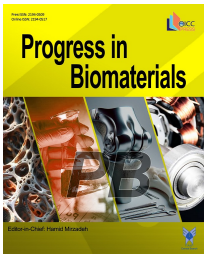

Prog. Biomater. 2026; 15(1) : 80-88

Progress in Biomaterials (PIBM)

https://doi.org/10.57647/pibm.2026.152603

Research Article

RNA-Seq Analysis Revealed the Suppressor Effects of Silybinin in Gastric and Breast Cancers Through the Downregulation of FGF and Wnt Signaling in Silybinin-Driven Modulation of ADSCs in Tumor Microenvironment

Zahra Derakhshandeh[1], Keyvan Ansari Shiri[2], Soheila Zamanlui Benisi[2,*], Saeed Hesami Tackallou[1,*]

[1]*Department of Biology, CT. C., Islamic Azad University, Tehran, Iran*
[2]*Department of Biomedical Engineering, CT. C., Islamic Azad University, Tehran, Iran*

[*]**Corresponding authors:** soh.zamanluibenisi@iauctb.ac.ir, and tackallou@gmail.com

Article History

Received:
12 July 2025

Revised:
29 January 2026

Accepted:
12 February 2026

Published in Issue:
31 March 2026

Abstract:

Adipose-derived mesenchymal stem cells (ADSCs) are key elements of the tumor microenvironment (TME), driving oncogenic advancement through paracrine signaling, epithelial-mesenchymal transition (EMT), and angiogenesis. Silybinin (SB), flavonoid from Silybum marianum, illustrated anticancer potential; however, impacts on ADSCs in breast and gastric cancers remain poorly understood.

Human (ADSCs) treated with various SB concentration, and viability was assessed by MTT assay to detect the optimum dose. Gene expression profiling was performed by RNA-sequencing (Illumina HiSeq 4000). Differentially expressed genes (DEGs) were detected using HISAT2 and NOISeq ($\log2|FC| \geq 1$, $p \leq 0.05$, and FDR ≤ 0.1), followed by KEGG enrichment analysis and qRT-PCR validation.

1- MTT assay demonstrated low-dose SB (0.005-0.5 µg) increased ADSCs viability ($p < 0.01$), while higher doses (10-50 µg) induced cytotoxicity ($p < 0.05$); 0.5 µg was optimal. 2- SB modulated expression of 324 genes (210 downregulated, 114 upregulated), enriching breast and gastric cancer pathways. Four oncogenic genes, FGF1, FGF5, FGF18, and TCF7 were downregulated, regulators of FGF-FGFR and Wnt/β-catenin signaling sustaining tumor growth, metastasis, and EMT. 3- qRT-PCR confirmed these findings ($P < 0.05$). Downregulation of FGF1, FGF5, and FGF18 inhibits proliferative and angiogenic signaling, while reduced TCF7 suppresses Wnt-driven stemness, promoting apoptosis.

Silybinin reprograms ADSCs within the TME by downregulating FGF1, FGF5, FGF18, and TCF7, key drivers of FGF-FGFR and Wnt/β-catenin-mediated tumor progression, reducing ADSC-mediated tumor support, increasing apoptosis, positioning it as a candidate for disrupting ADSC-cancer crosstalk.

Keywords: ADSCs; Silybinin; Gastric cancer; Breast cancer; RNA-sequencing

Cite this article: Derakhshandeh Z, Ansari Shiri K, Zamanlui Benisi S, Hesami Tackallou, S. RNA-Seq Analysis Revealed the Suppressor Effects of Silybinin in Gastric and Breast Cancers Through the Downregulation of FGF and Wnt Signaling in Silybinin-Driven Modulation of ADSCs in Tumor Microenvironment. Prog. Biomater. 2026;15(1), 80-88. https://doi.org/10.57647/pibm.2026.152603

1. Introduction

Cancer is one of the most important health issues and second leading cause of deaths worldwide [1, 2]. The tumor microenvironment (TME) as a chemically and mechanically complex niche [3] consists of various cell types including tumor cells, tumor stromal cells (stromal fibroblasts, endothelial cells mesenchymal stem cells, and immune cells like microglia, macrophages and lymphocytes) and the non-cellular components of extracellular matrix such as collagen, fibronectin, hyaluronan, and laminin [4, 5]. These cellular components of tu-

mor possess pro or anti- tumor effects due to complex interactions through cytokines, exosomes, cell adhesion, co-stimulation and co-inhibition, thus understanding the role of these cells as the non-malignant part of the TME can be an efficient approach to developing new cancer diagnosis and therapies [6].

Mesenchymal stem cells (MSCs) (6) with the ability of self-renewal and multiple differentiation, as an undeniable component in the tumor microenvironment, have been extensively researched in recent years. They are recruited into TME (7) and stimulate tumor or non-tumor cells by releasing endocrine and paracrine signals [7]. According to experimental assays stem cells can increase the migration, invasion, angiogenesis and tumorigenesis of cancer cells. In addition, the increased expression of specific mesenchymal markers leads to endothelial mesenchymal transition (EMT) in tumor cells and promotes a stemness phenotype in some cancer cells such as cervical cancer [8]. Interestingly, a previous study has shown that adipose derived stem cells (ADSCs) stimulate breast cancer cells to secrete TGF β, which promotes tumor migration and EMT in the advanced stages of breast cancer [9]. Therefore, it seems necessary to provide therapeutic methods that can prevent tumor proliferation, angiogenesis, and invasion by affecting the tumor microenvironment cells, especially adipose derived stem cells.

