RESEARCH ARTICLE

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Decreased *SLC16A13* Expression Level Can Increase Apoptosis in KATO2 Cell Line, A Promising Biomarker

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Abstract

Objective: Gastric cancer is a prevalent cancer type worldwide, and significant research efforts are focused on finding effective treatments. Recent studies have highlighted the importance of plasma membrane carriers, particularly solute carriers, in cancer progression. The *SLC16A* family, notably the *SLC16A13* gene, plays a critical role in cancer development and tumor growth. This study aims to explore the impact of reducing *SLC16A13* expression in gastric cancer cells on their survival, proliferation, and metastatic potential. **Methods:** Gastric cancer cells (KATO2) were cultured in RPMI medium supplemented with 10% fetal bovine serum. The cells were then transfected with SLC16A13 si-RNA to lower gene expression. The effects of this si-RNA on cell death and apoptosis were assessed using MTT and flow cytometry assays. Cell migration capabilities were evaluated using the scratch test. Western blot and Real-Time PCR were employed to measure *SLC16A13* expression levels and protein detection. Additionally, RT-PCR was used to analyze changes in genes related to apoptosis and cell migration. **Results:** The reduction of *SLC16A13* expression following si-RNA transfection significantly increased apoptosis and cell death in the KATO2 cell line after 72 hours ($P < 0.0001$). Furthermore, the study revealed that decreased *SLC16A13* expression did not impact cancer cell migration. Cell viability, assessed by MTT assay, showed a significant decrease at 48 and 72 hours post-transfection ($P < 0.0001$). **Conclusion:** The findings indicate that targeting *SLC16A13* can effectively increase cell death and apoptosis in gastric cancer cells, making it a viable therapeutic target.

Keywords: Gastric cancer- apoptosis- SLC16A13- si-RNA- real time-PCR

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Introduction

According to the International Cancer Society's 2018 statistics report, gastric cancer remains the fifth most commonly diagnosed cancer in hospitals globally and the third leading cause of cancer-related deaths as of 2020. Gastric cancer (GC) arises from a confluence of genetic and environmental factors, such as a familial predisposition, unhealthy dietary habits, frequent alcohol consumption, smoking, Helicobacter pylori infection, and Epstein-Barr virus (EBV) exposure [1, 2]. At present, the main tumor markers utilized within the clinic for early detection of GC are not very accurate, so they cannot be used to definitively prognostic and diagnose gastric cancer [3]. Therefore, it is very important to find accurate biomarkers for CG early detection, since most people don't have any symptoms until it is already at an advanced stage [4]. The SLC16 family, part of the solute carrier (SLC) group, consists of transporters that shuttle monocarboxylates (MCTs), spanning from SLC16A1 to SLC16A14 (Halestrap and Denton 1974). Specific members, such as MCT1 and MCT4, facilitate the transport of L-lactate crucial for the metabolic processes of cancer cells, with expression levels varying across different tumor types and stages (Ganapathy et al. 2009; Bosshart et al. 2021). Overexpression of the metastasis-associated colon cancer-1 transcription factor in gastric cancer cells leads to an increase in MCT1 protein levels (Wang et al. 2017a). MCTs 1–4 play a pivotal role in regulating intracellular pH levels by transporting substances like lactate (Halestrap 2013). These transporters are known to be upregulated in various cancers, including breast, bone, colon, bladder, prostate, and renal cancers, correlating with poorer clinical outcomes [5].

RNA interference (RNAi) is a sequence-specific, post-transcriptional gene silencing mechanism that results in the degradation of homologous mRNAs. This powerful technology enables the study of gene function and expression through the use of short interfering RNAs (siRNAs), targeting genes with high specificity

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and efficiency (Zarredar et al. 2018; Kamran et al. 2021). Given the unclear role of different SLC16A family members in human cancers, our study aims to investigate the effects of suppressing SLC16A13 on the stability of gastric cancer cells.

Materials and Methods

Cell Culture and Transfection Human gastric cancer cells (KATO2) were acquired from the Pasteur Institute in Tehran, Iran. These cells were cultured in Roswell Park Memorial Institute-1640 medium (Gibco, cat no. 51800035) enriched with 10% fetal bovine serum (FBS) (Gibco, CA, cat no. 42G4184K). For transfection, we used 1×10^6 KATO2 cells and the electroporation method in a 5% CO_2 incubator. Transfection was performed using a Bio-Rad Gene Pulser Xcell. The transfection mixture consisted of HEPES, NaCl, KCl, and $Na_2HPO_4.7H_2O$ in specified proportions. An electric pulse of 140V (exponential) for 20 ms was applied to introduce 1µg of shRNA into the cells within a cuvette. Six hours post-transfection, the cells were supplemented with RPMI medium containing 20% FBS and incubated for an additional 48 hours. Subsequent assays included MTT, western blot, quantitative Real-Time PCR, and Annexin-V/PI.

