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Baicalin Inhibits Human Cervical Cancer Cells by Suppressing Protein Kinase C/Signal Transducer and Activator of Transcription (PKC/STAT3) Signaling Pathway

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Background: Like other human cancers, the malignancy of cervical cancer is also characterized by abilities of proliferation, migration, and invasion. Protein kinase C-zeta (PKCζ) has been highly correlated with several human cancers. Baicalin was proven to regulate PKC. This study aimed to investigate the anti-cancer effect and involved molecular mechanisms of baicalin on human cervical cancer.

Material/Methods: Baicalin at various concentrations was used to treat 2 human cervical cancer cell lines HeLa and SiHa. The proliferation was assessed by 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenylterazolium bromide (MTT) assay. The apoptosis was detected by terminal transferase UTP nick end labeling (TUNEL) assay. Wound healing assay and Transwell assay were used to evaluate the migration and invasion respectively. Western blotting was performed to assess the protein expression levels.

Results: Baicalin administration significantly reduced the viability by facilitating the apoptosis in HeLa and SiHa cells. Baicalin treatment also significantly reduced the wound closure and cell amount invaded as measured by Transwell assay. The expression levels of PKCζ, survivin, matrix metalloproteinase (MMP)2, MMP9 as well as the phosphorylation of signal transducer and activator of transcription (STAT) 3 were reduced in baicalin administrated cervical cancer cells.

Conclusions: Baicalin exerted anti-cancer effects on human cervical cancer cells by targeting STAT3 regulated signaling pathways.

MeSH Keywords: Medicine, Chinese Traditional • Protein Kinase C • Uterine Cervical Neoplasms

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Background

Worldwide, cervical cancer is one of the most common cancers diagnosed in the female population. The incidence and mortality rates are higher in developing countries due the higher infection rate of human papillomavirus (HPV) [1]. Currently the treatment options for cervical cancer are surgery, chemotherapy, and radiotherapy [2]. Recently, the novel therapeutic approach is concurrent chemoradiotherapy (CRRT) which was proven effective in increasing the 5-year survival rate of cervical cancer patients [3]. However, the prognosis of cervical cancer patients at advanced stage is still poor due to the cancer's potent abilities of proliferation, invasion, and metastasis. Thus, a capable anti-cancer agent for targeting and inhibiting proliferation, invasion, and metastasis simultaneously would be of high scientific and clinical value for cervical cancer patients.

It has been established that the protein kinase C (PKC) is associated with malignancy of tumors and was first identified as a receptor for tumor-promoting phorbol esters [4]. PKCs are composed of large subfamilies of various isoforms including the conventional PKCs (cPKCs), novel PKCs (nPKCs), and atypical PKCs (aPKCs) [5]. Unlike cPKCs and nPKCs, the downstream signaling of aPKCs are different. aPKCs are characterized by their unique N-terminal regulatory domain which interacts with partitioning- defective (PAR)-3 and PAR-6. These PAR proteins play critical roles in cell proliferation, division, and polarization. Previous studies have indicated that the interactions between aPKCs and PAR proteins are correlated with malignant capabilities of metastatic carcinomas [6].

As a member of aPKCs, the increased expression of PKCζ was reported to be associated with human cancer by regulating the mitogenic, migrative, and apoptotic intracellular signaling [7]. Signal transducer and activator of transcription (STAT)3 was identified as a downstream effecter of PKCζ8. The activation and nuclear translocation of STAT3 participated in triggering expression of several genes involved in neoplasia and metastasis [9]. It was described previously that the blocking of aPKCs signaling inhibited the transformed growth and invasion of human pancreatic cancer cells [10]. Baicalin is a flavonoid extracted from a Chinese medical herb named *Scutellaria baicalensis Georgi* which has been applied in Traditional Chinese Medicine (TCM) since ancient times. Modern pharmacological investigations revealed the biological activities of baicalin, such as anti-oxidant, anti-fibrosis, anti-bacterial, and anti-inflammatory effects [11]. Previous studies have indicated the anti-cancer activity of baicalin against multiple human cancers including hepatic cancer, lung cancer, and lymphoma [12–14]. There are very few studies investigating the anti-cancer effects of baicalin on human cervical cancer. Moreover, a previous study suggested the regulation effect of baicalin on PCK15. Thus, we proposed the hypothesis that baicalin could suppress human cervical cancer by regulating PKC- associated pathways.

