Cytotoxicity of SHIP2 Silencing in MDA-MB-231 Breast Cancer Cell Line

Rua Abbas Naser*, Inam Sameh Arif*, Basma Talib Al-Sudani*, Sayed Mahmood Alqallaf**

Department of Pharmacology and Toxicology, College of Pharmacy, Mustansiriyah University, Baghdad, Iraq.

****Pharmacy program, College of Health Sciences, University of Bahrain, Kingdom of Bahrain.***

Article Info:

Received 1 May 2025
Revised 1 July 2025
Accepted 4 Aug 2025
Published 31 Dec 2025
Corresponding Author email:
rua.alhamdy@uomustansiriyah.edu.iq
Orcid: https://orcid.org/0000-0002-7249-8974

DOI: https://doi.org/10.32947/ajps.v25i5.1332

Abstract:

Background: Breast cancer is a serious global health risk to women. Compared to other forms of BC. Triple negative breast cancer is characterized by a poor prognosis, high levels of aggressiveness and proliferation, and rapid progression. The phosphoinositide 3-kinase/ protein kinase B/ mechanistic target of rapamycin signaling pathway is commonly over-activated in human cancers and plays a role in BC survival, proliferation and angiogenesis. The SH2-containing 5′ inositol phosphatases 1 and 2, contribute to the regulation of the phosphoinositide 3-kinase/ protein kinase B signaling pathway that has a role in progression of cancer.

Objective: To address the cytotoxic effect of SH2-containing 5′ inositol phosphatases 2 silencing in MDA-MB-231 BC cell line.

Methods: The MDA-MB-231 cells were cultured in Dulbecco's modified Eagle's medium with low glucose, with and without SHIP2- *small interfering* ribonucleic acid for SH2-containing 5′ inositol phosphatases 2 transfection. The cytotoxicity of SH2-containing 5′ inositol phosphatases 2 silencing was assessed by [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay. Apoptosis was assessed using Annexin V-fluorescein isothiocyanate/ propidium iodide *staining.*

Results: Transfection of MDA-MB-231 BC cells with (0.04 µM) of SHIP2-siRNA significantly reduced cell viability at 24 hours post-transfection, and significantly induced apoptosis compared to control untreated cells. **Conclusion:** The present study provided evidence that SHIP2-siRNA reduced viability and induced apoptosis at 24 hours post-transfection in MDA-MB-231 BC cells.

Keywords: Apoptosis, MDA-MB-231 breast cancer cell line, SHIP2 silencing.

السمية الخلوية لاسكات التعبير الجيني ل SHIP2 في خط خلايا سرطان الثدي MDA-MB-231

رؤى عباس ناصر*، انعام سامح عارف*، بسمة طالب السوداني*، سيد محمود القلاف**

**فرع الادوية والسموم، كلية الصيدلة، الجامعة المستنصرية، بغداد، العراق.*

***برنامج الصيدلة، كلية العلوم الصحية، جامعة البحرين، مملكة البحرين.*

الخلاصة:

الخلفية: يشكل سرطان الثدي تهديدًا صحيًا كبيرًا للنساء في جميع أنحاء العالم. يتميز سرطان الثدي الثلاثي السلبي بسوء التشخيص، وانتشاره العالي، وعدوانيته، وتطوره السريع مقارنة بأنواع أخرى من سرطان الثدي. ينشط بشكل مفرط مسار **فوسفوإينوزيتيد 3-كاينيز/ بروتين كاينيز بي/ الهدف الميكانيكي للرابامايسين في كثير من الأحيان في السرطانات البشرية** ويلعب دورًا في تكاثرخلايا سرطان الثدي وبقائه وتكوين الأوعية الدموية. **إن إنزيمات الفوسفاتيز المحتوية على SH2** 1 و2 تنظم مسار فوسفوإينوزيتيد **3-كاينيز/ بروتين كاينيزبي** الذي يُساهم في تطور السرطان. الهدف: لتقييم السمية **الخلوية** لكتم التعبير الجيني ل**إنزيم الفوسفاتيز المحتوية على SH2 نوع 2** في خلايا سرطان الثدي MDA-MB-23 .

