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REVIEW ARTICLE

Glycogen Synthase Kinase-3 (GSK-3) Inhibitors as a New Lead for Treating Breast and Ovarian Cancer

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Abstract: A serine/threonine-protein kinase, recognized as Glycogen Synthase Kinase-3 (GSK-3), is documented as a regulator of assorted cellular roles. GSK-3 activates by phosphorylation and thereby controls the action of many physiological, messenger, and membrane-bound structures. GSK-3α and GSK-3β are two vastly homologous forms of GSK-3 in mammals. Recent information has recommended that GSK-3β is a constructive controller of cancer cell proliferation and a promising key target against cancer cells. GSK-3 is overexpressed in various tumor types, including ovarian tumors. In human breast carcinoma, it has been revealed that the overexpression of GSK-3β was linked with breast cancer patients. The inhibition of GSK-3 or inhibitors of GSK-3 is a promising therapeutic tactic to overcome breast and ovarian cancer. This article features an important aspect of inhibitors of Glycogen Synthase Kinase-3 as a new lead for treating breast and ovarian Cancer.

Keywords: Glycogen synthase kinase-3, breast cancer, ovarian cancer, tumor, cell cycle, proliferation.

1. INTRODUCTION

Glycogen synthase kinase-3 (GSK-3), an enzyme initially exposed to the world due to its capability to inhibit the glycogen synthase by phosphorylation, is primary for the downregulation of glycogen [1, 2]. GSK-3, a serine/threonine-protein kinase, is documented as a regulator of assorted cellular events [3]. It activates by phosphorylation and controls the action of many physiological, messenger, and membrane-bound structures [4]. Moreover, GSK-3α and GSK-3β are two vastly homologous forms of GSK-3 in mammals [5, 6]. Current researchers have advocated that GSK-3β inhibitors positively regulate cancer cell proliferation and have a versatile potential as a therapeutic target in cancer. It is overexpressed in various tumor types, including ovarian tumors [7]. In humans, breast neoplasm has been regulated by GSK-3β phosphorylation, enabling its decrease in the breast cancer patients [8].

The inhibition of GSK-3 or inhibitors of GSK-3 is an encouraging therapeutic tactic to overcome breast and ovarian cancer. This article features an important aspect of these inhibitors, *i.e*., as a new lead for treating breast and ovarian Cancer.

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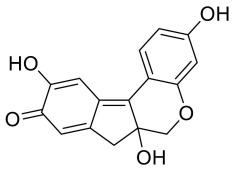
2. GSK-3 INHIBITORS FOR THE TREATMENT OF BREAST CANCER

2.1. Brazilein



3,6a,10-trihydroxy-6a,7-dihydroindeno[2,1-*c*]chromen-9(6*H*)-one

Brazilein is a phytoconstituent obtained from a plant called *Caesalpinia sappan*, which showed biological actions as heart stimulant [9], immunosuppressant [10], neuroprotective agent [11] as well as an anti-cancer agent [12]. Based on these results, it could be thought that brazilein avoided the elimination of ABCB1 carrier to conquer ABCB1-facilitated multidrug-resistance in human cancer cells [13]. On this basis, the scientist investigated the anti-cancer response of brazilein in humanoid breast cancer MCF-7 cell lines. It was found that breast cancer is 28%, among all cancerous problems found in females and anticipated to be 15 percent among the cancerous mortalities in females [14, 15].

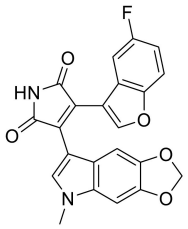
The introduction of innovative cancer therapy has remained a vital technique for resolving breast cancer. *C. sappan* Linn., the evergreen plant commonly spread in China, has its utility in primary remedy to suppress inflammatory responses, stimulate blood flow and cure coagulation

problems [16, 17]. Earlier experiments have shown that the isolates in chloroform from *C. sappan* Linn. caused cell fatality of the cells taken from the head, *i.e*., HNSCC4, and from the neck HNSCC31 [18]. Within this investigation, brazilein isolated in *C. sappan*, a contemporary remedy consumed by the people of China for decades, demonstrated potential anticancerous action in MCF-7 cancerous colonies isolated from the humanoid breast.