Cell Viability Assay (MTT) Cell viability was assessed using the MTT assay. Post-transfection, KATO2 cells were seeded in 96-well plates. After 48 hours of incubation, MTT solution (Sigma-Aldrich, St. Louis, Missouri, cat no. M8180) dissolved in phosphate-buffered saline was added to each well (50 µL per well containing 100 mL of RPMI). The plates were incubated in a CO_2 incubator for 4 hours, followed by the addition of 100µL Dimethyl Sulfoxide (DMSO). The mixture was agitated at 1,000 RPM before cell viability was measured using an ELISA reader at 570 nm (Biotek, ELx800, US).

Scratch-Wound Motility Assay The migration ability of KATO2 cells was evaluated using a scratch assay. Cells were seeded at 4×10^5 cells/well in a 6-well plate and allowed to adhere for 24 hours. A scratch was made using a yellow pipette tip, followed by a wash with PBS. The cells were imaged immediately using a light microscope and then incubated at 37°C with 5% CO_2. Further images were taken at 24 and 48 hours to assess migration into the wound area. This assay was replicated three times.

Annexin V-FITC/PI Assay Apoptosis was quantified using the Annexin V-FITC/PI Apoptosis Detection Kit (Immunostep, Salamanca, Spain, lot no. 665580). Cells were treated with effective concentrations of therapeutics, harvested according to the manufacturer's instructions, washed in cold PBS, and stained with Annexin V and PI. Following a 15-minute incubation, cells were analyzed on a BD FACSCalibur flow cytometer, with FlowJo-V10 software used to determine the percentage of apoptotic cells.

Total RNA Isolation and Reverse Transcription Total RNA was extracted from transfected cells using RiboEx reagent (Gene All, Korea, cat no. 300-001). RNA quality and quantity were verified using a NanoDrop spectrophotometer and gel electrophoresis. cDNA synthesis was conducted using the BioFact™ RT-Kit (cat no. BR123-R10k) in a 20 µl reaction volume according to the manufacturer's protocol (Table 1).

Quantitative Real-Time PCR The expression levels of *SLC16A13* and related genes (*BAX, BCL2, CASPASE-3, CASPASE-9, E-CADHERIN*) were quantified using the RealQ plus Master Mix Green (Amplicon, cat no. A324499) on a StepOneTM qRT-PCR System (Applied Biosystem, California, USA). The housekeeping gene GAPDH was used as a reference. Primer sequences and specific conditions are detailed in Table 2.

Protein Extraction and Western Blot Analysis Protein samples were extracted using RIPA buffer (Santa Cruz Biotech, USA, cat no. sc-24948) and quantified. Proteins (100 µg) were separated on a 12.5% SDS-PAGE gel and transferred onto PVDF membranes. The membranes were blocked with 3% bovine serum albumin and incubated with primary antibodies against SLC16A13 (IU2H10, Novus Biologicals) and β-actin (ab8227, Abcam). Detection was performed using an HRP-conjugated secondary antibody and visualized with enhanced chemiluminescence (Roche Diagnostics GmbH, Germany).

Statistical Analysis Data were analyzed using GraphPad Prism (Version 6.0, San Diego, CA). Statistical significance among groups was determined using two-way ANOVA with Tukey's multiple comparisons test, considering $P < 0.05$ as significant.

Results

SLC16A13 Expression Downregulated After siRNA Transfection in KATO2 Cell Line Figure 1 illustrates the initial high expression level of SLC16A13 in the KATO2 cell line ($P < 0.001$). Post-transfection with SLC16A13 siRNA, a significant reduction in expression was observed at 48 hours ($P < 0.0001$), identified as the optimal time point (Figure 1A). This reduction was corroborated by western blot analysis (Figure 1B). Hence, the 48-hour mark was selected as the most effective time for siRNA intervention.

Impact of SLC16A13 Downregulation on KATO2 Cell Migration The influence of SLC16A13 downregulation on cell migration was evaluated using a wound-healing assay. The results indicated that decreased SLC16A13 expression does not significantly alter the migratory capability of KATO2 cells (Figure 2).

