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Research Article
Siomycin A Induces Cytotoxicity in Gastric Cancer Cells by Targeting AKT/FOXM1 Axis

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Abstract

Background and Objective: Globally, Gastric Cancer (GC) is one of the leading causes of death associated with cancer. Over-expression of FOXM1 (forkhead box M1) has been observed in various cancers, implying that it plays a role in cancer progression. The study aims to examine the effect of Siomycin A on the AKT/FOXM1 signalling pathway, which can open new avenues in GC treatment. **Materials and Methods:** The cytotoxicity of Siomycin A was monitored on GES and SGC-7901 cell lines using the MTT assay. Effects on migratory ability and apoptosis were studied in the presence or absence of Siomycin A. Finally, the expression pattern of Bax, Bcl2, cleaved Caspase-3, FOXM1, AKT and pAKT was monitored to study the effect of Siomycin A. **Results:** FOXM1 was found to be highly over-expressed in GC cells. Siomycin A reduced the viability of gastric cancer cell line, SGC-7901, in a dose-dependent manner with minimal toxicity on normal gastric epithelial cells, GES. Furthermore, Siomycin A significantly induced apoptosis, altered the ratio of pro-and apoptotic markers and inhibited the migratory properties of SGC-7901 cells. Treatment of SGC-7901 cells with Siomycin A significantly downregulated AKT phosphorylation and FOXM1 expression. **Conclusion:** The results show Siomycin A prevented GC cell proliferation by downregulating the AKT/FOXM1signalling pathway. Furthermore, it is possible to infer from this study that Siomycin A may be used in the treatment of GC.

Key words: AKT/FOXM1 axis, anticancer, gastric cancer, siomycin A, apoptosis, migration, akt phosphorylation

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Gastric cancer, which accounts for about ten percent of the global cancer mortality, is one of the world's most common cancers[1]. Due to the lack of early clinical signs, patients with GC are usually diagnosed later, resulting in an exceptionally poor rate of survival. Early detection and treatment of gastric cancer are therefore critical for reducing the high mortality rate[2]. The major chemotherapeutic agents used to treat GC include irinotecan, fluoropyrimidines (capecitabine and S-1) etc[3,4]. However, some of them have major side effects during therapy[5,6]. As a result, the exploration of new chemotherapeutic agents is needed for the treatment of GC.

FOXM1 is part of the family of transcription factor forkhead box (Fox)[7], which was known to be overexpressed in many aggressive human cancers like lung, brain, liver, breast, prostate, colon and cervix[8-14]. Targeting FOXM1 may impede cell migration, invasion and proliferation in differentcarcinomas[15]. Furthermore, overexpression of FOXM1 in cancer cells has shown resistance to oxidative stress-mediated apoptosis or premature senescence[16]. FOXM1 is over-expressed in gastric cancer and is linked to a poor prognosis andchemoresistance[17,18]. Also, FOXM1 has been reported to promote angiogenesis, proliferation and metastasis in human gastric cancer[19]. As a result, targeting FOXM1 may be a promising approach for treating gastric cancer[20,21].

Siomycin A is a sulphur-containing thiazole antibiotic that specifically inhibits Gram-positive bacteria. Siomycin A inhibits translation during the translocation process by binding to 23S rRNA on the 50S ribosomal subunit. The anticancer property of Siomycin A is well documented[22,23]. In epithelial cancer cells, Siomycin Awas was reported to induce apoptosis via lysosomal permeabilization[24]. Furthermore, in several cancer cells, Siomycin A has been known to downregulate the expression of Forkhead box M1 (FOXM1) transcription factor at both the protein and mRNA levels[25,26]. However, the effect of Siomycin A on GC cells has not been explored. Thus, in the present study, we have investigated the impact of Siomycin A on the AKT/FOXM1 axis in gastric cancer cells.

MATERIALS AND METHODS

Study area: The study was carried out at the Department of Traditional Chinese Medicine, Xinjiang Uiger Municipal People's Hospital, China. The duration of the study was 1 year and 3 months, extending from December, 2019-February, 2021.

Cell culture: The human gastric adenocarcinoma cell line (SGC-7901) and normal human gastric mucosa epithelial cell line (GES) have been obtained from the American Type Culture Collection (ATCC) cell repository. GES and SGC-7901 cells were cultivated with the addition of 10% Foetal Bovine Serum (FBS, Gibco, Thermo Fisher Scientific, Inc.) and 100 U mL^{-1} penicillin (Gibco, Thermo Fisher Scientific, Inc.) in Dulbecco's Modified Eagle Medium (DMEM). Cells were maintained at 37°C in a humidified atmosphere with 5% CO_2. An inverted microscope was used to study the morphology of the cells.