In this regard, developing novel agents to prevent numerous side effects of chemicals or drugs and targeting TME, are quite attractive [10]. Many recent studies have scientifically investigated the use of natural-derived components or micronutrients, and their potent benefits on human health [11]. Flavonoids are a group of plant derived polyphenolic substances with anti-oxidant possessions that can be exploited in cancer therapy [12].

Silybinin (SB, $C_{25}H_{22}O_{10}$) is a flavonoid extracted from silybum marianum flavonolignan (known as milk thistle), with natural anti-inflammatory properties inhibiting oxidative stress [13], anti-lipid peroxidation effect, elimination of free radicals, inhibiting the activity of lipoxygenase, maintaining stability of cell membrane, and antitumor effects in numerous cancers [14].

The purpose of this study was to observe the silybinin's effects in ADSCs, to examine whether silybinin modulates the expression of genes involved in gastric and breast tumors microenvironment.

2. Material and methods

2.1 Cell culture and SB-treatment

hADMSCs were obtained from Stem Cell Technology Research Center and cultured in a low-glucose Dulbecco's Modified Eagle's Medium (DMEM; BioMEDIA) supplied with 10% fetal bovine serum (FBS; Gibco TM), 100 U/mL penicillin and 100 µg/mL streptomycin, at 37 °C/5% CO_2. The cells were plated into 75 cm^2 tissue culture flasks and incubated until reaching a confluence between 70 and 80%. The culture medium was changed every 3 days.

Silybinin was purchased from Sigma Chemicals (Sigma-Aldrich, Shanghai) and 1 mg of silybinin was dissolved in 10 mL of sterile dimethyl sulfoxide (DMSO). Therefore, the concentration of silybinin solution in DMSO will be 100 µg/mL. The appropriate volume of silybinin solution and the volume of DMEM + 10% FBS culture medium required for each 1200 µL well, according to the desired dose of silybinin, was calculated by the following formula, and represented in Table 1.

Fourth passage culture of hADMSCs were divided and cultured in control (silybinin 0 µM) and silybinin groups at above concentrations for 24 h.

Table 1. Calculating appropriate volume of silybinin solution and culture medium required for each well, according to the desired dose of silybinin.

D_{SB} (µg)	V_{SB} (µL)	V_w (µL)
0.05	0.6	1199.4
0.1	1.2	1198.8
0.5	6	1194
0.7	8.4	1191.6
1	12	1188
10	120	1080
20	240	960
50	600	600
100	1200	0

V_{SB} = 1200 (µL) × D_{SB} (µg)/100 (µg/mL); V_w = 1200 (µL) − V_{SB}; (V_{SB}: Volume of silybinin solution in each well, D_{SB}: Desired dose of silybinin, V_w: Volume of culture medium in each well).

2.2 Cell proliferation assay

Cell proliferation of hADMSCs in control and SB-treated groups was evaluated by The MTT (3-[4,5-dimethylthiazole-2-yl]-2,5-diphenyltetrazolium bromide) assay, 24 hours after treatment. Briefly, a suspension containing 1×10^4 cells/mL from control and SB-treated groups was seeded in triplicates into 96-well plates and incubated at 37 °C in a 5% CO_2 atmosphere. The medium was removed after 24 h of incubation and MTT was dissolved in sterile PBS at a concentration of 5 mg/mL, added to the wells, and incubated for 4 hours. After removing the supernatant, 100 µL DMSO was added to dissolve the insoluble Formazan product. The results were obtained by measuring the absorbance at 570 nm with an ELISA reader.

2.3 RNA extraction and cDNA library construction

Total RNA was isolated from human adipose derived mesenchymal stem cells in control and SB-treated groups, on day 12 after treatment (D14), using Qiagen RNeasy Mini kit, according to the manufacturer's instructions (QIAGEN, Germany), then samples were quantified using a Nanodrop ND-1000 (Thermo Fisher Scientific) spectrophotometer. RNA concentration and integrity were evaluated using Agarose Gel Electrophoresis and Bioanalyzer 2100 (Agilent Technologies Inc. CA, USA), only samples with an RNA integrity number (RIN) greater than 8 were considered for subsequent analysis.

https://doi.org/10.57647/pibm.2026.152603

RNA-seq library construction was performed using a Kapa Hyper Prep Kit (Kapa Biosystems) and subjected to 150 bp for sequencing.

2.4 RNA sequencing and data analysis

hADMSCs cultured in the presence and absence of silybinin were subjected to RNA sequencing on an Illumina HiSeq 4000 platform at Beijing Novogene Bioinformatics Technology Co., Ltd (China). FastQC v0.11.5 (http://www.bioinformatics.babraham.ac.uk/projects/fastqc/) was conducted for quality control of sequencing reads to remove adapters and low-quality data. After filtering, sequenc¬es were aligned to the Homo sapiens (human) genome, GRCh38 (hg38), using HISAT2 aligner v2.1.0. FeatureCounts v1.5.0 was used to count the number of uniquely mapped read pairs with gene annotations. Differential gene expression values were determined using NOISeq v2.22.0 based on an 80% probability threshold. Then differentially expressed genes(DEGs) with a fold change (FC) higher than 2 or less than −2 (log 2|FC| >= 1), a p-value ≤ 0.05, and adjusted p-values (FDR) ≤ 0.1 were considered to compare the groups of study.

2.5 Functional enrichment analysis

To achieve practical knowledge about the signaling pathways induced by SB treatment, the Kyoto Encyclopedia of Genes and Genomes (KEGG) database was used for pathway enrichment analysis. Initially, the list of differentially expressed genes (DEGs) was uploaded as input, and statistically significant signaling pathways with p-value ≤ 0.05 were extracted for further analysis.