الطرق: زُرعت خلايا MDA-MB-231 في وسط إيجل المُعدّل من دولبيكو مع نسبة منخفضة من الجلوكوز، مع أو بدون حمض الريبونوكلييك المتداخل الصغير ل**إنزيم الفوسفاتيز المحتوية على SH2 نوع 2.** تم تقييم السمية الخلوية لكتم التعبير الجيني ل**إنزيم الفوسفاتيز المحتوية على SH2 نوع 2** باستخدام اختبار [3-(4,5-ثنائي ميثيل ثيازول-2-يل) -2,5-ثنائي فينيل تترازوليوم بروميد]. تم استخدام صبغة أنيكسين في-فلوريسين إيزوثيوسيانات/ يوديد البروبيديوم لتقييم موت الخلايا المبرمج.

النتائج: أدت معاجة خلايا سرطان الثدي MDA-MB-231 باستخدام (0.04 ميكرومولار) من حمض الريبونوكلييك المتداخل الصغير ل**إنزيم الفوسفاتيز المحتوية على SH2 نوع 2** إلى انخفاض معنوي في حيوية الخلايا بعد 24 ساعة من النقل الجيني، كما أدى إلى تحفيز معنوي لعملية الموت الخلوي المبرمج مقارنةً بالخلايا الضابطة غير المعالجة.

الاستنتاج: قدمت الدراسة الحالية دليلًا على أن حمض الريبونوكلييك المتداخل الصغير ل**إنزيم الفوسفاتيز المحتوية على SH2 نوع 2.** يسبب انخفاض في الحيوية ويسبب حدوث الموت الخلوي المبرمج بعد 24 ساعة في خلايا سرطان الثدي MDA-MB-231.

الكلمات المفتاحية: موت الخلية المبرمج، خط خلايا سرطان الثدي MDA-MB-231، كتم التعبير الجيني ل SHIP2.

Introduction:

Breast cancer (BC) is a serious global health risk to women. BC accounted for more than 12.5% of all new instances of cancer worldwide in 2023, making it the most common type of cancer (1). BC is considered to be the most common type of cancer in women (2). Additionally, in developed nations, it is the primary cause of cancer-related mortality among women (3). Triple negative breast cancer (TNBC) is characterized by a poor prognosis, high levels of aggressiveness and proliferation, and rapid progression (4). The clinical landscape of TNBC is significantly affected by immunotherapy, targeted therapy, and radiation therapy (5). However, due to the heterogeneity of the disease, poor prognosis, and the absence of well-defined molecular targets, TNBC is facing enormous challenges in clinical treatment (6). Therefore, there is a crucial demand to find more effective treatment strategies for TNBC. The phosphoinositide 3-kinase (PI3K)/ protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) pathway is necessary for cell growth, proliferation, as well as survival (7). This signaling pathway is among the most frequently hyperactivated in human cancers and is aberrantly modified in almost 70% of BC cases (8). The SH2-containing 5′ inositol phosphatases, SHIP1 and SHIP2, contribute to the regulation of the PI3K/AKT signaling pathway that has a role in progression of cancer (9). SHIP2 catalyzes the hydrolysis of the 5′ phosphate on phosphatidylinositol (3,4,5)-trisphosphate (PI(3,4,5)P3) to produce *phosphatidylinositol (3,4)-bisphosphate* (PI(3,4)P2) (10). Hydrolysis of PI(3,4,5)P3 is usually considered as a terminator of Akt signaling, similar to the known tumor suppressor gene PTEN (11). However, the function of SHIP2 in cancer is controversial, as it can exhibit both pro- and anti-tumorigenic effects depending on cell