Cytotoxicity assay: We tested Siomycin A-induced cytotoxicity in GES and SGC-7901 cell lines using the MTT (3-(4,5-dimethyl thiazolyl-2)-2,5-phenyltetrazolium bromide) assay. In 96-well plates, cells (1×10^4 cells per well) were 1st plated and allowed to grow up to 70% confluency. Cells were then treated with varying concentrations of Siomycin A (0-50 μM) for 24 hrs. After treatment, MTT (5 mg mL^{-1}) solution was added to each well and incubated at 37°C for 2 hrs. The formation of the purple coloured complex was measured by measuring the absorbance at 570 nm, using an ELISA reader[27].

Wound healing assays: In 24-well plates, SGC-7901 cells were grown (1×10^5 cells/well) and scratched using the bottom of pipette tips (200 μL). After washing the plates using PBS to eliminate detached cells, they were incubated with or without 5 μM Siomycin A solution and incubated for 24 hrs. At 0 and 24 hrs after treatment, cell migration was detected using a phase-contrast microscope at 100× magnification. ImageJ software version 1.50 was used to calculate and quantify migrating cells in the denuded region[27].

Apoptosis detection assay: Induction of apoptosis was detected in Siomycin A treated cells following the manufacturer's instructions, using the Cell Death Detection ELISA plus kit (Sigma Aldrich, Merck KGaA)[28]. At first, 2×10^4 SGC-7901 cells were grown into each well of 96-well plates for 24 hrs. Cells were then treated with 0, 2.5 and 5 μM of Siomycin A and incubated for 24 hrs. An ELISA reader (PerkinElmer) was used to evaluate absorbance at a wavelength of 405 nm.

Western blot analysis: Western blot analysis was used to determine the expression of various proteins such as Bax, Bcl2, cleaved Caspase-3, FOXM1, AKT and pAKT[27]. The cells were collected and then washed in cold PBS (pH 7.4). Ice cold lysis buffer was used to lyse the cells (50 mM tris-HCl, 150 mM NaCl,

1 mM EGTA, 20 mM NaF, 100 mM Na3VO4, 1% NP 40, 1 mM Phenylmethanesulfonyl fluoride (PMSF), 10 µg mL^{-1} aprotinin and 10 µg mL^{-1} leupeptin, pH 7.4) for 30 min followed by centrifugation at 12000 g for 30 min at 4°C. The protein concentration of the supernatant was measured by using Bradford assay with Bovine Serum Albumin (BSA) as a standard. Protein samples (50 g) were segregated on a 10% Sodium Dodecyl Sulphate-Polyacrylamide Gel Electrophoresis (SDS PAGE) gel before being electro-transferred to polyvinylidene difluoride membranes. Overnight, the blots were blocked with 5% skimmed milk. The membrane was incubated with multiple monoclonal antibodies (1:1000 dilution) for 4 hrs at room temperature in separate experimental sets. After that, the membrane was incubated with the HRP-conjugated secondary antibody (1:2000 dilution, Santa Cruz Biotechnology) following a wash of tris-buffered saline containing 0.1 percent Tween 20. A chemiluminescence kit from Thermo Fisher Scientific (Waltham, MA) was used to visualize the protein bands and the bands were quantified by using ImageJ software version 1.50.

Statistical analysis: All results are presented as the Mean±SEM of n independent measurements as indicated in the figure legends. Treated and control groups were compared by student's t-tests using the software GraphPad Prism 6. Comparison between the multiple groups was made by analysis of variance test using Newman-Keuls post-analysis. The study considered the value of $p<0.05$ to be significant.