2.6 Real time PCR

RT-PCR was performed on day 12 after treatment (D14) to confirm selected DE genes involved in cancer signaling pathways, resulted by RNA sequencing. Total RNA was extracted using the Qiagen RNeasy Mini Kit, according to the manufacturer's instructions (QIAGEN, Germany) and 1 µg of total RNA was transcribed to complementary DNA (cDNA) using the Qiagen QuantiTect Reverse Transcription Kit. The quantitative real-time polymerase chain reaction (qPCR) was performed on a Rotor-Gene 6000 real-time PCR machine (Corbett Research, Qiagen, Germany). Amplification was done at 95 °C (1 min), and then, 40 cycles at 95 °C (15 s), 55 °C (30 s), and 72 °C (30 s) (at 95 °C for 90 s followed by 40 cycles, each cycle lasting 15 s at 95 °C and 30 s at 55 °C). Real-time PCR was performed in a 15 µL reaction mixture containing 7.5 µL of MasterMix SYBR Green PCR (Applied Biosystems), 0.75 µL of each primer (Table 2), 3 µL DNase- and RNase-free water, and 3 µL of cDNA from each sample. The sequences of the forward and reverse primers were shown in Table 2. Quantity of expressed mRNA in each sample was normalized to that of β-actin, as endogenous housekeeping gene, using the $2^{-\Delta\Delta ct}$ method. Figure 1 illustrates the scheme of analysis.

2.7 Statistical analysis

All experiments were performed with four replicates. Statistical analyses were performed using SPSS (IBM SPSS Statistics, USA) software. p-value < 0.05 was considered statistically significant.

3. Results

3.1 The effect of SB treatment on cell viability

Following 24 h of SB treatment of hADMSCs with different silybinin doses (Table 1), an MTT assay was performed and resulted data revealed a significant increase in MSCs survival for 0.5 µg silybinin (V_{SB} = 6 µL, V_w = 1194 µL) compared to the other groups.
As shown in Fig. 2 cell proliferation increased significantly (p-value < 0.01) as the concentration of silybinin in the culture medium increased from 0.005 µg to 0.5 µg, however, cell viability showed a remarkable decrease (p-value < 0.05) with a further increase in the drug dose, so that higher doses (10 to 50 µg) revealed cytotoxicity and inhibited cell growth. Therefore, the results of the MTT test demonstrated that the dose of 0.5 µg is the optimal dose for treating cells with SB.

3.2 Differential gene expression and pathway enrichment analysis

To determine the DEGs in SB-treated cells, RNA-seq analysis was performed using Illumina HiSeq 4000 platform, 12 days after treatment. A total of 47.5 million and 53.1 million reads with a read length of 150 bp were aligned to the Homo sapience reference genome (GRCh38) in the control and SB-treated groups, respectively, of which 46.1 million (97.18%) and 51.5 (96.87%) million reads were mapped to reference genome for each group. 324 transcript IDs were identified as

Table 2. Primer sequences for RT-PCR.

Primer name	Forward sequence	Reverse sequence
FGF1	ATGGCACAGTGGATGGGACAAG	TAAAAGCCCGTCGGTGTCCATG
FGF5	CCCGGATGGCAAAGTCAATGG	TTCAGGGCAACATACCACTCCCG
FGF18	TGCTTCCAGGTACAGGTGCT	GCTGCTTACGGCTCACATCG
TCF7	CTGACCTCTCTGGCTTCTACTC	CAGAACCTAGCATCAAGGATGGG
β-Actin	CACCATTGGCAATGAGCGGTTC	AGGTCTTTGCGGATGTCCACGT

https://doi.org/10.57647/pibm.2026.152603

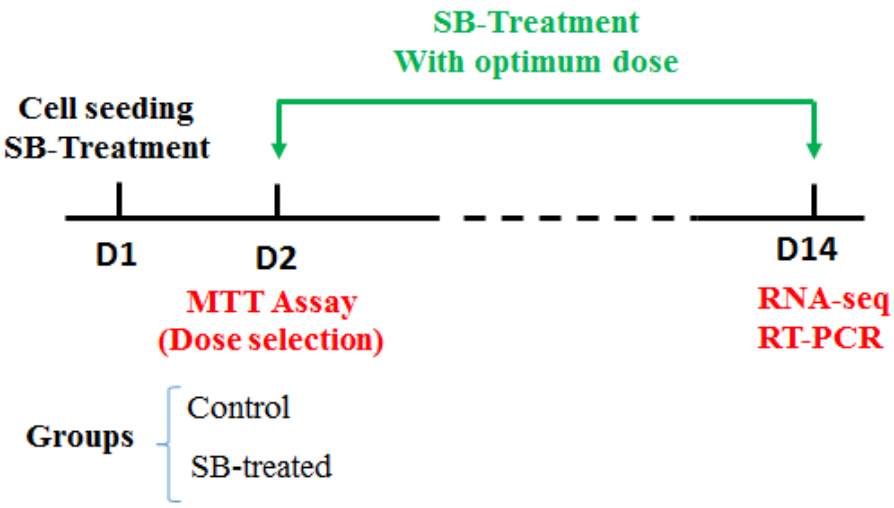

Figure 1. The time frame of our experimental design. Following the seeding of human adipose-derived mesenchymal stem cells, SB treatment with different silybinin concentrations was performed and MTT assay was conducted after 24 h (D2) for selecting the optimum dose. To explore the effect of silybinin on the cells, RNA-seq, and RT-PCR were subsequently conducted after 12 days of treatment (D14).

differentially expressed genes with a probability threshold of ≥ 80%, of which 210 genes showed significant down-regulation, while 114 genes have considerable up-regulation. Among these DE genes, the top ten that revealed the greatest increase or decrease in expression compared to the control group were shown in Table 3.