In this study, the anti-cancer effect of baicalin was observed in 2 human cervical cancer cell lines (HeLa and SiHa). The involvement of PKCζ/STAT3 signaling was also investigated as a possible molecular mechanism. We believe that results from this study could not only add more information concerning the mechanisms of pathogenesis of cervical cancer, but also contribute to accumulating evidence supporting potential application of baicalin as an anti-cancer agent in cervical cancer patients.

Material and Methods

Agents and antibodies

Agents and antibodies included: baicalin (Sigma-Aldrich, Cat# 572667), TUNEL kit (Roche, Cat# 11684795910), PKCζ antibody (Cell Signaling Tech, Cat#9372, 1: 4000), STAT3 antibody (Cell Signaling Tech, Cat#4368, 1: 2000), phosphorylated STAT3 antibody (p-STAT3, Cell Signaling Tech, Cat#8119, 1: 2000), Survivin antibody (Abcam, Cat#ab76424, 1: 4000), matrix metalloproteinase (MMP)2 antibody (Abcam, Cat#ab37150, 1: 4000), MMP9 antibody (Abcam, Cat#ab38898, 1: 4000), Histone H3 antibody (Abcam, Cat#ab8580, 1: 4000), and GAPDH antibody (Sigma-Aldrich, Cat#G9545, 1: 6000).

Cell lines and treatment

Human cervical cancer HeLa and SiHa cells were purchased from China Center for Type Culture Collection (CCTCC). Cells were maintained in Dulbecco modified eagle medium (DMEM, Hyclone) supplemented with 10% fetal bovine serum (FBS, Hyclone), penicillin (100 U/mL, Sigma-Aldrich) and streptomycin (100 mg/mL, Sigma-Aldrich) in a humidified cell incubator providing 5% CO_2 and 95% fresh air at 37°C. Cells were exposed to baicalin for 48 hours at 10, 20, 30, and 40 mmol/L.

Cell viability assessments

The cell viability was assessed by 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenylterazolium bromide (MTT) assay in accordance with previous descriptions. Briefly, cells were seeded into a 96-well cell culture plate at density of 5×10^3/well. Cells were treated with baicalin as described. Cells in each well were incubated with MTT (5 mg/mL, Sigma-Aldrich) at 37°C for 4 hours. The resulted formazan crystals were dissolved by dimethyl sulfoxide (DMSO). The absorbance at 490 nm was determined by a plate reader. The cell viability was calculated by the formula: $(OD_{treatment}/OD_{control})\times100\%$.

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Cell apoptosis detection

Cell apoptosis was detected by terminal transferase UTP nick end labeling assay (TUNEL) assay. Cultured cells were fixed with neutral buffered formaldehyde. A TUNEL kit was used to detect the apoptotic cells in according to the protocol provided by the manufacturer. An inverted fluorescent microscope was used to observe the cells and to capture the fluorescent images.

Cervical cancer cell migration evaluation

In this study, wound healing assay was used to evaluate the migration ability of cervical cancer cells. Briefly, cells were seeded and further cultured in 60 mm-culturing dishes and received above described treatment of baicalin accordingly. The wound was formed by using a 2-mm-wide razor and the edges were marked. After treatment, the cells were fixed by neutral buffered formaldehyde which was subjected to 4',6-diamidino-2-phenylindole, dihydrochloride (DAPI) fluorescent staining. An inverted fluorescent microscope was used to observe the cells and to capture the fluorescent images. Wound closure was measured by analyzing the captured images.

