancer role.[5]

Many of the GSK-3 inhibitors in development are also powerful CDK inhibitors, which is a major result. GSK-3 is one of the most closely related enzymes in the CDK family. CDK inhibitors are anti-cancer agents that cause apoptosis in a wide range of cell lines. It's unclear how much GSK-3 inhibition adds to previously published findings about CDK inhibitors and their effect on cancer, but it's likely that concurrent GSK-3 inhibition contributes to CDK inhibitors' therapeutic properties. Agents for clinical application, on the other hand, must be able to target the correct enzymatic pathway. Inhibition of non-specific protein kinases by ATP site-directed inhibitors could have far-reaching consequences. The vast majority of GSK-3 inhibitors identified to date are in this category. All of them have a lot of additional kinase activity, which limits their drug development options. Only ATP-non-competitive GSK-3 selective inhibitors constitute an effective strategy for developing true therapeutically useful medicines. [5]

With the availability of specifically designed transgenic animal models, the relevance of GSK-3 as a therapeutic target may be tested. As the body of evidence pointing to GSK-3 having a seminal role in neurodegeneration is substantial, a lot of work has been developed in this area. Several transgenic animal models, including different species as lampreys, mice or rats, provide currently an in vivo model in which therapies for neurodegenerative diseases can be assessed. Up to date three transgenic mice that over express GSK-3 in the nervous system have been reported. Conversely GSK-3 knockout mice die during embryonic life pointing to the crucial role of this kinase in development. These in vivo genetic techniques have also clearly established the role of GSK-3 in neurodegeneration, making the conditional transgenic model an exceptional tool for testing the neuroprotective effect of the upcoming GSK-3 specific inhibitors.[13]

Despite GSK-3's extraordinary evolutionary resilience, each new substrate that emerged, as well as each new mechanism that regulates GSK-3 activity, gave additional potential areas that could be vulnerable to disease-related insults. Self-activating processes, in which GSK-3 encourages its own further activation, may be especially essential in various illnesses and therapeutic approaches, according to our findings. Several pathways were discovered here by which GSK-3 can further boost its own activation if a compartment of GSK-3 is inappropriately activated early in an illness. As a result, it's easy to see how a minor GSK-3 dysregulation can get exacerbated as a disease continues, promoting pathology. [3]

To put it another way, reducing disease-related self-amplification of GSK-3 activity may be enough to be therapeutically useful, and it's certainly more likely to be tolerated than total GSK-3 suppression. [3]

Our understanding of the molecular mechanisms behind GSK-3 signalling pathways has expanded significantly as a result of extensive research. We now have the technology to search for and identify novel GSK-3 inhibitors that are both powerful and selective. Furthermore, the crystal structure of GSK-3 provides a powerful tool for medicinal chemists to boost their inventiveness in the design of particular inhibitors that target specific amino acids inside the enzyme. In conclusion, basic and applied research have provided an adequate technological platform for the development of selective GSK-3 inhibitors to inhibit and delay the progression of neurodegeneration, among other important pathologies for which a specific treatment is expected to emerge in the coming decades.[13]

❖ **Centrosome regulation by GSK-3 beta inhibitors**

Following centrosome abnormalities, inhibition of GSK-3 beta caused two forms of cell death: apoptosis and mitotic catastrophe. Mitotic spindle deformations were produced by GSK-3 beta inhibitors, which disturbed centrosome control. As a result, chromosome mis-segregation occurred, leading to chromosomal instability. In cell lines with an intact apoptosis pathway, these mitotic aberrations resulted in apoptotic cell death. Furthermore, in cell lines lacking apoptotic pathways, these anomalies resulted in mitotic catastrophe. This paper proposes a novel molecular mechanism for GSK-3 beta inhibitors' anti-proliferative effects: Inhibition of GSK-3 beta causes centrosome dysregulation and mitotic abnormalities, which leads to cell death and mitotic catastrophe.[21]

3.4. COMBINING GSK-3 INHIBITORS WITH CHEMOTHERAPEUTICS, RADIATION OR AUTOPHAGY INHIBITORS

GSK-3 is a versatile enzyme that phosphorylates a wide spectrum of protein substrates, changing their stability in the process. When GSK-3 phosphorylates a protein, it is commonly but not always destroyed. Because GSK-3 phosphorylates so many proteins, these phosphorylation events can either suppress or activate a process (for example, phosphorylation of the SNAIL transcription factor, which normally promotes invasion, can block invasion) (e.g., phosphorylation of p27Kip-1 which normally suppresses cell growth and cell growth now occurs after GSK-3 phosphorylation of p27Kip-1). This disparity in outcomes could explain why this is the case. It's impossible to say whether GSK-3 inhibitors will help or hurt in terms of cancer progression. [15]