type (12). SHIP2 has been identified as a negative modulator of PI3K/AKT signaling (84, 207). However, increasing evidence suggests that PI(3,4)P2 is essential for AKT activation, implying that SHIP2 possesses proto-oncogenic activity (13). It has been reported that SHIP2 functions as a tumor suppressor in in squamous cell carcinoma and in some glioblastoma cells (14). SHIP2 is over-expressed in certain types cancers, including BC, colon cancer and glioma, and has been associated with poor prognosis (15). Moreover, it has been demonstrated that SHIP2 is involved in tumor formation and metastasis in MDA-MB-231 BC cells (16). MDA-MB-231 cells are considered to have TNBC (17), and in this study these cells have been used as an in vitro model for TNBC. In this study we aimed to address the apoptotic effect of SHIP2 silencing in MDA-MB-231 BC cell line.

Material and methods:

Cell line and culture conditions:

The MDA-MB-231 cell line was purchased from (ATCC, USA). The MDA-MB-231 cells were cultured in Dulbecco's modified Eagle's medium (DMEM) with low glucose (Capricorn Scientific, GmbH, Germany), supplemented with 10% fetal bovine serum (FBS) (Capricorn Scientific, GmbH, Germany) and 1% penicillin/streptomycin (Capricorn Scientific, GmbH, Germany). The cells were maintained at 37°C, 95% humidified atmosphere, and 5% CO2. The culture medium was removed every 2 days and the cells were passaged after reaching a confluency of 70–90%. From a previous study, the concentration of (0.04 µM) of SHIP2- small interfering ribonucleic acid (siRNA) at 24 hours post-transfection was found to induce significant reduction in mRNA expression of SHIP2 (18).

Cell viability assay:

4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was used to determine the cytotoxicity of SHIP2 silencing on MDA-MB-231 cells (19). Cells were seeded at a density of 5000 cells/well of 96-well plates in antibiotic-free low glucose DMEM media supplemented with FBS. The plates were then incubated at 37°C in a humidified incubator with 5% CO2 until the cells reached approximately 80% confluency. The cells were then transfected with (0.04 µM) of SHIP2-siRNA (Catalog no. sc-39077) from (Santa Cruz Biotechnology, Inc., USA) using i-Fect transfection reagent (MyBiosource, Inc., USA). The cells were grown in transfection medium (Santa Cruz Biotechnology, Inc., USA) and incubated for 5 hours at 37°C in a humidified incubator with 5% CO2. After incubation, the cells were supplied with DMEM growth media with the normal FBS and antibiotics concentrations (10% and 1%, respectively) and incubated for 24, 48 and 72 hours. In the control group, the cells were treated the same at transfected group but they were transfected with negative control (NC)-siRNA (Catalog no. sc-37007) (Santa Cruz Biotechnology, Inc., USA) instead of SHIP2-siRNA.

Apoptosis assay:

An annexin V-fluorescein isothiocyanate (FITC) and propidium iodide (PI) apoptosis detection kit (Elabscience, USA) was used to evaluate cell apoptosis. Cells were seeded in 6-well plates at a density of 2 X 10^5/ well in antibiotic-free low glucose DMEM media supplemented with FBS. The plates were then incubated at 37°C in a humidified incubator with 5% CO2 until the cells reached approximately 80% confluency. The cells were then transfected with (0.04 µM) of SHIP2-siRNA (Catalog no. sc-39077) from (Santa Cruz Biotechnology, Inc., USA) using i-Fect transfection reagent (MyBiosource, Inc., USA). The cells were grown in transfection medium (Santa Cruz Biotechnology, Inc., USA) and incubated for 5 hours at 37°C in a humidified incubator with 5% CO2. After incubation, the cells were supplied with DMEM growth media with the normal FBS and antibiotics concentrations (10% and

1%, respectively) and incubated for 24 hours. In the control group, the cells were treated the same at transfected group but they were transfected with NC-siRNA (Catalog no. sc-37007) (Santa Cruz Biotechnology, Inc., USA instead of SHIP2-siRNA. After incubation, cells were collected using trypsin and then washed twice with cold phosphate buffer saline (PBS). To resuspend the cells, 1X annexin V binding buffer (100 µl) was added. According to the manufacturer's protocol, 2.5 µl of Annexin V-FITC and 2.5 µl of PI were added to the cell suspension. After that, the cell suspension was left for 15 minutes at room temperature in the dark. Cells were assessed by flow cytometry (BD FACSVerseTM), and the percentages of apoptotic cells was calculated using FlowJo 10.2 software (TreeStar, Ashland, OR, USA) (20).