Cervical cancer cell invasion assessment

The cell invasion capacity of cervical cancer cells was assessed by Transwell assay with Matrigel-coated Transwells (BD). This assay was carried out according to the manufacturer's instructions. Briefly, the upper surfaces of these Transwells were coated with Matrigel. Cells were seeded to the wells at density of 3.5×10^4/well with serum-free medium. Cells were then received treatment of baicalin as described. The lower well was filled with medium supplemented with 10% FBS. After 20-hour incubation, the cells remaining on the upper wells were removed and the cell number invaded through the wells was counted.

Western blotting

Cells were homogenized and lysed with RIPA lysis buffer system (Santa Cruz) supplemented with phenylmethanesulfonylfluoride or phenylmethylsulfonyl fluorid (PMSF, Santa Cruz). A cytoplasm protein extraction kit (Santa Cruz) and a nuclear protein extraction kit (Beyotime) were used to extract the cytoplasmic and nuclear protein respectively from cancer cells according to the manufacturer's instructions. The concentrations of the protein samples were determined by using a BCA protein assay kit (Invitrogen). Proteins were separated after subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and transferred electronically to the polyvinylidene fluoride (PVDF) membranes. Primary antibodies against PKCζ, STAT3, (p-STAT3), survivin, MMP2, MMP9, Histone H3 and GAPDH were used to incubate the membranes at 4°C for 10 hours. After washing with Tris-buffered saline supplemented with 0.1% Tween 20 (TBST), the membranes were further incubated with HRP-conjugated secondary antibodies (Abcam). Then the membranes were developed by Luminal/Enhancer reagent (Millipore) and visualized on x-ray films. Images were captured by a scanner and analyzed by ImageJ software.

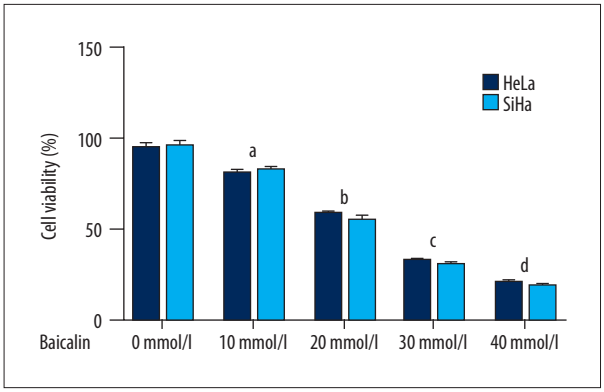

Figure 1. Columns indicated the cell viabilities of cultured HeLa cells (dark blue) and SiHa cells (light blue) treated with baicalin at concentrations of 0, 10, 20, 30, and 40 mmol/L respectively. [a] Differences were significant when compared with 0 mmol/L ($P<0.05$); [b] differences were significant when compared with 10 mmol/L ($P<0.05$); [c] differences were significant when compared with 20 mmol/L ($P<0.05$); [d] differences were significant when compared with 30 mmol/L ($P<0.05$).

Statistics

In this study, the data was presented in a (mean ± standard deviation) manner and input into Excel (Microsoft). The data was analyzed by software SPSS (SPSS). The differences between groups were analyzed by Student's *t*-tests and one-way ANOVA. The post-hoc test was carried out by LSD tests. The differences were considered statistically significant when *P* value <0.05.

Results

Baicalin treatment reduced cervical cancer cell viability in a concentration- dependent manner. The results are demonstrated in Figure 1. After incubated with baicalin for 48 hours, the viability of cervical cancer HeLa and SiHa cells decreased significantly in a baicalin concentration- dependent manner.

Baicalin treatment induced cervical cancer cell apoptosis in a concentration-dependent manner. The results are demonstrated in Figure 2. TUNEL assay was employed to detect the apoptotic cells in this study. It turned out that 48-hour incubation with baicalin significantly induced the apoptosis of cervical cancer cells in a concentration-dependent manner.