Decrease in Cell Viability Due to SLC16A13 Downregulation MTT assays revealed that suppression of SLC16A13 expression significantly reduced KATO2 cell viability at various intervals-24, 48, and 72 hours-with P-values of <0.01, <0.0001, and <0.0001, respectively (Figure 3). This suggests a consistent detrimental effect

Table 1. Sequence of *SLC16A13* siRNA

SLC16A13 si-RNA	GGACC TTGTA ACAGA AGCAT TCAAG AGATG CTTCT GTTAC AAGGT CCTTT TTT
	CCTGG AACAT TGTCT TCGTA AGTTC TCTAC GAAGA CAATG TTCCA GGAAA AAA

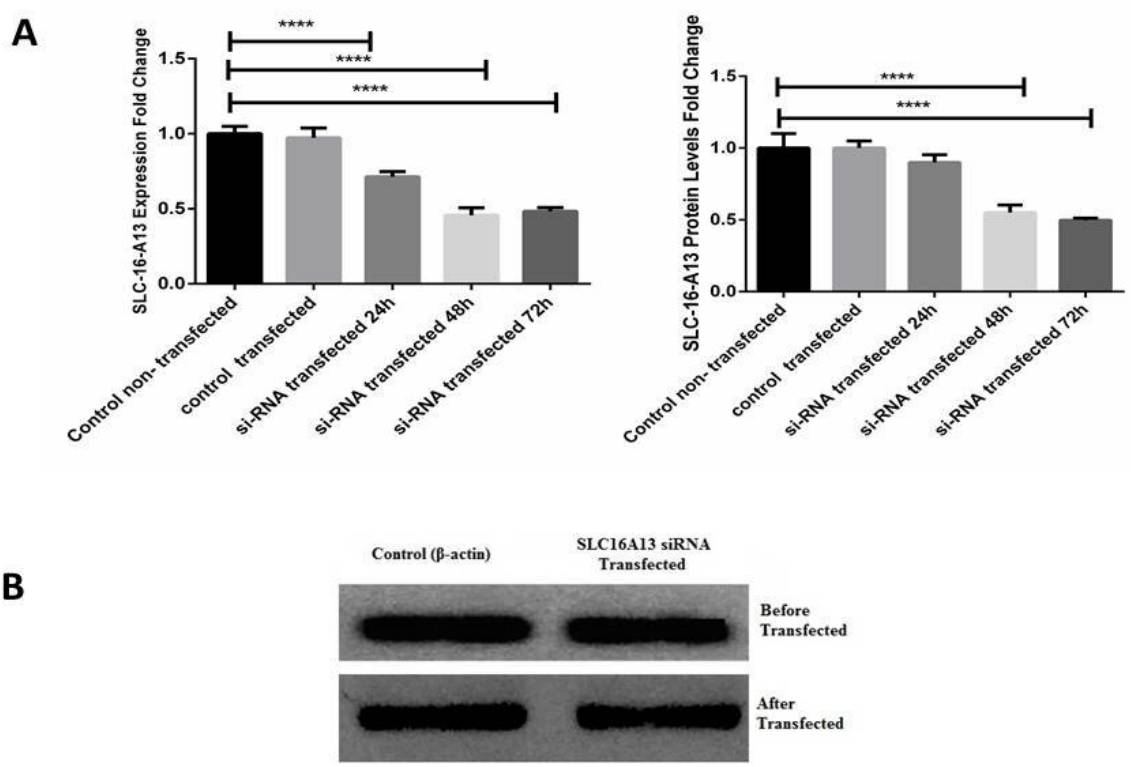

Figure 1. *SLC16A13* mRNA and Protein Level Following the siRNA Knockdown. (A) qPCR and western blot analysis of *SLC16A13* expression levels following the treatment of KATO2 cells with SLC16A13 si-RNA. 24h, 48h and 72h after transfection, mRNA expressions of transfected and control cells were evaluated. Transfection of KATO2 cells with SLC16A13 siRNA, but not control scrambled shRNA, remarkably attenuated SLC16A13 expression. Data are shown as mean SEM of triplicate experiments. (B) The control and transfected cells subjected to western blot analysis at 48h after transfection. Results are demonstrative of the decrease in transfected cell in after si-RNA transfection, as compared to the protein level in negative control group (scrambled siRNA). Anti- β-actin antibody was served as internal control.

on cell survival post-transfection across all time points.