Statistical analysis:

Analysis of data was performed using GraphPad Prism software version 8.0 (GraphPad Software, Inc., San Diego, CA, USA). All data were represented as the mean ± standard deviation (SD). A two-way analysis of variance (two-way ANOVA) was used for comparison between groups. $P < 0.05$ was considered to be statistically significant.

Results:

The results of MTT that SHIP2-silencing reduced cell viability of MDA-Mb-231 BC cells in a time dependent manner. The results revealed that cell transfection with (0.04 µM) of SHIP2-siRNA has resulted in significant reduction in cell viability of MDA-MB-231 BC cells at 24 hours post-transfection, while no significant effect was observed at 48 and 72 hours as shown in **(Table 1.1)**. The percentage of the viable, apoptotic and necrotic cells in each quadrant was calculated utilizing Flow Jo TM V 10.10 software (TreeStar, Ashland, OR, USA). The results of flowcytometry demonstrated that SHIP2 silencing 24 hours post-transfection induced apoptosis in MDA-MB-231 BC cells as shown in (**Figure 1A**) compared to the control untreated cells, the rate of early, late and total apoptosis of the SHIP2-siRNA group was significantly increased ($P < 0.01$, $P < 0.001$, $P < 0.0001$ respectively) as shown in in (**Figure 1B**). These results indicated that silencing of SHIP2 with (0.04 µM) of SHIP2-siRNA has significantly resulted in apoptosis in MDA-MB-231 BC cells at 24 hours post-transfection.

Table 1.1 The effect of SHIP2 silencing on viability of MDA-MB-231 breast cancer cells compared to the control group treated with NC-siRNA. For each assay, n= 2. The data are represented by mean ± SD of two independent experiments. The results were analyzed using two-way ANOVA. *P* < 0.01 compared to the control group.**

Time post-transfection	% Viability	
	NC-siRNA	SHIP2-siRNA
24 hours	98.43 ± 2.21	82.1 ± 1.31**
48 hours	98.31 ± 4.03	91.99 ± 1.27
72 hours	97.08 ± 3.79	96.09 ± 7.45