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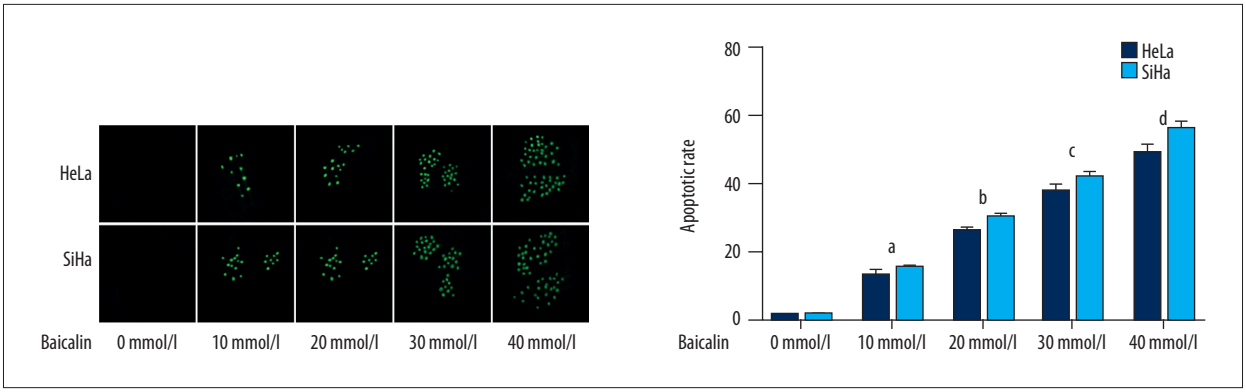

Figure 2. The upper panel demonstrated the captured images of TUNEL assay in HeLa cells and SiHa cells respectively. Apoptotic cells were tagged with green fluorescence. Columns on the lower panel indicated the apoptotic percentage of HeLa cells (dark blue) and SiHa cells (light blue) treated with baicalin at concentrations of 0, 10, 20, 30, and 40 mmol/L respectively. [a] Differences were significant when compared with 0 mmol/L (P<0.05); [b] differences were significant when compared with 10 mmol/L (P<0.05); [c] differences were significant when compared with 20 mmol/L (P<0.05); [d] differences were significant when compared with 30 mmol/L (P<0.05).

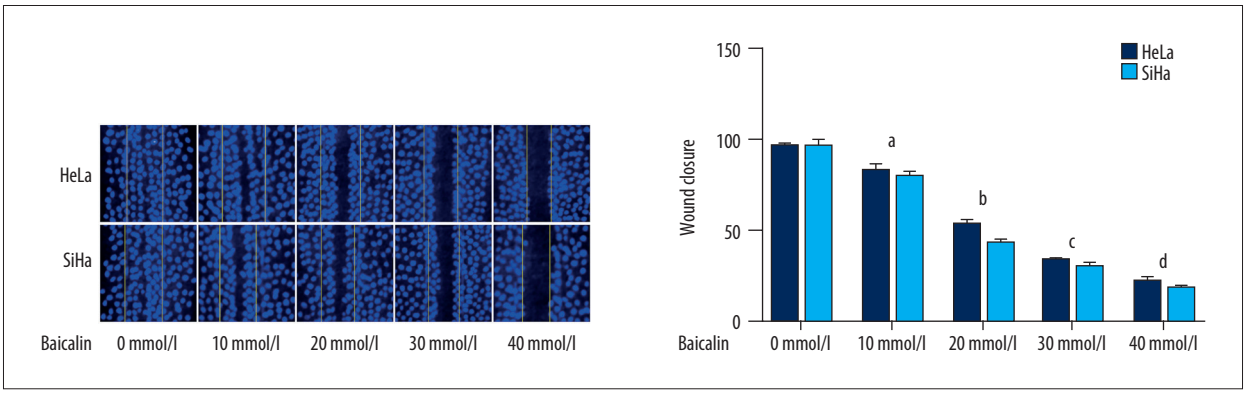

Figure 3. The upper panel indicated the captured images of wound healing assay. The nuclei of cells were tagged with DAPI staining. Columns on the lower panel indicated the wound closure of HeLa cells (dark blue) and SiHa cells (light blue) treated with baicalin at concentrations of 0, 10, 20, 30, and 40 mmol/L respectively. [a] Differences were significant when compared with 0 mmol/L (P<0.05); [b] differences were significant when compared with 10 mmol/L (P<0.05); [c] differences were significant when compared with 20 mmol/L (P<0.05); [d] differences were significant when compared with 30 mmol/L (P<0.05).