The involvement of the CD1 pathway caused cell proliferation, innervated through GSK-3β as per the exhaustive examinations carried out in the literature. Moreover, all advancement in the cell cycle is specifically regulated *via* CDK complexes. CD1 attaches to CDK4 or 6, serially adding phosphate group in descendant target protein retinoblastoma (Rb), and resulting in the production of E2F protein of the Rb / E2F complex [19, 20]. 'Discharging Rb from the E2F transcriptional factor enabled the transcription of target genes whose roles were important for the shift from G1 to S' [21, 22]. In the aforementioned analysis, wherein reduced expression of CD1 was identified by brazilein treatment, prevented the proliferation in cells across the G1/S interface as a part of the cell cycle [15].

β-Catenin, the representative for the Wnt signaling pathway is able to proliferate, differentiate, initiate apoptosis for patient survival, thereby delaying mortality, [23, 24]. CD1 was attributed as a master regulator for the Wnt/β-Catenin signaling transduction pathway [25]. These findings revealed that the obstruction of the β-Catenin pathway was linked with the downregulation of CD1 through brazilein. GSK-3β, a serine/threonine-protein kinase primarily inhibited by the Akt-governed phosphorylation of serine 9, contributed to β-Catenin aggregation and triggered the generation of target genes comprising CD1 [26, 27]. The phosphorylation in the GSK-3β was another important feature in the Akt [28, 29]. The phosphorylation level was reduced by Brazilein in the Akt and GSK-3β (Ser 9), which stimulated GSK-3β, ensuing deprivation of phosphorylated β-Catenin through 26S proteasome. Conclusively, the studies recorded the brazilein persuaded cell death and growth suppression of cancerous MCF-7 colonies of humanoid breast origin by downregulating CD1 protein and mRNA representation, facilitated *via* Akt/GSK-3β/β-Catenin path [15].

2.2. 9-ING-41



3-(5-fluorobenzofuran-3-yl)-4-(5-methyl-5*H*-[1,3]dioxolo[4,5-*f*]indol-7-yl)-1*H*-pyrrole-2,5-dione

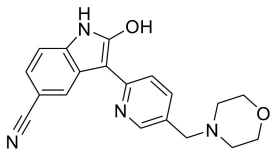
9-ING-41 is an important GSK-3 competitive ATP inhibitor molecule that inhibits both alpha and beta isoforms but has a specific binding affinity to GSK-3β among the 320 associated enzymes of the family [30-32]. It has been established that there is a link between GSK-3β and an incorrect diagnostic approach when utilizing GSK-3β as a diagnostic tool for breast cancer suffering patients [33]. Breast cancer suffering patients show GSK-3β upregulation reflecting a 2.7 and 1.7-times raised danger indistinct reoccurrence of five- and ten-years post-resection, correspondingly [33]. Scientists discovered the aberrant nuclear accumulation of GSK-3β in 5 humanoid breast cancerous colonies and 89 from 128 (70%) humanoid breast carcinomas, however, no upregulation of GSK-3β was noticed during the clinical examination of benign breast tissue [34]. These consequences advocate that the finding related to aberrant nuclear accretion of GSK-3β during biopsy specimens has benefited the pathological finding of breast malignancy, and strengthen the involvement of GSK-3β in the sufferers of these malignancies upon the treatment of GSK-3. For the accomplishment of examinations among such cancerous cases of breasts, an investigation guided the pharmacological suppression of GSK-3 through 9-ING-41 [35], underlying the possibility of cancerous breast colonies *in-vitro* [8]; coherent consequences studied by Shin *et al*. showed that the demolishment of GSK-3β manifestation considerably reduced the breast cancer cell proliferation [36]. Compound '9-ING-41' possesses a specific binding affinity to GSK-3 over 320correlated enzymes by at least one order of magnitude, comprising directly connected serine/threonine kinase enzymes [35]. *In-vitro* outcomes exhibited 9-ING-41 and effective interception for breast cancerous cell enlargement [8]. The treatment by 9-ING-41 boosted the anti-cancer consequence of irinotecan (Camptothecin-11), used for cancerous breast colonies *in-vitro* [8]. Employing breast PDX tumor replicas ascertained by metastatic pleural expressions and found in patients with progressive, chemorefractory breast cancer established that 9-ING-41 with anti-tumor results were exhibited by CPT-11, controlling the regression of instituted breast PDX tumors *in-vivo* [8]. Unstated consequences favor conceptualizations, directing that GSK-3 reduces chemoresistance in breast cancer, and affirming 9-ING-41 as a new GSK-3 pursued mediator that encourages therapy for metastatic breast cancer. During breast cancer reproductions, 9-ING-41 anticancer pursuit establishes different *in-vitro* and *in-vivo* models of cancers of the ovary, pancreas, and kidney and preliminary drug metabolism and pharmacokinetics along with toxicological report favoring the expansion of the research for scientific transformation [35, 37, 38].