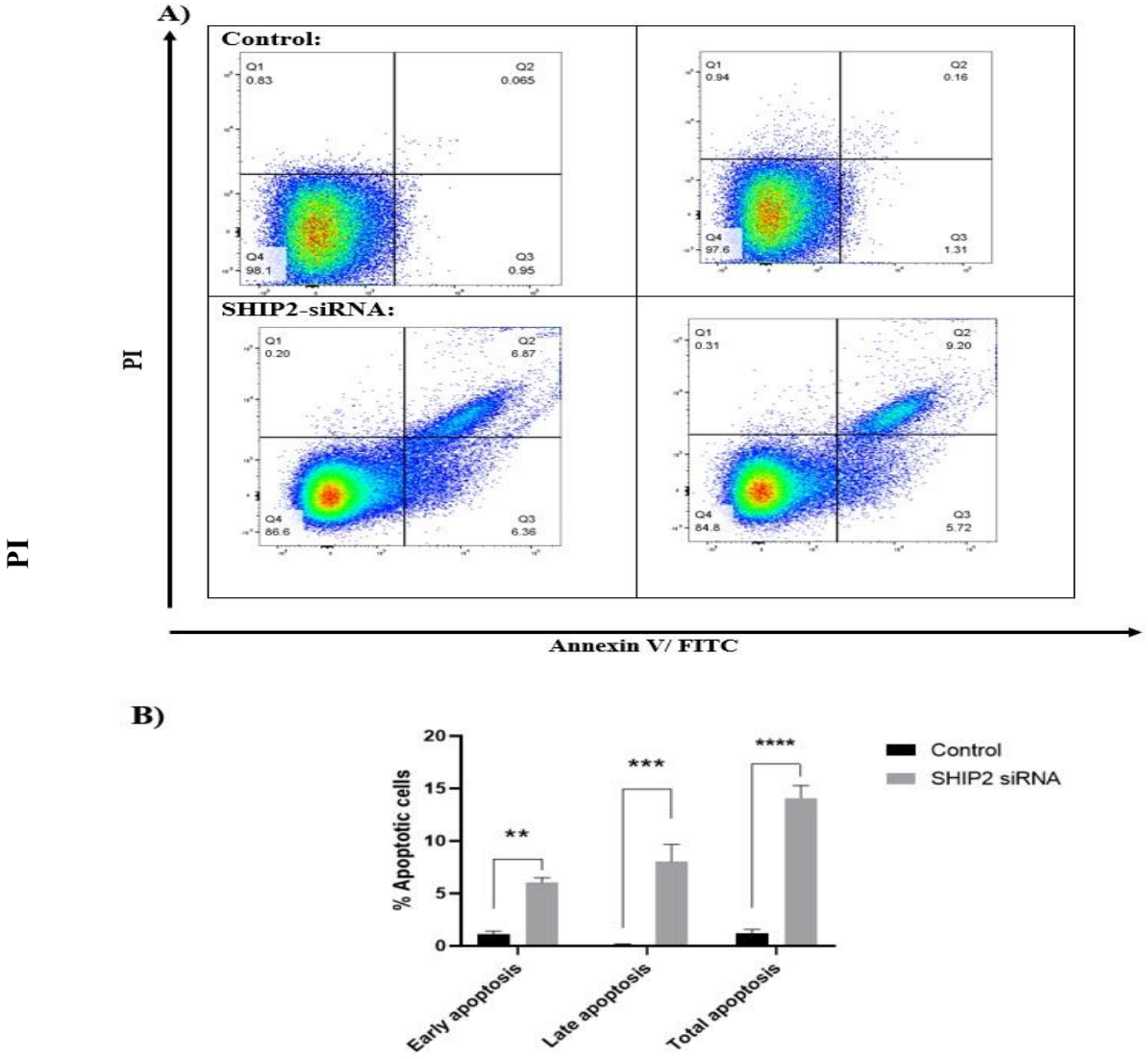

Figure 1. Effects of SHIP2 silencing on apoptosis of MDA-MB-231 breast cancer cells. A) Apoptosis of MDA-MB-231 breast cancer cells after transfection with (0.04µM) SHIP2-siRNA for 24 hours. Cells were stained with Annexin V-FITC/PI. Apoptosis was measured by flowcytometry. B) Rate of early, late and total apoptosis of MDA-MB-231 breast cancer cells compared to control group. The data are represented by mean ± SD (n=2). The results were analyzed using two-way ANOVA. *****P* **< 0.01, ******P*** **< 0.001, ****P < 0.0001.**

Discussion:

BC is thought to be the most prevalent type of cancer in women globally (21). Despite of advances in basic research and treatment of TNBC, poor clinical outcomes occur due to a combination of delayed diagnosis, the aggressive nature of this disease and the absence of suitable endocrine and targeted therapy (22). The PI3K product phosphatidylinositol (3,4,5)-trisphosphate (PI(3,4,5)P3) is a well-known potent activator for survival of cancer cells via promoting AKT activation (15). Due to its ability to dephosphorylate PI(3,4,5)P3, it was first proposed as a tumor suppressor (23). However, *phosphatidylinositol (3,4)-bisphosphate* (PI(3,4)P2) which is the product of SHIP2 dephosphorylation of PI(3,4,5)P3 is more efficient than PI(3,4,5)P3 at binding the AKT PH domain,