Baicalin treatment inhibited migration of cervical cancer cells in a concentration-dependent manner. Figure 3 demonstrates the results of the wound healing assay which was used to evaluate the migration of cervical cancer cells. The baicalin treatment significantly decreased the wound closure percentage of both HeLa and SiHa cervical cancer cells. The inhibition effect was in a baicalin concentration-dependent manner.

Baicalin treatment suppressed the invasion capacity of cervical cancer cells in a concentration-dependent manner. The results of Transwell assay are demonstrated in Figure 4. The treatment of baicalin decreased the cervical cancer cell number invaded through the Matrigel. The inhibitory effect of baicalin on the invasion ability of cervical cancer was in a concentration-dependent manner.

Baicalin administration suppressed the PKCζ/STAT3 signaling in cervical cancer cells. As shown in Figure 5, the expression levels of proteins of PKCζ/STAT3 signaling were demonstrated. The baicalin administration inhibited expression level of PKCζ, nuclear translocation and the phosphorylation level of STAT3 in cervical cancer cells in a concentration-dependent manner. As a result, the protein expression levels of PKCζ/STAT3 signaling targeted genes, including Survivin, MMP2, and MMP9 were also downregulated by baicalin administration in a concentration-dependent manner.

Discussion

Like other human cancers, the malignancy of cervical cancer is characterized by cancer cells' potent capacities of proliferation,

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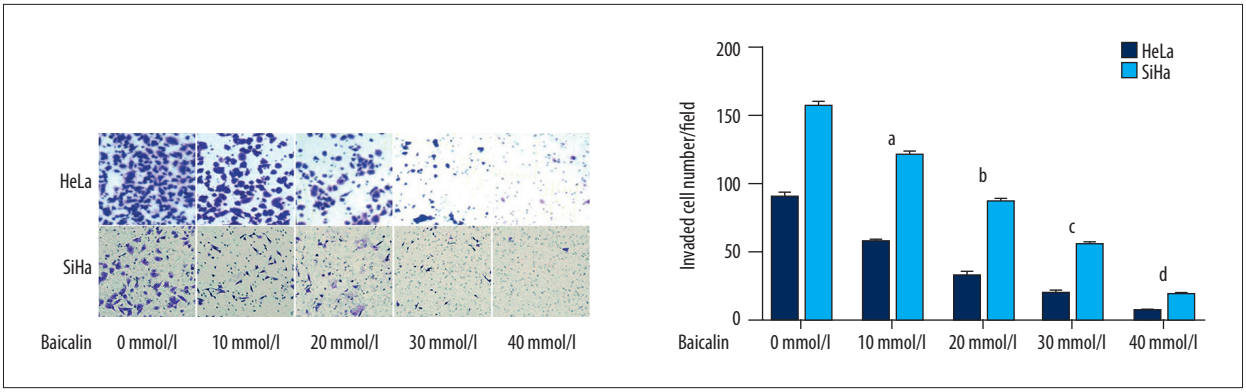

Figure 4. The upper panel indicated the captured images of Transwell assay. The cells invaded through the Matrigel were positively stained. Columns on the lower panel indicated the cell number invaded through the Matrigel per field (5 fields were observed) of HeLa cells (dark blue) and SiHa cells (light blue) treated with baicalin at concentrations of 0, 10, 20, 30, and 40 mmol/L respectively. [a] Differences were significant when compared with 0 mmol/L (P<0.05); [b] differences were significant when compared with 10 mmol/L (P<0.05); [c] differences were significant when compared with 20 mmol/L (P<0.05); [d] differences were significant when compared with 30 mmol/L (P<0.05).

invasion, and metastasis. Thus, an ideal anti-cancer agent could be able to inhibit proliferation, invasion, and metastasis simultaneously by targeting certain intracellular signaling pathways. In this study, we proved that baicalin dramatically reduced the cell viability, migration and invasion in 2 human cervical cancer HeLa and SiHa cell lines. Our results indicated that baicalin exerted its anti-cancer activity by impairing the activation of PKCζ/STAT3 signaling pathway.