3. GSK-3 INHIBITORS FOR THE TREATMENT OF OVARIAN CANCER

Glycogen synthase kinase-3β (GSK-3β) is a serine/threonine kinase having diverse roles in several kinds of cancers [26, 39, 40]. The literature review indicates that the "hyper--activation" of GSK-3β may have a role as an oncogene in numerous types of human cancer, comprising of colon cancer [41], osteosarcoma [42], oral cancer [43], and malignant melanoma [44]. Also, it was found that the expression of GSK-3β is considerably advanced in ovarian carcinoma tissues [45]. Overall, it may be said that GSK-3β plays a vital

part in tumorigenesis, *i.e*., tumor generation and its development. Currently, GSK-3β knockdown and GSK-3β inhibitors have been revealed to impede the explosion of malignant cells in pancreatic [46], prostatic [47], and colonic [48] cancers, and in leukemia [49]. However, in ovarian cancer the inhibitors of GSK-3β have not yet been much explored.

3.1. AZD1080



2-hydroxy-3-(5-(morpholinomethyl)pyridin-2-yl)-1*H*-indole-5-carbonitrile

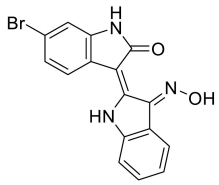
AZD1080 possesses novelty, potentiality, selectivity, orally bioactivity, and is known to be a permeable brain inhibitor of GSK3, inhibiting human GSK3 alpha and GSK3 beta with 6.9 nM and 31 nM Ki, correspondingly [50]. Chen *et al.* in 2016, exposed the two cancer colonies of ovaries, *i.e*., A2780 and OVCAR3 to AZD1080, for studying the processes of amplification, state of the cycle as well as the regular movement of cells and migration of cells through the extracellular matrix. Phalloidin labeling was performed to produce lamellipodia. Cyclin-dependent kinase 2, cyclin-dependent kinase 1, matrix metalloproteinase-9, and B-cell lymphoma through extra-large reverse transcription-polymerase chain reaction and Western blot were conducted to test precise mRNA and protein expression levels of GSK-3β [51]. Most of the studies displayed that GSK-3β transcription or anomalous kinase activity can upsurge the multiplication of the cell and its feasibility and encourage malignant cell transformation, indicating oncogenesis [46, 52-55]. A group of scientists described the GSK-3β inhibitors that can prevent cell growth by modifying CDKs [50].

CDKs attach to cyclins, producing composites possessing protein kinase activity, supporting cell cycle phase evolution, starting DNA creation, and controlling cellular transcription and other events [56, 57]. CDK1 activation stimulates cells to reach the mitosis phase in prostate cancer while fostering MMP2 and MMP9 expression in tumor invasion and intensifying tumor growth [58]. Downregulated CDK2 expression amplified the proportion of cells in G1 in hepatocellular malignancy and diminished cyclin D1 expression [59]. Investigations have revealed that the suppression of GSK-3β through the β-catenin signaling pathway directs the reduction of cyclin D1, MMP9, and Bcl-xL [59-63].