resulting in its phosphorylation and its full membrane activity (24). SHIP2 is linked to the activation of the PI3K/AKT signaling pathway and plays a significant regulatory role in malignant tumors (25). It has been proposed that SHIP2 contribute to the development of breast cancers via activating the AKT signaling pathway (26). Additionally, migration and SHIP2 overexpression are shown to be tightly associated, suggesting that SHIP2 has an oncogenic role in BC (27). In this study, the results of MTT assay revealed a time-dependent reduction in cell viability that the reduction in cell viability decreases upon increasing the time post-transfection) of MDA-MB-231 BC cells following SHIP2-siRNA transfection. At 24 hours post-transfection, cell viability decreased significantly compared to the control. Our result is consistent with the findings from previous studies, although on distinct cell lines, demonstrating that SHIP2 knockdown reduced proliferation of MCF-7 BC cells and human laryngeal squamous cell carcinoma Hep-2 cells (10, 27). Taken together, our finding highlighted the role of SHIP2 to promote cell survival. However, the present study did not show significant reduction in cell viability after 48- and 72-hours post-transfection with SHIP2-siRNA. This could be due to insufficient downregulation, if any present, to reduce cell viability at the same time point. Additionally, siRNA can be degraded by cytoplasmic exonucleases, decreasing its concentration and activity. Moreover, the reduction in gene silencing overtime may be due to dilution as a result of some degree of cell division (28, 29).

The PI3K/AKT pathway is an essential signaling cascade that controls metabolism, cell growth, and survival (30). The PI3K/AKT signaling pathway is crucial for controlling apoptosis, and activating it can prevent apoptosis through a number of different mechanisms. The active AKT can phosphorylate Caspase-3, an essential pro-apoptotic factor, inactivating it and preventing its pro-apoptotic effects (31). The impact on cell proliferation, migration, invasion, and apoptosis is frequently used to assess the role of specific genes in cancer development (32, 33). In this study, the impact of SHIP2 silencing on apoptosis of MDA-MB-231 BC cells has been evaluated. The results revealed that transfection of MDA-MB-231 cells with (80 pmol) SHIP2-siRNA has significantly resulted in apoptosis at 24 hrs post-transfection. Furthermore, the rates of early, late and total apoptosis were significantly higher in transfected cells compared to the control untreated cells. Our finding is in agreement with prior studies demonstrating that SHIP2 silencing with siRNA has also induced apoptosis in MCF-7 BC cells and human laryngeal squamous cell carcinoma Hep-2 cells. These two studies have further investigated the role of caspase 3, and demonstrated that SHIP2 silencing resulted in significant increase in caspase-3 (10, 27). From a previous study SHIP2 silencing with siRNA resulted in significant reduction of phospho-AKT in MDA-MB-231 BC cells (18). This would suggest that apoptosis induced by SHIP2 silencing in the present study may possibly mediated through suppression of AKT signaling. However, further study is needed to elucidate the underlying mechanism for SHIP2 silencing induced apoptosis in MDA-MB-231 BC cells.

In conclusion the present study provided evidence that SHIP2-siRNA reduced cell viability and induced apoptosis at 24 hours post-transfection in MDA-MB-231 BC cells, and this would provide a promising cytotoxic strategy against TNBC cells.

References:

1- Ge A, He Q, Zhao D, Li Y, Chen J, Deng Y, et al. Mechanism of ferroptosis in breast cancer and research progress of natural compounds regulating ferroptosis. Journal of cellular and molecular medicine. 2024;28(1):e18044.
2- Al-Saigh TH, Al-bayati SA, Abdul-mawjood SA, Ahmed FA. Breast