The PKC family consists of multiple serine/threonine kinases which are evolutionarily conserved and distributed in many human organs and tissues. By regulating targeted signaling pathways, PKCs are critical for maintaining the cellular biological processes such as cell proliferation, migration, differentiation, apoptosis and autophagy [4,16,17]. Expression alteration and dysregulation of PKCs are often associated with many human diseases including diabetes, autoimmune diseases, neurodegenerative diseases, and cardiovascular diseases [18]. Altered PCK expression levels have also been indicated to be associated with a range of human malignant cancers [19]. A number of different PKC isoforms were identified to participate in malignant cancers by contributing to cell transformation, tumor invasion, metastasis, and angiogenesis. Previous studies suggested a member of aPKC, the PKCζ, played a critical role in multiple human cancers [8]. For instance, depletion of PKCζ suppressed proliferation of human colon cancer cells [20]. Moreover, elevated PKCζ expression was found to be associated with the invasive phenotype of several human cancers such as breast cancer, prostate cancer, and glioblastoma [7,21,22]. Several previous studies pointed out that baicalin exerted the capability of regulating PKC activity and related pathways [23]. Though there were very few related studies, a previous investigation pointed out that baicalin reduced phosphorylation levels of PKC in human hepatoma cells [24].

In the current study, we investigated the anti-cancer effects of baicalin as a PKCζ inhibitor on human cervical cancer cells. Baicalin effectively suppressed activation of PKCζ by reducing its autophosphorylation. The results turned out that the administration of baicalin dramatically reduced cell viability, migration and invasion of HeLa cells and SiHa cells in a concentration- dependent manner.

STAT3 was one of the downstream effecter of PKCζ whose activation depends on phosphorylation [25]. STAT3 is recognized as a transcription factor conducting the cancer- promoting signals and its activation is a hallmark of several human cancers [26]. Our results showed that the phosphorylation as well as nuclear translocation of STAT3 was significantly reduced by the administration of baicalin in human cervical cancer cells. After activated by phosphorylation at Tyr705, STAT3 would translocate to the nucleus and act as a sensitive molecular on/off switch for the transcription initiation of its targeted genes such as Survivin and MMPs [27,28]. Survivin is an anti-apoptotic protein which prevents the cleavage activation of caspase cascade to halt apoptosis [29]. In this study, we found that baicalin treatment decreased the expression level of survivin in cervical cancer cells. As a result, the apoptotic rate increased in cervical cancer cells treated with baicalin. By degradation of the extracellular matrix and alteration the interaction between cancer cells and extracellular matrix, MMP2 and MMP9 play a critical role in the process of invasion and migration [30]. It has been established that the transcriptions of MMP2 and MMP9 are promoted by STAT3 activation [28]. In this study, we found that the baicalin treatment dramatically downregulated the expression levels of MMP2 and MMP9 in cervical cancer cells. Thus, as evidenced by wound healing assay and Transwell assay, migration and invasion were inhibited by baicalin.