According to pathway enrichment analysis, 2 cancerous pathways including gastric cancer, and breast cancer were induced by SB treatment (Table 4).
Among them, 4 DEGs were common in these cancers and showed significant up/down-regulation, as shown in Table 4.

3.3 Confirmation of DEGs by RT PCR

In order to investigate the gene expression changes generated by RNA-seq analysis, the expression of four DEGs including FGF1, FGF5, FGF18, and TCF7 was examined using qRT-PCR on day 12 after treatment (D14) in both groups. Since these genes are common in both cancers signaling pathways and play an important role in cancer growth and development, as well as EMT, they have been selected. As shown in Tables 5, RNA-seq results were confirmed by qRT-PCR and these 4 genes were significantly down-regulated ($p < 0.05$) in line with our RNA-seq data (Fig. 3; Table 5).

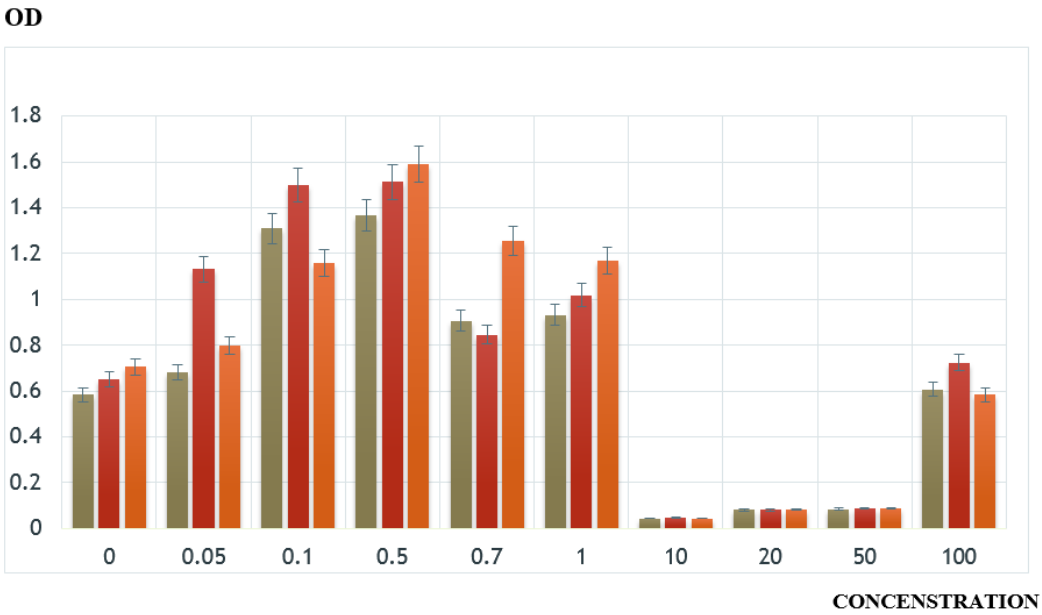

Figure 2. MTT assay shows a significant increase in cell viability for 0.005 µg to 0.5 µg SB concentration, and a significant decrease for 0.5 µg to 50 µg SB concentration (** p-value < 0.01), (*p-value < 0.05). The values are expressed as means (±SEM; $n = 3$).

https://doi.org/10.57647/pibm.2026.152603

Table 3. Top ten DEGs based on RNA-seq results.

Gene symbol	Gene name	Fold change (RNA-seq)
ARHGDIB	Rho GDP dissociation inhibitor beta	−14.66
CD36	CD36 molecule	−8.6
PKP3	plakophilin 3	−7.20
FSIP1	fibrous sheath interacting protein 1	−7.0
CRABP2	cellular retinoic acid binding protein 2	−5.4
TRABD2B	TraB domain containing 2B	10.5
PENK	proenkephalin	10.0
ABCA10	ATP binding cassette subfamily A member 10	5.16
RAB27B	member RAS oncogene family	4.0
ETNK2	ethanolamine kinase 2	3.45

Table 4. Induced signaling pathways by SB-treatment.

Gene Set	Description	Size	P Value
hsa05224	Breast cancer	147	0.044497
hsa05226	Gastric cancer	149	0.046372

4. Discussion

ADSCs (adipose tissue-derived stem cells) as multipotent mesenchymal stem cells, are the abundant and available subset of cells [15] in adipose tissues, as well as tumor microenvironment (TME). They exhibit mechanical and biochemical interactions with tumor cells [16]. Moreover, they possess crucial role in tumor growth and progression [17]. ADSCs can be attracted to solid tumors and affect other cells in the TME through secreting paracrine cytokines and growth factors [18]. They can promote the inflammatory microenvironment [19, 20], increase tumor vascularity [21], make tumor cells aggressive [22] and differentiate into cancer-associated fibroblasts CAFs [23]. Therefore, they serve as an considerable promoter for tumor survival, proliferation, migration [24, 25, 26], invasion [27, 28] and chemo-resistance [29]. According to this role of ADSCs in TME, targeting these cells as a therapeutic approach can be an effective treatment for controlling the various types of cancers. In this study, the effect of SB on ADSCs in regard to regulating the gene expression in mRNA level has been evaluated using RNA-seq. According to signaling pathway analysis induced by SB treatment, the Gastric and Breast Cancer pathways were revealed with regulating the expression of FGF1, 5, 18 and TCF7 genes. Fibroblast growth factors (FGFs) are comprising 22 secretion proteins, secreted by cancer cells or surrounding stromal cells, so that dysregulation of the FGF signaling pathway plays an important role in the tumor microenvironment [30]. Moreover, fibroblast growth factor receptors (FGFRs) are highly conserved transmembrane tyrosine kinase receptors (TKRs) which FGF-FGFR pathway contribute