Cancer in Mosul: A Survival Analysis. Al Mustansiriyah Journal of Pharmaceutical Sciences. 2020;20(2):31-6.
3- Bedewi BK, Jasim GA, Abbas IS, Al-Sudani B. Cytotoxicity of Cryptochlorogenic acid against Breast cancer cell line (MCF7) isolated from Moringa oleifera Leaves Cultivated in Iraq. Al Mustansiriyah Journal of Pharmaceutical Sciences. 2022;22(2):35-43.
4- Salih AI, Al-Sudani BT, Mshimesh BA-R. Targeting POLD1 to suppress the proliferation and migration of breast cancer MDA-MB-231 cell lines by downregulation of SIRT1. Toxicology Research. 2024;13(4):tfae111.
5- Vagia E, Mahalingam D, Cristofanilli MJC. The landscape of targeted therapies in TNBC. Cancers. 2020;12(4):916.
6- Zhang J, Zhou K, Lin J, Yao X, Ju D, Zeng X, et al. Ferroptosis-enhanced chemotherapy for triple-negative breast cancer with magnetic composite nanoparticles. Biomaterials. 2023;303:122395.
7- Peng Y, Wang Y, Zhou C, Mei W, Zeng CJFio. PI3K/Akt/mTOR pathway and its role in cancer therapeutics: are we making headway? Front Oncol. 2022;12:819128.
8- Zhang H-p, Jiang R-y, Zhu J-y, Sun K-n, Huang Y, Zhou H-h, et al. PI3K/AKT/mTOR signaling pathway: an important driver and therapeutic target in triple-negative breast cancer. Breast Cancer. 2024;31(4):539-51.
9- Zhang H-p, Jiang R-y, Zhu J-y, Sun K-n, Huang Y, Zhou H-h, et al. PI3K/AKT/mTOR signaling pathway: an important driver and therapeutic target in triple-negative breast cancer. Breast Cancer. 2024;31(4):539-51.
10- Tang T, Xiao ZY, Shan G, Lei HB. Descending-SHIP2-mediated radiosensitivity enhancement through PI3K/Akt signaling pathway in laryngeal squamous cell carcinoma. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2019;118:109392.
11- Hoekstra E, Das AM, Willemsen M, Swets M, Kuppen PJ, van der Woude CJ, et al. Lipid phosphatase SHIP2 functions as oncogene in colorectal cancer by regulating PKB activation. Oncotarget. 2016;7(45):73525-40.
12- Vincenzi M, Anna Mercurio F, Di Natale C, Palumbo R, Pirone L, La Manna S, et al. Targeting Ship2-Sam with peptide ligands: Novel insights from a multidisciplinary approach. Bioorganic chemistry. 2022;122:105680.
13- Gozzelino L, De Santis MC, Gulluni F, Hirsch E, Martini M. PI(3,4)P2 Signaling in Cancer and Metabolism. Front Oncol. 2020;10:360.
14- Yu J, Ryan DG, Getsios S, Oliveira-Fernandes M, Fatima A, Lavker RM. MicroRNA-184 antagonizes microRNA-205 to maintain SHIP2 levels in epithelia. Proceedings of the National Academy of Sciences of the United States of America. 2008;105(49):19300-5.
15- Pedicone C, Meyer ST, Chisholm JD, Kerr WGJC. Targeting SHIP1 and SHIP2 in Cancer. Cancers. 2021;13(4):890.
16- Ghosh S, Scozzaro S, Ramos AR, Delcambre S, Chevalier C, Krejci P, et al. Inhibition of SHIP2 activity inhibits cell migration and could prevent metastasis in breast cancer cells. Journal of cell science. 2018;131(16).
17- Salih AI, Mshimesh BA-R, Al-Sudani BTA-RJoMS. Investigating the Effect of EX-527 as SIRT1 Inhibitor in Breast Cancer Cell Line. Al-Rafidain Journal of Medical Sciences. 2024;7(1 (Special)):S64-9.
18- Al-Hamdy RAN, Arif IS, Al-Sudani BT. SHIP2 Silencing Enhances Erastin Cytotoxicity in MDA-MB-231 Breast Cancer Cell Line. Al-Rafidain Journal of Medical Sciences. 2025;8(2):182-7.