RESULTS

Siomycin A exhibited selective antiproliferative activity against human gastric cancer cells: The MTT assay has been used to evaluate Siomycin A's (Fig. 1a) antiproliferative activity in normal human gastric mucosa epithelial cell line (GES) and human gastric adenocarcinoma cell line (SGC-7901). Siomycin A reduced the viability of SGC-7901 with an IC_{50} value of 5 µM. However, at 5 µM of siomycin, the viability of normal gastric mucosa epithelial cells (GES) was decreased by 16%. This decreased cytotoxicity on the normal GES cell line suggests

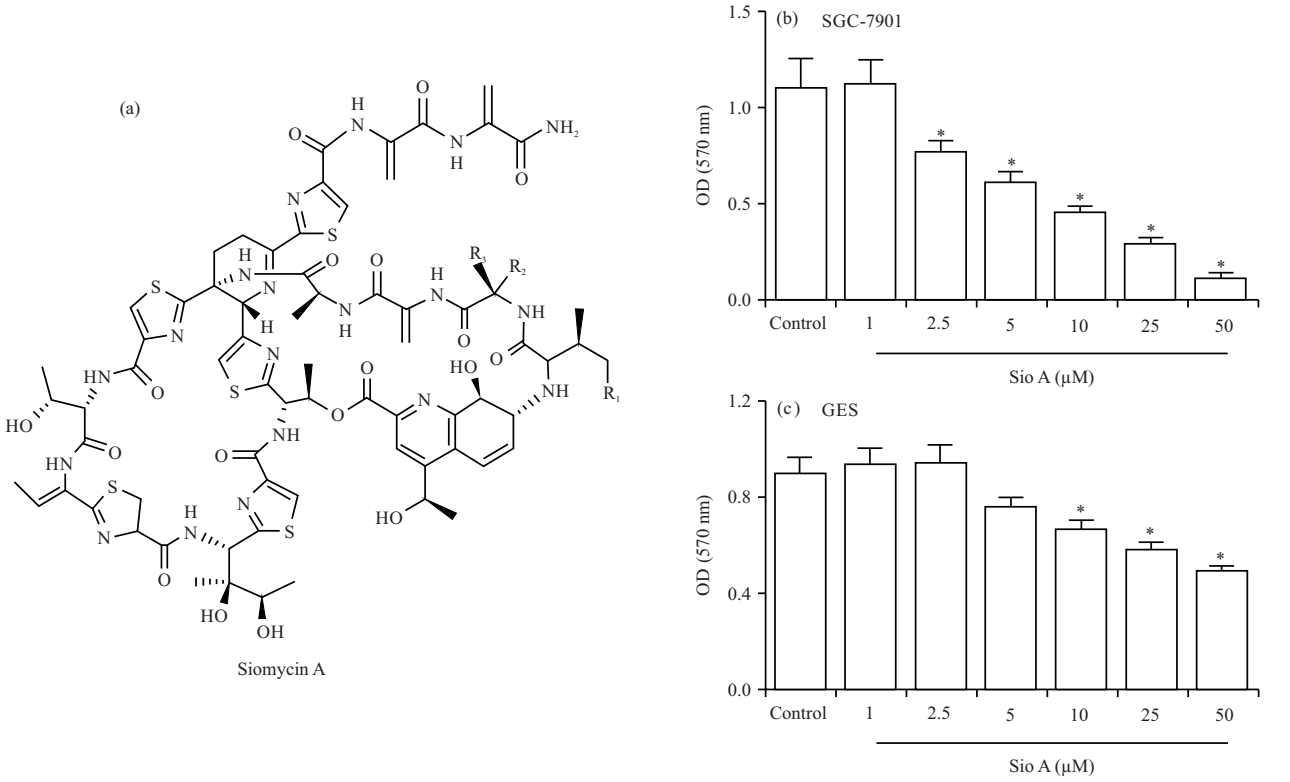

Fig. 1(a-c): Effect of Siomycin A on cell viability of gastric normal and cancer cells, (a) Chemical structure of Siomycin A, (b) Reduced viability of human gastric adenocarcinoma cells (SGC-7901) was measured by MTT assay in the presence of various concentrations of Siomycin A and (c) Reduced viability of normal human gastric mucosa epithelial cells (GES) was measured by MTT assay in the presence of various concentrations of Siomycin A

Values reported are Mean±SEM of the 3 independent experiments, value of *p<0.05 calculated as compared to untreated cells