Increased Apoptosis in *KATO2* Cells Following SLC16A13 Downregulation Flow cytometry analysis demonstrated a significant increase in apoptosis in KATO2 cells, especially 48 and 72 hours post-transfection with SLC16A13 siRNA (Figure 4). This indicates a crucial role of SLC16A13 in cell apoptosis regulation.

Modulation of Apoptosis-Related Genes by SLC16A13 Downregulation

Quantitative Real-Time PCR results, 48 hours post-transfection, showed significant alterations in apoptosis-related genes. CASPASE-3 and BAX expression levels increased ($P<0.001$ and $P<0.01$, respectively), while *BCL-2* expression decreased ($P<0.001$). However, changes

Table 2. Sequence of Genes

Genes	Sequences	Annealing temp (°C)
SLC16A13	Forward: 5' CCCAAACTCAGTTCCACCCTC 3'	60
	Reverse: 5' GAGCTCGGAGCTGAGCTAGT 3'	
GAPDH	Forward: 5' AAGGTGAAGGTCGGAGTCAAC 3'	60
	Reverse: 5' GGGGTCATTGATGGCAACAA 3'	
BAX	Forward: 5' GACTCCCCCCGAGAGGTCTT 3'	59
	Reverse: 5' ACAGGGCCTTGAGCACCAGTT 3'	
BCL2	Forward: 5' GAGCGTCAACCGGGAGATGTC 3'	59
	Reverse: 5' TGCCGGTTCAGGTACTCAGTC 3'	
Caspase-3	Forward: 5' ATGGTTTGAGCCTGAGCAGA 3'	59
	Reverse: 5' GGCAGCATCATCCACACATAC 3'	
Caspase-9	Forward: 5' GCAGGCTCTGGATCTCGGC 3'	59
	Reverse: 5' GCTGCTTGCCTGTTAGTTCGC 3'	
E-cadherian	Forward: 5'AAG AAG CTG GCT GAC ATG TAC GGA3'	59
	Reverse: 5'CCA CCA GCA ACG TGA TTT CTG CAT3'	

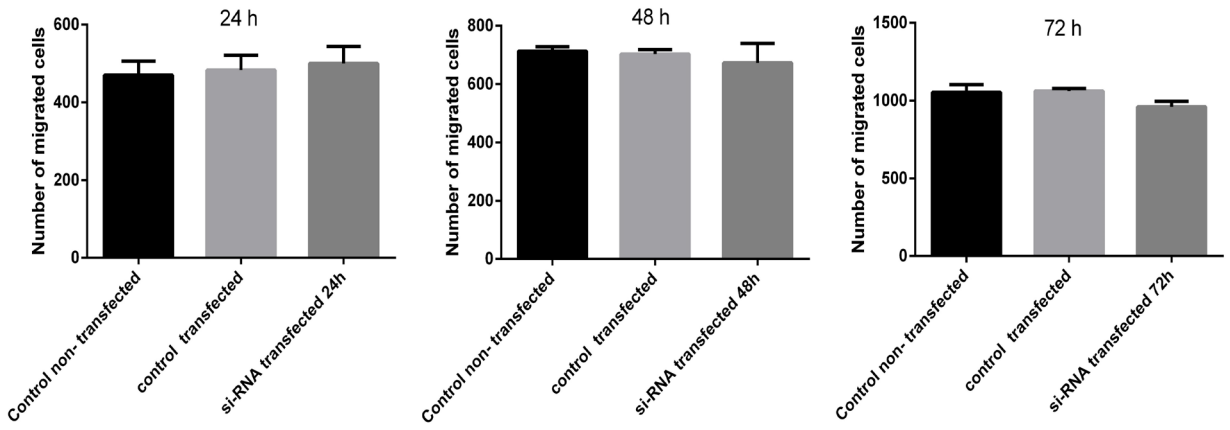

Figure 2. In order to Determine the *SLC16A13* Effect on Cell Migration of *KATO-2* Cells, the Wound Healing Assay was Performed. Observing the *KATO2* cells in wound area for 24, 48 and 72 hours exhibited that silencing *SLC16A13* has no effect on migration ability of KATO2 cells.