The effects of GSK-3 inhibitors, radiation, and chemotherapy in combination were studied. Several GSK-3 inhibitors have been discovered to boost the chemosensitivity of particular cancer cells. GSK-3 inhibition worked as a tumour suppressor in circumstances where GSK-3 was acting as a tumour promoter. Combining GSK-3 inhibitors with paclitaxel improved the mortality of non-small cell lung cancer cells, according to research (NSCLC). Microtubule stability is regulated by GSK-3, which aids in the precise alignment of chromosomes on the metaphase plate. GSK-3 is overexpressed and hyperactivated in certain NSCLCs. Some synergistic effects were discovered to be caused by a defect in chromosomal alignment. GSK3 activity was first thought to be diminished in NSCLC due to an increase in phosphorylation of the enzyme's inhibitory N-terminal serine phosphorylation site (Ser21 on GSK3 and Ser9 on GSK-3 beta). However, it was demonstrated that GSK-3 Ser21/9 phosphorylation was elevated in NSCLC tumour tissue as compared to patient-matched normal lung tissue, and that this inhibitory effect was counteracted by the enzyme's overexpression. It's also shown that, rather of the expected decline, this resulted in an overall net increase in protein kinase activity. This has clinical significance because it has been shown that elevated GSK-3 beta expression in NSCLC is linked to a poor patient prognosis. A recent first-in-human phase I trial showed that intravenous administration of the GSK-3 inhibitor, LY2090314, in combination with pemetrexed and carboplatin was tolerated at a safe dose, with mesothelioma and NSCLC patients demonstrating the most promising reduction in tumour size from baseline. [16]

3.4.1. Breast cancer

Breast cancer is the most frequent malignancy among females worldwide. Despite major breakthroughs in breast cancer early detection and surgical treatment, as well as neo adjuvant and adjuvant therapy, over 30% of breast cancer patients may develop incurable metastatic disease. Traditional chemotherapeutic treatments have had little influence on the progression of metastatic disease. Metastatic breast cancer is an incurable disease with a significant unmet medical need, with median survival rates varying from one to four years depending on the subtype. It is crucial to develop new focused therapeutic drugs.[22]

Glycogen Synthase Kinase-3 (GSK-3) is a serine/threonine protein kinase that was originally discovered to be a key enzyme in glycogen metabolism but is now recognised to regulate a wide range of cellular functions. GSK-3 phosphorylates a variety of metabolic, signalling, and structural proteins, altering their activity. GSK-3 has been considered a prospective tumour suppressor in the past due to its ability to phosphorylate and so target pro-oncogenic molecules such as c-Jun, c-Myc, cyclin D1, and beta catenin for ubiquitin-dependent proteosomal degradation. GSK-3 may be employed as a cancer therapeutic target in human leukaemia, pancreatic cancer, colon cancer, bladder cancer, renal cancer, and breast cancer, according to new research. In human breast cancer, overexpression of GSK-3 has been associated to a variety of indicators of poor prognosis, with patients with GSK-3 expression in the highest quartile (246 of 1686 cases) having a 2.7 and 1.7-fold higher chance of distant relapse 5 and 10 years following tumour excision, respectively. In a recent study, knocking down GSK-3 significantly slowed the growth of breast cancer cells. GSK-3 knockdown had only a minor effect on proliferation in four breast cancer cell lines, indicating that GSK-3 is a prospective therapeutic target for the treatment of breast cancer.[22]

Several studies show that pharmacological inhibition of GSK-3 by two novel ATP competitive small molecule GSK-3 inhibitors, 9-ING-41 and 9-ING-87, reduced the viability of breast cancer cells but had little effect on non-tumorigenic cell growth, based on the potency of

their antiproliferative activity against pancreatic and ovarian cancer cells in vitro, as well as supportive ADMET and PK studies. 9-ING-41 treatment improved the anticancer effect of irinotecan (CPT-11) on breast cancer cells in vitro. From metastatic pleural effusions obtained from cancer patients, two patient-derived xenograft tumour models (BC-1 and BC-2) were developed. In mice with progressing, chemo resistant breast cancer, 9-ING-41 was demonstrated to improve the efficacy of the chemotherapeutic drug CPT-11 in vivo, resulting in the shrinkage of existing BC-1 and BC-2 tumours. This study shows that inhibiting GSK-3 might be a good way to beat chemoresistance in metastatic breast cancer. [22]

3.4.2. Ovarian Cancer

The most deadly gynaecological disease in women is ovarian cancer. The primary pharmacological treatment for ovarian cancer is paclitaxel induced carboplatin, however most women acquire drug resistance and the illness recurs, necessitating the use of other therapies. The Wnt pathway has been linked to a variety of malignancies, including ovarian cancer, although just a few research have looked into pharmacological inhibitors of this route as cancer treatments.[26]