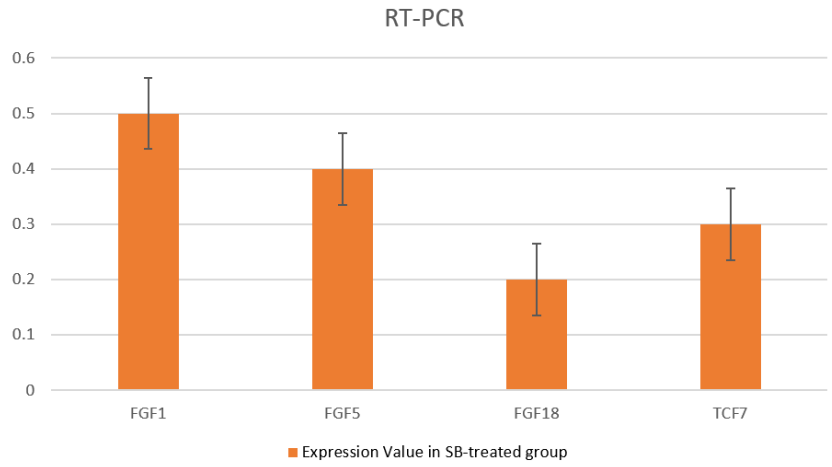

Figure 3. The expression levels for the candidate genes relative to β-actin as control (see Table 3). The values are expressed as means (±SEM; $n = 3$), (**p < 0.001); (*p < 0.05).

https://doi.org/10.57647/pibm.2026.152603

Table 5. Selected DEGs based on RNA-seq data which was confirmed by qPCR.

Gene symbol	Fold change (RT-PCR)	Fold change (RNA-seq)
FGF1	0.5	−8.9
FGF5	0.4	−4.0
FGF18	0.2	−5.6
TCF7	0.3	−6.7

to a broad range of biological events, including tissue development, angiogenesis, regeneration, tumorigenesis, and cancer cells invasiveness [31].

Fibroblast growth factor 18 (FGF18), a glycosylated secretory protein, whose overexpression has been identified as a potential prognostic biomarker in several neoplasms including hepatocellular cancers, gastric cancer, colorectal cancer, and ovarian cancer [32, 33, 34, 35]. According to a study by Yang et al. [36], overexpression of FGF18 leads to increased expression of E-cadherin and decreased expression of N-cadherin and Vimentin in clear cell renal cell carcinoma (ccRCC), showed the inhibitation of EMT in ccRCC cells. Since EMT has a close relationship with the PI3K/Akt pathway [37], they suggest that FGF18 is a potential molecular target for ccRCC treatment and that overexpression of FGF18 inhibited EMT via the PI3K/Akt pathway in ccRCC. Additionally, the role of up-regulated FGF18 as a downstream target of β-catenin was observed in colorectal cancers (CRC) [33]. Therefore, the activation of FGF18 inhibits carcinogenesis by regulating EMT, which is a novel prognostic biomarker and therapeutic target for clinical intervention of cancers [36]. Zhang et al. investigated the expression and regulatory mechanisms of FGF18 in gastric cancer. They found that the overexpression of FGF18 was observed in genomically stable and chromosomal instability subtypes of gastric cancer (GC) and associated with poor survival. Moreover, inhibited tumor formation abilities, induced G1 phase cell cycle arrest and enhanced anti-cancer drug sensitivity were obtained by knocking FGF18 down. As shown by microarray gene expression profiling, treating GC cells with human recombinant FGF18 or FGF18-conditioned medium accelerated tumor growth through activation of ERK-MAPK signaling [38]. According to our RNA-seq and RT-PCR results, FGF18 showed a remarkable decreased expression in SB treated cells compared to control, which demonstrates the potential therapeutic capability of this flavonoid. Furthermore, the decrease in the expression level of fibroblast growth factor 1 (FGF1) was identified in our study based on RNA-seq and RT-PCR assays. FGF1 has been involved in a wide variety of several malignant diseases and takes part in the tumorigenesis of CRC. It is elevated in CRC tissues and linked with poor prognosis, so that high level FGF1 expression was associated with markedly shorter survival [39]. In another study by Liu et al. the higher FGF1 expression rate in gastric adenocarcinoma compared to adjacent tissue was reported. Moreover, this increased expression is significantly associated with lymph node invasion, distant metastasis, and differentiation [40]. The action of FGFs, particularly FGF1 and FGF2, has been correlated with chemoresistance in many types of cancer. In this regard, Szymczyk et al. [41] showed that FGF1 prevents drug-induced apoptosis. Based on recent studies FGF1 induces the invasion and metastasis of tumor cells and promotes the proliferation and migration ability of tumor cells [42, 43, 44, 45]. Cancer-associated fibroblasts (CAFs) are one of the most abundant cellular components of the stroma in various epithelial tumors, including breast carcinoma. Among all growth factors/cytokines secreted by CAFs, FGFs emerged as the most powerful mediators of breast cancer progression, function of steroid hormone receptors and resistance to endocrine therapies. Fibroblast growth factor-5 (FGF5) belongs to the FGF family that plays vital roles in the transduction of signals, embryonic development, tissue maintenance, and wound healing. Researchers have found that breast cancer patients with low FGF5 expression have better clinical outcomes, suggesting the importance of FGF5 in breast cancer progression [46]. Another study by Lua et al. [47] investigated the inhibitory effect of miR-873 targeting FGF5 on EMT of GC cells in vitro. In addition, FGF5 was observed to be overexpressed in gastric cancer tissues and has better diagnostic efficacy in GC [47]. Since EMT has a vital role in growth and survival of tumor cells [48], FGF5 controls the EMT of the stomach and small intestine by regulating cell division [49]. According to our experimental results, FGF5 showed a remarkable decreased expression in SB treated cells compared to control, which revealed inhibitory effect in growth and survival of tumor cells. As the last gene in our selected list of DEs, transcription factor 7 (TCF7) plays an essential role in Wnt signaling by interacting with β-catenin and mediating the transcription of target genes [50]. Based on emerging evidence, the up-regulation of TCF7 promotes progression of many types of cancers, such as prostate cancer, adrenocortical tumor, pancreatic cancer, renal cancer, and breast cancer [51, 52, 53, 54]. Xu et al. [55] have shown that the mRNA levels of TCF7 in GC tissues were significantly higher compared to corresponding tumor adjacent tissues. Moreover, TCF7 was significantly associated with low survival rates, positive lymphatic invasion, as well as tumor metastasis [55]. By assessing TCF7 expression in SB-treated cells and control groups, we demonstrated that silybinin can reduce the expression of TCF7 and have a positive role in the control of cancer progression and metastasis.