In brief, GSK-3β involves a tumorigenesis role and the promotion and growth of tumors by controlling the related genes. Consequently, inhibitors targeted at the downregulating expression of GSK-3β can play a role in tumor correction. Therefore, an analysis was programmed to determine the function of GSK-3β inhibitor, AZD1080, in the cell lines of ovarian malignancy. A new inhibitor of GSK-3β, AZD1080, has been stated to play a key function in diminishing the downstream, unfavorable results of the signaling pathway, triggered by numerous factors pertinent to the disease called Alzheimer's Disease [50]. Keeping these things in mind, Chen and his co-workers, in 2016, tested the specificity of AZD1080 (at ten micromol concentration) *versus* diverse protein kinases, particularly GSK-3β, CDK2, CDK1. The consequences indicated that AZD1080 has the potential to suppress GSK-3β in the strength ranging from 1 - 10 μmol/kg, presenting the possibility of acute oral dose-dependent medication. They proposed that AZD1080 at doses of 0.125 - 16.0 μM could prevent the development of ovarian cancer. Their consequences exhibited significant declines in the viability of cancer cells at the dosage of 1.0 μM.

Also, AZD1080 significantly reduced the protein and expression of GSK-3β, CDK2 and CDK1, cyclin D1, MMP9, and Bcl-xL mRNA. The tumor growth of A2780 and OVCAR3 was reduced together in a dose-dependent fashion, following the AZD1080 application. They additionally reported that through CDK control, AZD1080 prevents the development of filopodia and cell assault and metastasis, while reducing MMP9 protein expression [51].

3.2. (2Z,3E)-6-bromoindirubin-3′-oxime



(2*E*,3*E*)-6'-bromo-3-(hydroxyimino)-[2,3'-biindolinylidene]-2'-one

(2Z,3E)-6-bromoindirubin-3′-oxime interfere with the chemical pathway of ATP [64]. Previous studies described that (2Z,3E)-6-bromoindirubin-3′-oxime possess anticancerous response in breast and pancreas carcinogenic stem cells, osteogenic sarcoma, along with melanoma [65-68]. The scientist observed the inhibition of multiplication, infiltration, relocation of Ovarian Cancerous cells, along with the inhibition in the generation of cells filopodium by the drug (2Z,3E)-6-bromoindirubin-3′-oxime [69]. Vast GSK-3β studies have recommended that the activation of GSK-3β performs a significant task for tumor activity and growth, however, stimulation is dependent on the characteristics of the tumor. Ougolkov and his co-workers, in 2005, quantified the expression of GSK-3β in cancerous cells of the pancreas [70] and reported greater amounts of GSK-3β expression in the nuclei, which was strongly associated with the specificity of cancerous cells of the pancreas. Additional *in-vivo* studies reported the repression of GSK-3β action that pointedly prevents tumor development in rodents [70].

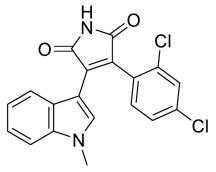
The glioma cell-line apoptosis was inhibited by utilizing GSK-3β inhibitor, LY2064827, through the c-MYC path [40]. GSK-3β activation may be linked *via* the dissemination of renal tumors. Correspondingly, the mitigation of GSK-3β by inhibiting the function of NF-κB can prevent the dissemination of renal tumors [71]. In a subtype of OC cells (SKOV3 cells), suppression of GSK-3β function can prevent its proliferation, and accelerate GSK-3β activity, which contributes to the spread of GSK-3β activity [72]. Recently,

Cao and his colleagues in 2006 have observed that GSK-3β amplification can facilitate the proliferation of OC cells [73]. Moreover, Fu and his co-workers have shown that the inhibition and aberrant induction of GSK-3β may lead to the development of OC and have a beneficial effect as an independent prognosis factor in patient populations with epithelial ovarian cancer. These studies indicate that GSK-3β can facilitate the spread/survival of different types of tumor cells.