Glycogen synthase kinase 3 (GSK-3), a downstream kinase in the Wnt signalling pathway that is overexpressed in serous ovarian cancer, could be a potential biological target for cancer therapy. In advanced stages of ovarian cancer, an increased level of GSK-3 beta is detected. The overexpression of GSK-3 beta increased proliferation of ovarian cancer cell lines indicating that this protein has a unique role in ovarian cancer. GSK-3 has a new involvement in ovarian cancer cell proliferation, perhaps through modulation of cell cycle progression and cyclin D1 expression. The findings show that GSK-3 is involved in the proliferation of ovarian cancer cells. In ovarian cancer, it's unclear if GSK-3 influences cell proliferation via NF-kB-mediated gene transcription. GSK-3 phosphorylates and inhibits glycogen synthase activity, causing glucose metabolism to rise. Cancer cells have a quick metabolism and high glucose requirements, and tumours rely on anaerobic pathways to convert glucose to ATP even when oxygen is abundant. Tumor cells maintain ATP synthesis by increasing glucose inflow to satisfy the energy demands of uncontrolled proliferation. As a result, active GSK-3 in ovarian cancer may enhance cell proliferation by blocking glycogen synthesis, resulting in excessive glucose consumption.[24]

One of the most challenging questions to answer when dealing with ovarian cancer is whether it is resistant to chemotherapy. This can happen through a variety of mechanisms, including activation of the nuclear factor NF-kB, which can lead to diminished cell death and drug resistance. Furthermore, increased levels of cyclin D1 expression have been linked to resistance to chemotherapy. GSK-3 increased the expression of cyclin D1 in ovarian cancer cells, implying that GSK-3 may be involved in chemotherapy resistance. As a result, combining normal chemotherapy with a GSK-3 inhibitor may be able to prolong the lives of ovarian cancer patients. Finally, these data imply that GSK-3 promotes ovarian cancer cell proliferation and that cyclin D1 may be involved in its regulation; however, the exact mechanisms are unknown at this time. [24]

To create, select, and test new maleimide-based GSK-3 inhibitors, researchers used the SKOV3 and OVCA432 serous ovarian cancer cell lines (GSK-3i). Out of a panel of 10 inhibitors, the GSK-3i 9ING41 inhibitor was found to be the most effective in vitro. Positive nuclear condensation with 4′6-diamidino-2-phenylindole (DAPI), PARP cleavage, and terminal deoxynucleotidyl transferase dUTP nick end Labeling (TUNEL) staining all suggested that 9ING41 accelerated apoptosis. The cleavage of caspase-3 triggered apoptosis. GSK-3i enhanced phosphorylation of the inhibitory serine residue of GSK-3 and decreased phosphorylation of the downstream target glycogen synthase in the OVCA432 and SKOV3 cell lines. According to an in vivo xenograft study using SKOV3 cells, 9ING41 reduced tumour formation in vivo. 9ING41 had a maximum tolerated dosage of more than 500 mg/kg in rats. According to a pharmacokinetic investigation, 9ING41 exhibited a bioavailability of 4.5 percent and was well dispersed in tissues. As a result, GSK-3 beta inhibitors, either alone or in combination with other medications, may slow the progression of serous ovarian tumours.[10]

3.4.3. Pancreatic Cancer

PDAC (pancreatic cancer) is a cancer with no cure and one of the lowest survival rates of any cancer. One of the main reasons for the poor outcome is the simultaneous activation of many pro-cancer pathways in cancer cells, which allows them to evade treatments aimed at suppressing a single oncogenic pathway. Gemcitabine, Abraxane, and the FOLFIRINOX combo regimen are the current standard regimens for most patients with PDAC chemotherapy and radiation. Each of these therapies is extremely hazardous, with only a sliver of long-term efficacy. The fact that the drugs themselves trigger pro-cancer pathways is one reason for their ineffectiveness. The mechanism by which these treatments cause resistance is unknown. Despite this, none of the existing treatments have had any effect on drug resistance or metastatic routes. Drugs that target several tumor-survival pathways are quickly gaining traction as a viable alternative to single-targeted therapy. Sorafinib and Lapatinib, for example, are pan-protein tyrosine kinase inhibitors that have been used to treat advanced kidney, liver, and breast cancers. However, similar drugs that target several pathways have yet to be developed for the treatment of PDAC. Post-translational and epigenetic changes have a big impact on cancer development. [27,28]