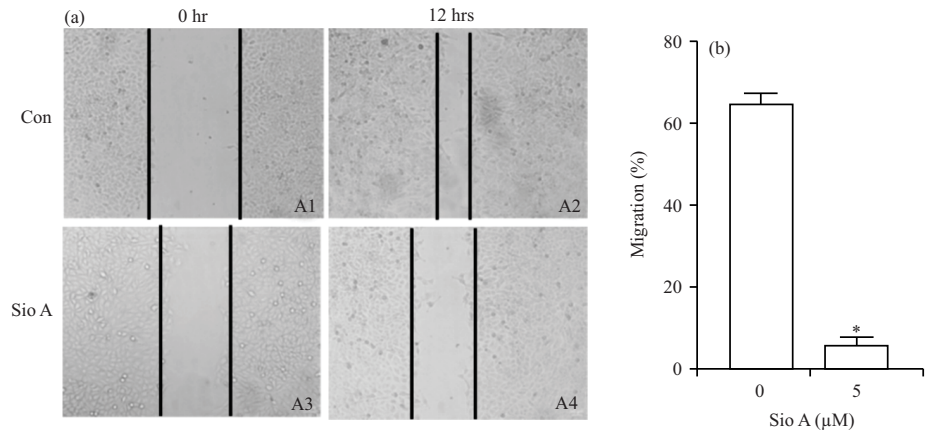

Fig. 2(a-b): Inhibition of cell migration in Siomycin A-treated SGC-7901 cells, (a) Inhibition of the migration of SGC-7901 cells in the absence and presence of Siomycin A for 24 hrs and (b) Graphical representation of inhibition of the migration of SGC-7901 by Siomycin A

Values reported are Mean±SEM of the three independent experiments, value of *p<0.05 calculated as compared to untreated cells

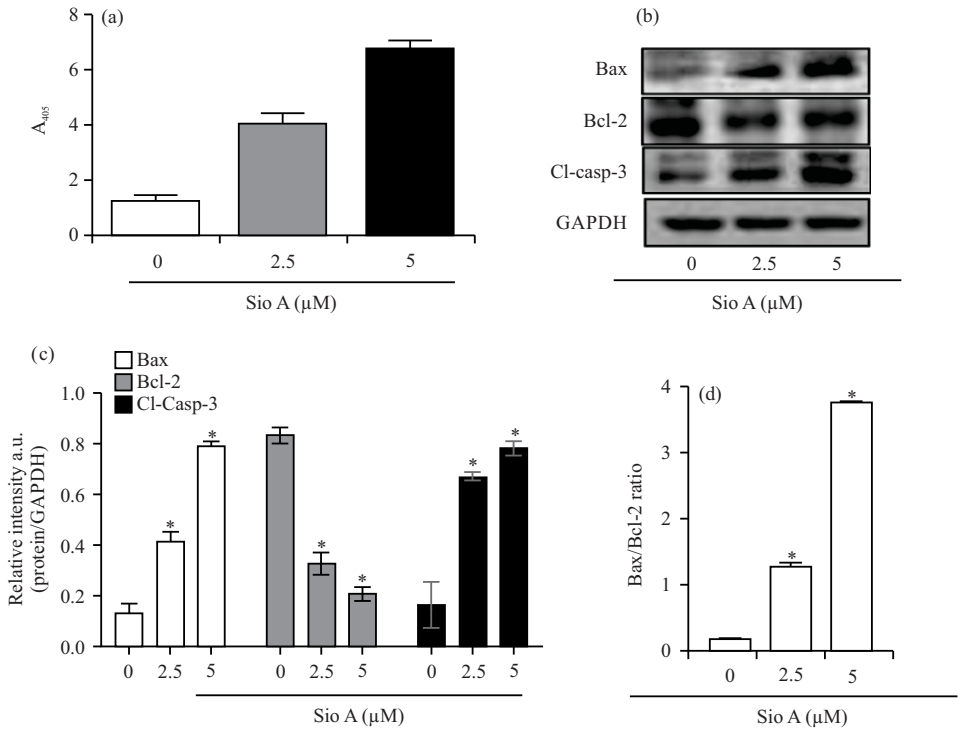

Fig. 3(a-d): Siomycin A induces apoptosis in SGC-7901 cells, (a) Apoptosis induction of human gastric adenocarcinoma cells (SGC-7901) was measured by cell death detection ELISA plus kit in the presence of various concentrations of Siomycin A, (b) Effect of Siomycin A treatment on Bax, Bcl2, GAPDH and cleaved Caspase-3 proteins of SGC-7901 cells. An equal amount of total cellular protein of control and Siomycin A treated SGC-7901 cells (as indicated) were analyzed by immunoblotting using respective antibodies, (c) Graphical representation of Bax, Bcl2 and cleaved Caspase-3 protein bands after densitometric quantification using ImageJ (NIH software) and (d) Graphical representation of Bax/Bcl-2 ratio in SGC-7901 in the presence of various concentrations of Siomycin A