The GSK-3β reduction may be the basis of OC therapy. The current study revealed that the dissemination of A2780 and OVCAR3 cells could be decreased by varying ratios of the GSK-3β inhibitor BIO. We also observed that BIO had a concentration-dependent decline in the number of cells in the S/M phase of the cell cycle, a decrease in the number of attacking and migrating cells, major improvements in the composition of the cytoskeleton, and a decrease in the capacity to form pseudopodia. The suppression of GSK-3β through the β-catenin signaling pathway and inhibition of NF-£B expression contributes to the depletion of cyclin D1 and decreases p21 and MMP9 function [42, 61, 62, 74, 75]. This has been tested by GSK-3β siRNA cells, which were transfected in ovarian cancer cells, contributing to cyclin D1 and MMP9 downregulation and P21 upregulation. These phenomena cause the arrest of the G1/S phases of the cell cycle and reduce the overexpression of cancer cells.

The forecast of few GSK-3 inhibitors by Moelcular Docking and ADMET discloses 6-bromoindirubin-3-oxime as a promising inhibitor [76]. Scientists exhibited that the GSK-3β inhibitor, (2Z,3E)-6-bromoindirubin-3′-oxime, can restrain the proliferation, invasion, and migration of ovarian cancer cells and decrease the development of filopodia. Consequently, (2Z,3E)-6-bromoindirubin-3′-oxime might be employed to get rid of ovarian cancer.

3.3. SB216763



3-(2,4-dichlorophenyl)-4-(1-methyl-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione

SB216763 is a lightweight, effectively targeted GSK-3 blocker that is presently being exploited to test GSK-3 activity [48, 77]. For minimizing oxidative damage, SB216763 was used to raise anti-oxidant levels of Nrf2 and heme oxygenase-1 (HO-1) by blocking GSK-3 throughout the liver and hippocampus [78]. For the reduction of the proliferation of cancer cells, the suppression of GSK-3 activity by SB216763 has been displayed [48]. Also, research findings have shown that the initiation of GSK-3 is connected to cancer invasion and therapeutic tolerance [7], representing that GSK-3 suppression can trigger instead of antagonizing the consequences of chemotherapeutic agents like the doxorubicin.

Therefore, we hypothesize that SB216763's suppression of GSK-3 activation abrogates DOX-induced ovarian toxic effects and preserves DOX's anti-cancer potential. At the same time, further research on the consequences of GSK-3 suppression and more pathological tests upon its safety of SB216763 on ovaries are required. GSK-3 may also be an enticing goal for the discovery and production of new medicines to safeguard the selection of ovaries throughout chemotherapy [79, 80].

4. AUTHORS' INSIGHT ON THE TOPIC

This article covers the GSK-3 inhibitors used for the inhibition of the Glycogen Synthase Kinase-3. These inhibitors are categorized into two categories, one for the treatment of breast cancer and another for ovarian cancer. The first category includes the Brazilein and 9-ING-41, whereas the second includes AZD1080, (2Z,3E)-6bromoindirubin-3'-oxime and SB216763. Through the downregulation of CD1 protein and mRNA expression, Brazilein persuaded cell destruction and theinhibition of cancerous MCF-7 cells, which have been regulated by the Akt/GSK-3β/β-Catenin cascade. 9-ING-41 suppressed the viability of breast cancer cells by the inhibition of GSK-3. Moreover, AZD1080 inhibits ovarian cancer progression by reducing the viability of cancer cells, along with the reduction in the protein and the expression of GSK-3β, CDK2, and CDK1, cyclin D1, MMP9, and Bcl-xL mRNA. The BIO inhibitor of GSK-3β inhibits ovarian cancer cell differentiation, infiltration, and spread and decreases the development of filopodia. By raising the amounts of the anti-oxidants Nrf2 and heme oxygenase-1 by GSK-3 inhibition, SB216763 ameliorates oxidative damage.

CONCLUSION

Conclusively, as inhibitors of GSK-3, Brazilein and 9-ING-41 are promising therapeutic tactics to overcome breast cancer, while AZD1080, (2Z,3E)-6bromoindirubin-3'-oxime, and SB216763 are promising therapeutic tactics to overcome ovarian cancer, . This article features an important aspect of the inhibitors of Glycogen Synthase Kinase-3, *i.e*., as a new lead for treating Breast and Ovarian Cancer.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors have no conflicts of interest, financial or otherwise.

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