Glycogen synthase kinase-3 beta (GSK-3-beta) is a widely expressed serine/threonine kinase implicated in metabolism, oncogenesis, and neurological diseases. By upregulating NF-kB activity in PDAC, GSK-3 beta activates pathways involved in cell proliferation, the production of pro-tumorigenic cytokines, and the development of apoptosis resistance. In an orthotopic model of PDAC research, a GSK-3 beta inhibitor lowered NF-kB activation and reduced tumour size. Surprisingly, inhibiting GSK-3 beta enhanced transcription factors such as SNAIL, which promote epithelial to mesenchymal transition (EMT). EMT pathways are responsible for tumour invasion and metastasis. The EMT transcription factor Zeb1 is associated with the mesenchymal phenotype in PDAC cells, and blocking GSK-3 beta causes EMT. GSK-3 beta appears to have two functions: (1) pro-cancer by promoting NF-kB activation, and (2) anti-cancer by inhibiting EMT and metastasis, according to these data. As a result, a strategy that relies solely on suppressing GSK-3 beta is problematic. Combining GSK-3 inhibitors with other small molecular chemotherapeutic medicines, on the other hand, may boost the efficacy of GSK-3 inhibitors in cancer patients. [27]

3.4.4. Hepatocellular carcinoma (HCC)

HCC is the fourth most prevalent tumour in the world, however treatment options are limited. GSK-3 beta expression and therapeutic implications in HCC are mostly unknown. GSK-3 beta is overexpressed in HCC, according to a recent study, and targeting GSK-3 beta can result in the degradation of c-FLIPL, a master anti-apoptotic regulator. Overexpression of GSK-3 beta promotes HCC cell proliferation,

colony formation, and tumour development, whereas Tideglusib, a GSK-3 beta inhibitor, inhibits HepG2/3 beta xenograft growth by 22.3 percent. Overexpression of functional GSK-3 beta has been shown to promote HCC development. Because overexpression of GSK-3 beta makes HCC resistant to chemotherapies like retinoid and sorafenib, the therapeutic value of targeting GSK-3 beta could be found in its conjunction with other anticancer medicines. Sorafenib, a multi-kinase targeted anti-cancer medication, is commonly used to treat HCC, however resistance to it is common. The effect of GSK-3 beta-mediated RAR beta inhibition on Sorafenib therapy response was investigated, and it was discovered that Sorafenib can significantly activate GSK-3 beta both in vitro and in the tumour microenvironment. Sorafenib treatment will result in abundantly overactive GSK-3 beta since GSK-3 beta is extensively expressed in HCC. As seen in multiple GSK-3 beta stable liver cell lines against their vector-transfected counterparts, overexpression of functional GSK-3 beta significantly inhibits sorafenib activity. In GSK-3 beta stable cell lines, where RAR beta is suppressed by GSK-3 beta, 9-cis-RA cannot promote RAR beta expression on its own. Tideglusib, which targets GSK-3 beta, can dramatically enhance 9-cis-RA activation of RAR beta-dependent signalling. Importantly, reactivating RAR beta-dependent signalling, which has been suppressed by GSK-3 beta overexpression, results in a completely unanticipated sorafenib therapy response (tumor Inhibition raised sharply from 48.3 percent to 93.4 percent).[30]

4. RESULTS AND DISCUSSION

Glycogen synthase kinase (GSK)-3 has emerged as one of the most promising therapeutic targets for cancer, Alzheimer's, stroke, and bipolar disorders, as well as noninsulin-dependent diabetic mellitus and inflammation. GSK-3's role in tumour formation and progression is controversial since it has a number of effects on cellular processes and pathways that differ between cell types. GSK-3 possesses both prooncogenic and tumor-suppressive characteristics, according to research. In any case, GSK-3 beta is a key regulator of nuclear factor (NF)B nuclear activity, suggesting that inhibiting GSK-3 beta could be useful in the treatment of a wide range of cancers with constitutively active NFB. GSK-3 inhibitors have been demonstrated to have anticancer activity in a variety of human cancer cells, and they may also help to promote a more effective immune response against tumour target cells, resulting in a two-fold therapeutic benefit. When used in combination therapy, they can improve tumour cell reactivity to chemotherapeutic drugs, enhancing the efficacy of therapies for breast, ovarian, pancreatic, and hepatic malignancies. In animal models, GSK-3 inhibitors have been proven to improve a surprisingly large range of illnesses and other medical issues. In most circumstances, therapeutic goals should not be targeted at obtaining a high degree of GSK-3 inhibition, as this would likely be harmful due to GSK-3's multiple functions. Instead, in the near future, the focus should be on finding drugs that specifically target GSK-3 in specific disease processes, such as drugs that target GSK-3-substrate interactions that are dysregulated in specific diseases, or drugs that weakly but sufficiently inhibit GSK-3 to prevent self-activation in pathological processes.

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