19- Hemmatzadeh M, Mohammadi H, Babaie F, Yousefi M, Ebrazeh M, Mansoori B, et al. Snail-1 silencing by siRNA inhibits migration of TE-8 esophageal cancer cells through downregulation of metastasis-related genes. Advanced pharmaceutical bulletin. 2018;8(3):437.
20- Al-khfajy WS, Arif IS, Al-sudani BT. Synergistic effect of obeticholic acid and fasting-mimicking on proliferative, migration, and survival signaling in prostate cancer. Pharmacia. 2022;69:579-87.
21- Luo SX, Liu JE, Cheng ASK, Xiao SQ, Su YL, Feuerstein M. Breast Cancer Survivors Report Similar Concerns Related to Return to Work in Developed and Developing Nations. Journal of occupational rehabilitation. 2019;29(1):42-51.
22- Li J, He D, Li S, Xiao J, Zhu Z. Ferroptosis: the emerging player in remodeling triple-negative breast cancer. Frontiers in immunology. 2023;14:1284057.
23- Ye Y, Ge YM, Xiao MM, Guo LM, Li Q, Hao JQ, et al. Suppression of SHIP2 contributes to tumorigenesis and proliferation of gastric cancer cells via activation of Akt. Journal of gastroenterology. 2016;51(3):230-40.
24- Fuhler GM, Brooks R, Toms B, Iyer S, Gengo EA, Park M-Y, et al. Therapeutic potential of SH2 domain-containing inositol-5′-phosphatase 1 (SHIP1) and SHIP2 inhibition in cancer. Molecular medicine. 2012;18:65-75.
25- Tang T, Xiao Z-Y, Shan G, Lei H-B. Descending-SHIP2-mediated radiosensitivity enhancement through PI3K/Akt signaling pathway in laryngeal squamous cell carcinoma. Biomedicine & Pharmacotherapy. 2019;118:109392.
26- Müller SM, Jücker M. The Functional Roles of the Src Homology 2 Domain-Containing Inositol 5-Phosphatases SHIP1 and SHIP2 in the Pathogenesis of Human Diseases. International journal of molecular sciences. 2024;25(10).
27- Zhou J, Di M, Han H, therapy. Upregulation of SHIP2 participates in the development of breast cancer via promoting Wnt/β-catenin signaling. OncoTargets. 2019:7067-77.
28- Ali Zaidi SS, Fatima F, Ali Zaidi SA, Zhou D, Deng W, Liu S. Engineering siRNA therapeutics: challenges and strategies. Journal of nanobiotechnology. 2023;21(1):381.
29- Arif T, Vasilkovsky L, Refaely Y, Konson A, Shoshan-Barmatz V. Silencing VDAC1 Expression by siRNA Inhibits Cancer Cell Proliferation and Tumor Growth In Vivo. Molecular therapy Nucleic acids. 2014;3(4):e159.
30- He Y, Sun MM, Zhang GG, Yang J, Chen KS, Xu WW, et al. Targeting PI3K/Akt signal transduction for cancer therapy. Signal transduction and targeted therapy. 2021;6(1):425.
31- Wu H, Li X, Feng M, Yao L, Deng Z, Zao G, et al. Downregulation of RNF138 inhibits cellular proliferation, migration, invasion and EMT in glioma cells via suppression of the Erk signaling pathway. Oncology reports. 2018;40(6):3285-96.
32- Liu RT, Cao JL, Yan CQ, Wang Y, An CJ, Lv HT. Effects of LncRNA-HOST2 on cell proliferation, migration, invasion and apoptosis of human hepatocellular carcinoma cell line SMMC-7721. Bioscience reports. 2017;37(2).
33- Wang Z, Li R, He Y, Huang S. Effects of secreted frizzled-related protein 1 on proliferation, migration, invasion, and apoptosis of colorectal cancer cells. Cancer cell international. 2018;18:48.