5. Conclusions

According to this experimental study, it can be concluded that FGF1, 5, 18 and TCF7 as considerable genes contributed to cancer progression and metastasis have shown significant down regulation in SB-treated ADSCs. Since ADSCs are an important part of TME, this treatment has significant therapeutic potential for various cancers, especially in gastric and breast tumors.

https://doi.org/10.57647/pibm.2026.152603

Ethical Approval

Regarding the ethical approval for the use of biological samples, specifically human adipose-derived stem cells, we would like to clarify that this research aspect refers to the previously published study titled "Enhanced Chondrogenic Differentiation of Human Bone Marrow Mesenchymal Stem Cells on PCL/PLGA Electrospun with Different Alignment and Composition," published in the International Journal of Polymeric Materials and Polymeric Biomaterials (DOI: https://doi.org/10.1080/00914037.2017.1297941).

For our current study, no new ethical approval was necessary as it builds upon the foundational work and ethical considerations detailed in the aforementioned publication.

RNA-Sequencing approach for exploring the osteogenic potential of silibinin on human adipose-derived mesenchymal stem cells, Stem cell technology research center (STRC), Iran university of medical science (IUMS), Islamic Azad university Central Tehran Branch, 162541195, 1401/03/17). Iranian calendar 06/07/2022 (June7,2022).

Authors contributions

Zahra Derakhshande and Keyvan Ansari Shiri carried out the literature search, experiments and data acquisition, participated in the study design, and drafted the manuscript. Soheila Zamanlui Benisi and Saeed Hesami Tackallou collected the data, participated in the study design, and helped draft the manuscript. All authors contributed to the article and approved the submitted version.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Pahlavan Y, Nasr MM, Abdolahinia ED, et al. Prominent roles of microRNA-142 in cancer. Pathol Res Pract 2020 :153220
2. Pourgholi A, Dadashpour M, Mousapour A, Amandi AF, and Zarghami N. Anticancer Potential of Silybinin Loaded Polymeric Nanoparticles against Breast Cancer Cells: Insight into the Apoptotic Genes Targets. Asian Pac J Cancer Prev 2021; 22:2587–96
3. Amos SE and Choi YS. The Cancer Microenvironment: Mechanical Challenges of the Metastatic Cascade. Frontiers in Bioengineering and Biotechnology 2021; 9:625859
4. Jahanban-Esfahlan R, Seidi K, and Zarghami N. Tumor vascular infarction:prospects and challenges. Int J Hematol 2017; 105:244–56
5. Baghban R, Roshangar L, Jahanban-Esfahlan R, Seidi K, Ebrahimi-Kalan A, Jaymand M, and Zare P. Tumor microenvironment complexity and therapeutic implications at a glance. Cell Communication and Signaling 2020; 18
6. Farc O and Cristea V. An overview of the tumor microenvironment, from cells to complex networks (Review). Experimental and Therapeutic Medicine 2021; 21:96
7. Wu S, Wang Y, Yuan Z, Wang S, Du H, Liu X, and Zhu X. Human adipose derived mesenchymal stem cells promote breast cancer MCF7 cell epithelial mesenchymal transition by cross interacting with the TGF β/Smad and PI3K/AKT signaling pathways. Molecular Medicine Reports 2018
8. Castro-Oropeza R, Vazquez-Santillan K, Díaz-Gastelum C, Melendez-Zajgla J, Zampedri C, Ferat-Osorio E, and Maldonado V. Adipose-derived mesenchymal stem cells promote the malignant phenotype of cervical cancer. Scientific Reports 2020; 10
9. Xie F, Ling L, Dam H van, Zhou F, and Zhang L. TGF β signaling in cancer metastasis. Acta Biochim Biophys Sin (Shanghai) 2018; 50:121–32
10. Marzieh N, Nosratollah Z, Kazem NK, and Mahdieh M. Curcumin and silybinin inhibit telomerase expression in T47D human breast cancer cells. Asian Pac J Cancer Prev 2013; 14:3449–53
11. Atanasov AG, Zotchev SB, Dirsch VM, and Supuran CT. Natural products in drug discovery: advances and opportunities. Nat Rev Drug Discov 2021; 20:200–216
12. Tavsan Z and Kayali HA. Flavonoids showed anticancer effects on the ovarian cancer cells: Involvement of reactive oxygen species, apoptosis, cell cycle and invasion. Biomed Pharm 2019; 116:109004
13. Chen J, Li DL, Xie LN, et al. Synergistic anti-inflammatory effects of silybinin and thymol combination on LPS-induced RAW264. 7 cells by inhibition of NF-κB and MAPK activation. Phytomedicine 2020; 78:153309
14. Feher J and Lengyel G. Silymarin in the prevention and treatment of liver diseases and primary liver cancer. Curr Pharm Biotechnol 2012; 13:210–7
15. De Francesco F, Giulia R, ĎAndrea F, et al. Human adipose stem cells: from bench to bedside. Tissue Eng Part B Rev 2015; 2:572–584
16. Poorolajal J and Jenabi E. The association between BMI and cervical cancer risk: a meta-analysis. Eur J Cancer Prev 2016; 25:232–238
17. Donnenberg Vera S, Ludovic Z, Peter RJ, et al. Regenerative therapy after cancer: what are the risks? Tissue Eng Part B Rev 2010; 16:567–575