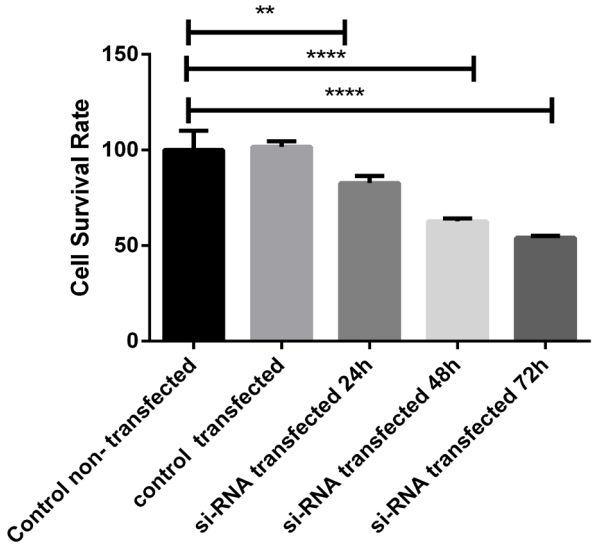

Figure 3. Knockdown of *SLC16A13* Suppress Cell Proliferation of *KATO2* Cell Line. Cell viability was evaluated by MTT 24h, 48 h and 72h after transfection of anti SLC16A13 si-RNA. As shown, compared to control and blank wells, si-RNA transfection reduces the viability of malignant cells.

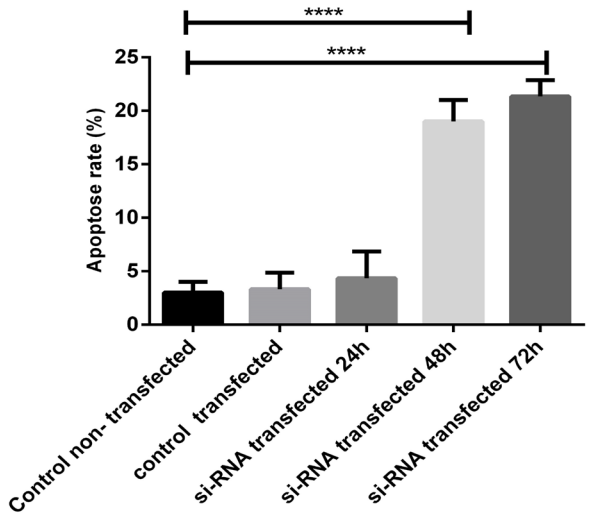

Figure 4. Silencing Effect of *SLC16A13* Gene Regulate the *BAX, BCL-2*, Caspase-3, Caspase-9 and E-Cadherin expression levels. The qRT-PCR analysis of these genes mRNA expression was measured in *KATO2* cells transfected with *SLC16A13* si-RNA. Following *SLC16A13* silencing, the mRNA level of *BAX,* Caspase-3 significantly increased however we observed significant reduction on *BCL-2* levels. The *SLC16A13* reduction has no effects on mRNA levels of Caspase-9 and E-Cadherian.

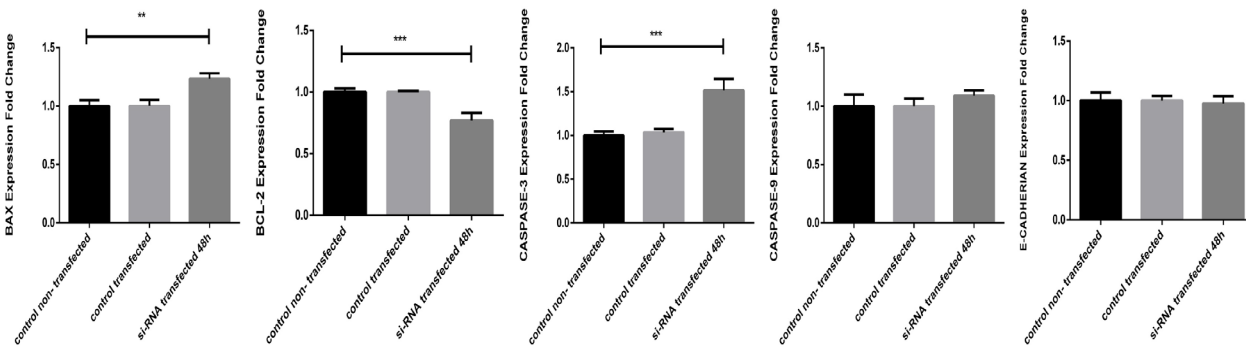

Figure 5. (A) SLC16A13 Knockdown increase the apoptosis level of KATO2 cells 48h and 72h after the transfection but has no effects on 24h. (B) Demonstration of the SLC16A13 Knockdown on KATO2 cells viability using Anexin_ PI test 48h after si-RNA transfection.

in E-CADHERIN and CASPASE-9 expression were not statistically significant (Figure 5). This suggests that SLC16A13 downregulation has a selective impact on apoptotic pathways in gastric cancer cells.