Values reported are Mean±SEM of the 3 independent experiments, value of *p<0.05 calculated as compared to untreated cells

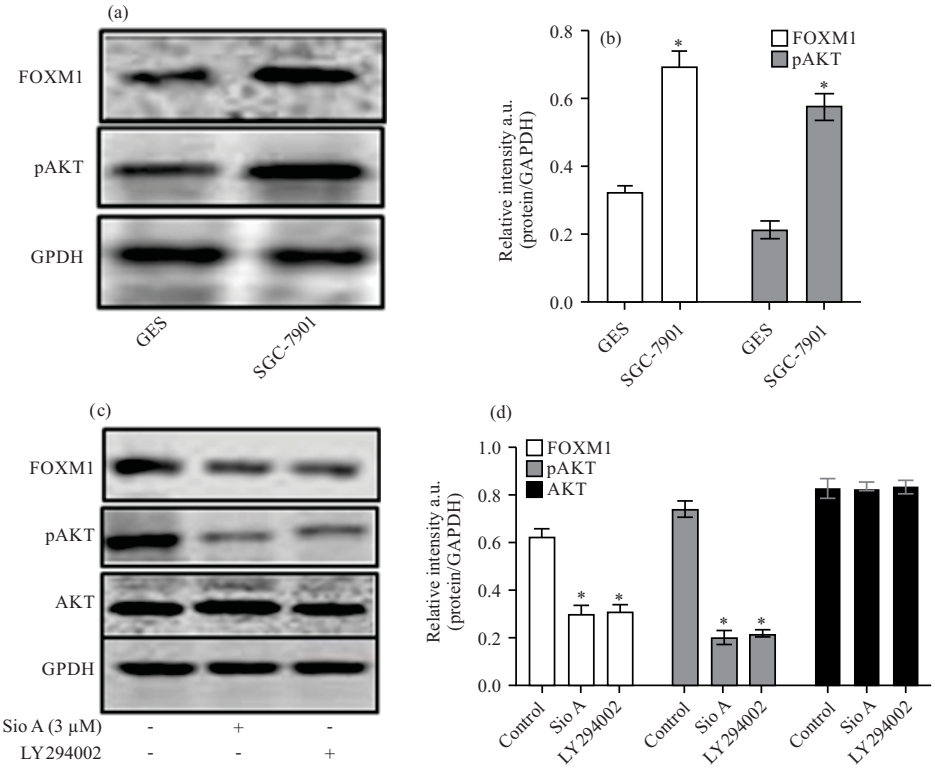

Fig. 4(a-d): Effect of Siomycin A on AKT/FOXM1 axis of gastric cancer cells, (a) Western blot analysis of FOXM1, pAKT and GAPDH proteins of GES and SGC-7901 cells (b) Graphical representation of FOXM1 and pAKT protein bands after densitometric quantification using ImageJ (NIH software), (c) Western blot analysis of FOXM1, pAKT, AKT and GAPDH proteins of Siomycin A and LY294002 treated SGC-7901 cells and (d) Graphical representation of FOXM1, pAKT and AKT protein bands after densitometric quantification using ImageJ (NIH software)

Values reported are Mean±SEM of the three independent experiments, value of *p<0.05 calculated as compared to GES cells and untreated cells

that Siomycin A has an anticancer activity specific to gastric cancer cells (Fig. 1b-c). The OD_{570} values plotted on the Y-axis are a representation of the viable cells that were detected by MTT assay.

Siomycin A suppresses the migration of human gastric cancer cells: A wound-healing assay was used to assess the impact of Siomycin A on cell migration. When compared to the untreated control, 5 μM Siomycin A substantially reduced SGC-7901 migration of GC cells in the wound healing assay. The results indicated that 5 μM Siomycin A only closed the gap created by the scratch by 5.74% in 24 hrs, whereas in untreated control, it was 64.75% (Fig. 2a). This data was graphically represented in Fig. 2b as percentage migration to the total gap made by the scratch.

Siomycin A induces apoptosis in human gastric cancer cells: SGC-7901 cells were treated with Siomycin A (0, 2.5 and 5 μM) for 24 hrs before being tested for apoptosis using the cell death detection ELISA PLUS. This experiment is based on DNA fragmentation, which is a key marker for apoptosis detection. When cells were treated with 2.5 and 5 μM Siomycin A, DNA fragmentation was nearly 4 and 6.8 times greater than in the untreated control. This indicates that Siomycin A dose-dependently induced apoptosis in the GC cell line (Fig. 3a).