18. Berry R, Rodeheffer MS, Rosen CJ, and Horowitz MC. Adipose tissue residing progenitors (adipocyte lineage progenitors and adipose derived stem cells (ADSC). Curr Mol Biol Rep 2015; 1:101–109
19. Dwyer RM et al. Monocyte chemotactic protein-1 secreted by primary breast tumors stimulates migration of mesenchymal stem cells. Clin Cancer Res 2007; 13:5020–5027
20. Chu Y et al. STAT3 activation by IL-6 from adipose-derived stem cells promotes endometrial carcinoma proliferation and metastasis. Biochem Biophys Res Commun 2018; 500:626–631
21. Lin G, Yang R, Lia B, et al. Effects of transplantation of adipose tissue-derived stem cells on prostate tumor. Prostate 2010; 70:1066–1073
22. Koellensperger E et al. Alterations of gene expression and protein synthesis in co-cultured adipose tissue-derived stem cells and squamous cell-carcinoma cells: consequences for clinical applications. Stem Cell Res. Ther. 2014; 5:65
23. Raghu K and Michael Z. Fibroblasts in cancer. Nat Rev Cancer 2006; 6:392–401. DOI: 10.1038/nrc1877
24. Rhyu JJ, Yun JW, Kwon E, Che JH, and Kang BC. Dual effects of human adipose tissue-derived mesenchymal stem cells in human lung adenocarcinoma A549 xenografts and colorectal adenocarcinoma HT-29 xenografts in mice. Oncol. Rep. 2015; 34:1733–1744. DOI: 10.3892/or.2015.4185
25. Yan Wang YC et al. Adipose-derived mesenchymal stem cells promote osteosarcoma proliferation and metastasis by activating the STAT3 pathway. Oncotarget 2017; 8:23803–23816
26. Li M et al. Human omental adipose-derived stem cells from donors with different body mass index had similar effects on proliferation and migration of endometrial cancer cells in vitro. J. Obstet. Gynaecol. Res. 2019; 45:417–427. DOI: 10.1111/jog.13820
27. Constantin J, Eckhard A, Gabriel W, and orhers. Adipose tissue derived stem cells differentiate into carcinoma-associated fibroblast-like cells under the influence of tumor derived factors. Cell Oncol 2011; 34:55–67
28. Eva K, Felix G, Fabian P, et al. Alterations of gene expression and protein synthesis in co-cultured adipose tissue-derived stem cells and squamous cell-carcinoma cells: consequences for clinical applications. Stem Cell Res Ther 2014; 6:65
29. Frees Kyle E, Lauren K, Edwards Robert P, et al. Adipose-derived stems cells and their role in human cancer development, growth, progression, and metastasis: a systematic review. Cancer Res. 2015; 75:1161–1168
30. Bittencourt MLF, Rodrigues RP, Kitagawa RR, and Cássia Ribeiro Gonçalves R de. The gastroprotective potential of silybinin against Helicobacter pylori infection and gastric tumor cells. Life Sciences 2020 :117977
31. Zhang Y, Ge Y, Ping X, Yu M, Lou D, and Shi W. Synergistic apoptotic effects of silybinin in enhancing paclitaxel toxicity in human gastric cancer cell lines. 2018; Molecular Medicine Reports
32. Shimokawa T, Furukawa Y, Sakai M, Li M, Miwa N, Lin YM, et al. Involvement of the FGF18 gene in colorectal carcinogenesis, as a novel downstream target of the β-catenin/T-cell factor complex. Cancer Res 2003; 63:6116–20
33. Wei W, Mok SC, Esther O, Sung-Hoon K, Gayatry M, and Birrer MJ. FGF18 as a prognostic and therapeutic biomarker in ovarian cancer. J Clin Invest 2013; 123:4435–48. DOI: 10.1172/JCI70625
34. Guo P, Wang Y, Dai C, Tao C, Wu F, Xie X, et al. Ribosomal protein S15a promotes tumor angiogenesis via enhancing Wnt/beta-catenin-induced FGF18 expression in hepatocellular carcinoma. Oncogene 2018; 37:1220–36. DOI: 10.1038/s41388-017-0017-y
35. Zhang J, Zhou Y, Huang T, Wu F, Pan Y, Dong Y, et al. FGF18, a prominent player in FGF signaling, promotes gastric tumorigenesis through autocrine manner and is negatively regulated by miR-590-5p. Oncogene 2019; 38:33–46. DOI: 10.1038/s41388-018-0430-x
36. Yang C, Zhang Z, Ye F, Mou Z, Chen X, Ou Y, and Jiang H. FGF18 Inhibits Clear Cell Renal Cell Carcinoma Proliferation and Invasion via Regulating Epithelial-Mesenchymal Transition. 2020; Frontiers in Oncology
37. Chang L, Graham PH, Hao J, Ni J, Bucci J, Cozzi PJ, et al. Acquisition of epithelial-mesenchymal transition and cancer stem cell phenotypes is associated with activation of the PI3K/Akt/mTOR pathway in prostate cancer radioresistance. Cell Death Dis 2013; 4:e875
38. Zhang J, Zhou Y, Huang T, et al. FGF18, a prominent player in FGF signaling, promotes gastric tumorigenesis through autocrine manner and is negatively regulated by miR-590-5p. Oncogene 2019; 38:33–46
39. Duan T, Zhou D, Yao Y, and Shao X. The Association of Aberrant Expression of FGF1 and mTOR-S6K1 in Colorectal Cancer. Front Oncol 2021; 11:706838
40. Niu J, Liu N, Zhang J, Sun S, Feng H, Qiao H, and Sun Q. Expression and clinical significance of fibroblast growth factor 1 in gastric adenocarcinoma. 2015; OncoTargets and Therapy:615