Discussion

Recent studies have highlighted the primary function of the monocarboxylate transporters (MCTs) 1-14 in shuttling molecules such as lactate, crucial for maintaining cellular acidity levels, particularly in tumor environments where glycolysis is heavily utilized for energy [6]. This traps these carriers in cancer because tumor cells rely heavily on glycolytic for energy. Cancer cells that have a lot of MCTs are better at maintaining the right pH level for tumor growth, which helps them proliferate [7, 8]. The overexpression of MCT1 and MCT4 has been found in various types of cancer, such as breast, bone, colon, and renal cancers. The presence of these transporters in the body has been connected to a poorer outlook in several types of cancer, such as bladder cancer (MCT1) and prostate cancer (MCT4) [5, 9]. Also, MCT2 has been suggested as a possible biomarker of prostate cancer. It can be used to identify cancerous glands, which helps make more accurate diagnoses [10].

In our study, we tried to evaluate *SLC16A13* gene suppressing by siRNA in gastric cancer. This study aimed to investigate the role of SLC16A13 in the growth and development of gastric cancer cells. As we know it is the first time that the role of the SLC16A13 is studied in gastric cancer. We found that suppression of the *SLC16A13* gene led to low expression of this gene in mRNA and protein levels after 48 h. Also, we found that SLC16A13 suppression reduced cell viability in KATO2 cell line. As well, SLC16A13 suppression led to increased BAX and CASPASE-3 expression levels and decreased BCL-2 expression levels in the KATO2 human gastric cancer cell line. Also, SLC16A13 suppression has no significant effect on the E-CADHERIAN and CASPASE-9 expression levels. So, it appears that suppression of the SLC16A13 induces the high expression of the BAX and CASPASE-3 and low expression of the *BCL-2* gene which promote cancer cell to more apoptosis. As you know BCL-2 is an anti-apoptosis molecule and SLC16A13 suppression leads to control of BCL-2 expression, and induces apoptosis in NSCLC [11].

In line with the show ponder, some research has detailed that the SLC family is dysregulated in lung adenocarcinoma and might serve as prognostic biomarkers [12, 13]. Also, Lehrer et al. showed that patients with higher expression levels of SLC18A1 had significantly better survival rates in lung cancer [13]. Furthermore, abnormal SLC38A3 expression leads to faster cell growth and invasion in different ways in non-small cell lung cancer cells. Experiments showed that when the *SLC38A3* gene is more expressed, the cells have more ability to migrate [14].

Zhao et al. indicated that SLC46A3 high expression level led to a reduction in the proliferation, migration, and invasion of hepatocellular cancer. Also, they revealed that high expression of the *SLC46A3* gene leads to better prognosis in HCC patients and helps reduce resistance to sorafenib and improve drug response [15]. Schumann et al. indicated that SLC16A13 and SLC2A1 expression levels were higher in lung cancer tissues which led to worse outcomes for patients, suggesting that they could be used for prognosis [16].

Zhu et al. found that SLC15A2 low expression was related to a worse outlook for lung cancer patients [17].

Xie et al. found that the SLC16A1 expression level was higher in metastatic melanoma and it is a poor prognosis biomarker for melanoma patients [18]. Sohrabi et al. revealed that *SLC16A2* and *SLC16A9* expression levels are important in breast cancer and are related to bad outcomes for breast cancer patients [19]. SLC16A3 is a protein strongly related to low oxygen levels in the body. Research has found that HIF-1 can increase the activity of the *SLC16A3* gene, which can lead to increased growth and progression of colon cancer [20].

Pervious research indicated that SLC16A7 up-regulation is related to prostate cancer progression [21]. Additionally, research has found that Mei et al. showed that SLC16A12 downregulation in renal clear cell carcinoma is correlated to a negative outcome and poor prognosis [22]. One of the important limitations of this study is that it would be better if we used several different Gastric cancers to evaluate the role of the *SLC16A13* gene in other cell lines. Also, it we must evaluate *SLC16A13* gene in vivo. In final, the SLC16 Members family especially SLC16A13 have potent biomarkers in tumor prognosis in many types of cancer. Also, SLC16 family members are concerned with tumor stem cells that make available new concepts for future cancer therapy.

Author Contribution Statement

All authors contributed equally in this study.

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