To further confirm Siomycin A-mediated apoptosis induction in GC cells, we used western blot analysis using antibodies that identify apoptosis-associated proteins. In this study, we tested the levels of expression of proteins involved in the apoptotic pathway, such as Bax, Bcl-2 and cleaved Caspase-3. Treatment with 5 μM Siomycin A increased expression of Bax (~4.6 folds) and cleaved Caspase-3 (~4.3 folds) proteins in a dose-dependent manner, while Bcl-2 expression was substantially reduced (~4 folds) as shown in Figures (Fig. 3b-c). An increase in Bax expression and subsequent downregulation of Bcl-2 is often related to apoptotic induction. The western blot results indicate a

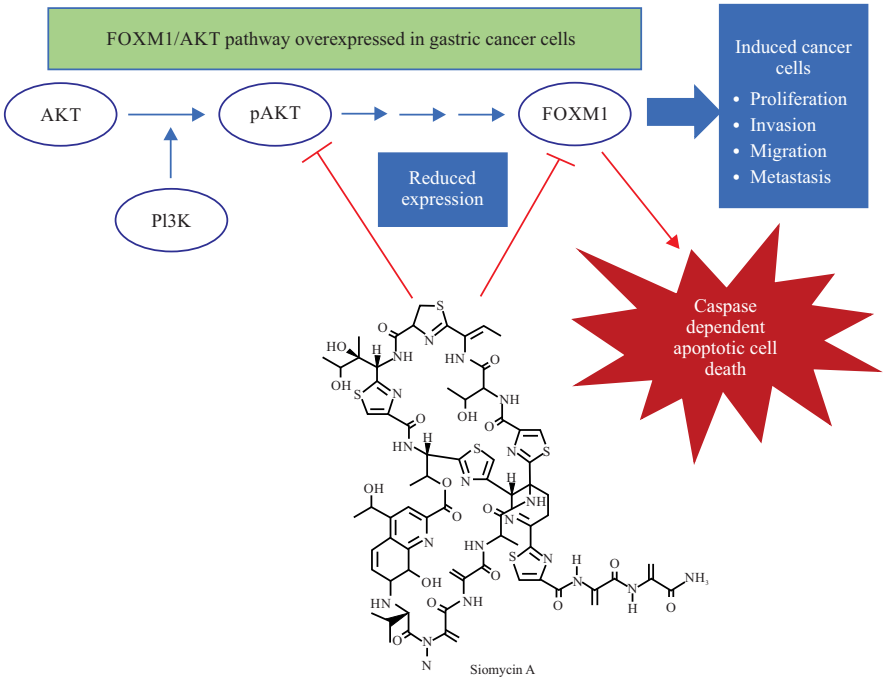

Fig. 5: Research model of this study

Siomycin A-induced apoptosis in gastric cancer cell line via the caspase-dependent pathway. The bax-Bcl2 ratio of more than 2 is an indicator of the susceptibility to apoptosis, which in this case is around 4 in presence of 5 µM Siomycin A (Fig. 3d). This graphical representation points to the fact that Siomycin A promotes apoptosis in GC cells.

Downregulation of AKT/FOXM1 axis by Siomycin A in gastric cancer cell line: FOXM1 is a transcription factor that promotes cancer cell development. We observed that FOXM1 expression is higher in SGC-7901 cells by 3-folds, compared to GES cells (Fig. 4a-b). pAKT is an active form of AKT that regulates cancer cell survival and metastasis. Interestingly, the expression of pAKT level was also significantly higher in SGC-7901 than in the GES cell line.

We further investigated whether Siomycin A had any effect on the expression of FOXM1 in GC cells. FOXM1 expression was reduced after Siomycin A treatment of the SGC-7901 cell line. We also tested p-AKT levels in SGC-7901 cells to examine the functional significance of Siomycin A-induced changes in AKT signalling cascade in gastric cancer cells. Siomycin A greatly reduced p-AKT levels while keeping AKT protein expression unchanged. The PI3K inhibitor LY294002 also decreased the expression of both pAKT and FOXM1 in the SGC-7901 cells. The result suggests that reduced AKT phosphorylation is associated with decreased FOXM1 expression (Fig. 4c-d).