41. Szymczyk J, Sochacka M, Chudy P, Opalinski L, Otlewski J, and Zakrzewska M. FGF1 protects FGFR1-overexpressing cancer cells against drugs targeting tubulin polymerization by activating AKT via two independent mechanisms. Front Oncol 2022; 12:1011762

42. King ML, Lindberg ME, Stodden GR, Okuda H, Ebers SD, Johnson A, et al. WNT7A/Beta-Catenin Signaling Induces FGF1 and Influences Sensitivity to Niclosamide in Ovarian Cancer. Oncogene 2015; 34:3452–62

43. Liu P, Zhang R, Yu W, Ye Y, Cheng Y, Han L, et al. FGF1 and IGF1-Conditioned 3D Culture System Promoted the Amplification and Cancer Stemness of Lung Cancer Cells. Biomaterials 2017; 149:63–76

44. Wu D, Yang B, Chen J, Xiong H, Li Y, Pan Z, et al. Upregulation of Long Non-Coding RNA RAB1A-2 Induces FGF1 Expression Worsening Lung Cancer Prognosis. Cancer Lett 2018; 438:116–25

45. Chen J, Zhou Z, Yao Y, Dai J, Zhou D, Wang L, and Zhang QQ. Dipalmitoylphosphatidic Acid Inhibits Breast Cancer Growth by Suppressing Angiogenesis via Inhibition of the CUX1/FGF1/HGF Signalling Pathway. J Cell Mol Med 2018; 22:4760–70

46. Li H, Yin H, and Yan Y. Circ_0041732 regulates tumor properties of triple-negative breast cancer cells by the miR-149-5p/FGF5 pathway. International Journal of Biological Markers 2022; 37:178–90

47. Lua G, Caob Q, Zhaoc H, Duand J, and Liu Z. Effects of miR-873 Targeted Regulation of FGF5 on Gastric Cancer and Its Related Mechanism. Revista Argentina de Clínica Psicológica 2020; XXIX:1030–40

48. Saxena M, Kalathur Ravi Kiran R, Neutzner M, et al. Correction: PyMT-1099, a versatile murine cell model for EMT in breast cancer. Sci Rep 2020; 10:11444. DOI: 10.1038/s41598-018-30640-1

49. Zhang J, Zhou Y, Huang T, et al. FGF18, a prominent player in FGF signaling, promotes gastric tumorigenesis through autocrine manner and is negatively regulated by miR-590-5p. Oncogene 2019; 38:33–46

50. Reya T. Clevers H: Wnt signalling in stem cells and cancer. Nature 2005; 434:843–50

51. Nikuseva-Martic T, Serman L, Zeljko M, et al. Expression of secreted frizzled-related protein 1 and 3, T-cell factor 1 and lymphoid enhancer factor 1 in clear cell renal cell carcinoma. Pathol Oncol Res 2013; 19:545–51

52. Leal LF, Bueno AC, Gomes DC, et al. Inhibition of the Tcf/beta-catenin complex increases apoptosis and impairs adrenocortical tumor cell proliferation and adrenal steroidogenesis. Oncotarget 2015; 6:43016–32

53. Pramanik KC, Fofaria NM, Gupta P, et al. Inhibition of beta-catenin signaling suppresses pancreatic tumor growth by disrupting nuclear beta-catenin/TCF-1 complex: Critical role of STAT-3. Oncotarget 2015; 6:11561–74

54. Park J, Schlederer M, Schreiber M, et al. AF1q is a novel TCF7 co-factor which activates CD44 and promotes breast cancer metastasis. Oncotarget 2015; 6:20697–710

55. Xu X, Liu Z, Tian F, Xu J, and Chen Y. Clinical Significance of Transcription Factor 7 (TCF7) as a Prognostic Factor in Gastric Cancer. Med Sci Monit 2019; 25:3957–63