Overview of the study: An overview of the study has been represented in Fig. 5. It is depicted how Siomycin A blocks the phosphorylation and subsequent activation of AKT, which leads to a downstream downregulation of FOXM1. The downregulation of the AKT/FOXM1 pathway leads to a decrease in invasiveness, migratory property and metastatic potential of GC cells, which finally leads to the caspase-dependent cell death of GC cells.

DISCUSSION

According to the findings of this study, Siomycin A substantially and dose-dependently suppressed GC cell proliferation. *In vitro* cell migration assays revealed that Siomycin A treatment substantially reduced cell migration in gastric carcinoma cell line SGC-7901. Furthermore, Siomycin A significantly induced apoptosis in gastric cancer cells as demonstrated by increased Bax/Bcl2 ratios and elevated levels of cleaved Caspase-3 proteins. The study also investigated whether Siomycin A alters the AKT signalling pathway, which is linked to FOXM1 in gastric cancer cells. Siomycin A significantly reduced AKT phosphorylation in gastric cancer cell lines. Additionally, we observed that the expression of both pAKT and FOXM1 was decreased by LY294002, a PI3K inhibitor. Thus, Siomycin A behaves similarly to the PI3K inhibitor, LY294002.

Siomycin A is a sulfur-containing antibiotic derived from an endophytic Actinomycin species found in *Acanthopanax*

senticosus, a medicinal plant, which has been shown to have anticancer activity against a wide range of cancer cells by inhibiting FOXM1, hindering cell proliferation and causing apoptosis[22,23]. Nevertheless, the anticancer properties of Siomycin A against Gastric Cancer (GC) and the associated molecular mechanism, have not been thoroughly investigated. This study took this opportunity to report the 1st study related to the effect of Siomycin A on GC cells. Previously reported studies have demonstrated that activation of FOXM1 is linked to the progression of human cancers[15], such as breast, liver and lung cancers and also associated with the poor prognosis[10,29,30]. Furthermore, several studies indicate that depletion or pharmacological inhibition of FOXM1 may significantly reduce cancer cell growth and migration[13,31]. FOXM1 has also been shown to facilitate the proliferation of gastric cancer cells by activating twist 1[32]. As a result, FOXM1might act as a promising target for the prevention and treatment of gastric cancer. FOXM1 is also known to regulate Akt signalling, which influences cell viability and metastasis[33,34].

The present study addresses the effect of Siomycin A on gastric cancer cells for the 1st time. Siomycin A has been shown in recent studies to produce ROS mediated cytotoxicity in ovarian cancer cells[35]. We feel Siomycin A induce similar effects in GC cells, thus suppressing cell proliferation. Siomycin A shows similar activity to PI3K inhibitor LY294002 in downregulating FOXM1 and p-AKT. This results in the induction of autophagy by elevating Bax/Bcl-2 ratio within the cell and reducing the migration ability and proliferation of gastric cancer cells. Similar results were reported in previous studies where Siomycin A was found to downregulated FOXM1 in other cancer types[25,36]. Siomycin A is also known to induce apoptosis in pancreatic cancer[23]. Hence, it is possible that Siomycin A, like LY294002, may suppress the expression of FOXM1 in GC cells through a similar pathway. It may be concluded that Siomycin A inhibits the oncogenic potential of GC cells by targeting the Akt/FOXM1 signalling.

CONCLUSION

The study focuses on how Siomycin A alters the AKT signalling pathway, which is linked to FOXM1 in gastric cancer cells. Siomycin A also significantly reduced AKT phosphorylation in gastric cancer cell lines. Additionally, we observed that the expression of both pAKT and FOXM1 was decreased by LY294002, a PI3K inhibitor. Hence, it is possible that siomycin A, like LY294002, may suppress the expression of FOXM1 in GC cells through a similar pathway. Thus, we may conclude that Siomycin A inhibits the oncogenic potential of GC cells by targeting the Akt/FOXM1 signalling.

SIGNIFICANCE STATEMENT

The study revealed the potential anticancer role of Siomycin A against GC. The mode of action of Siomycin A is uncovered where it is shown to downregulate the AKT/FOXM1 signalling cascade leading to caspase-dependent apoptosis. This can be beneficial for further drug development process against GC. Furthermore, researchers in future will be benefited from novel drug discovery against GC. Hence, Siomycin A or its further derivatives may be considered as a therapeutic regime against GC.

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