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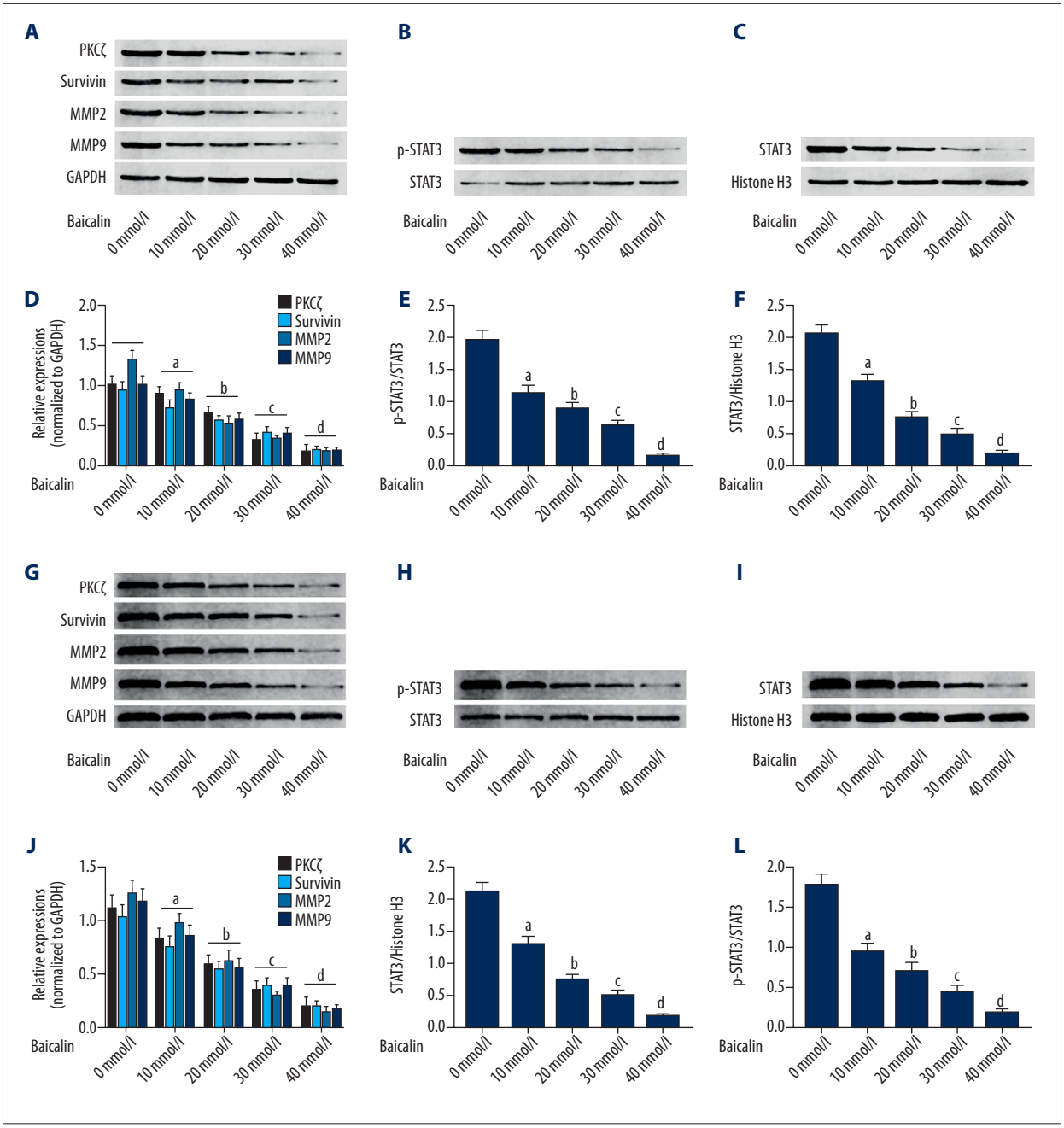

Figure 5. (**A**) The immunoblots of PKCζ, Survivin, MMP2, MMP9, and GAPDH in HeLa cells. (**B**) The immunoblots of p-STAT3 and STAT3 in HeLa cells. (**C**) The immunoblots of STAT3 and Histone H3 in nuclei of HeLa cells. (**D**) Columns indicated the relative expression levels of PKCζ, Survivin, MMP2, MMP9, and GAPDH in HeLa cells. (**E**) Columns indicated the phosphorylation level of STAT3 in HeLa cells. (**F**) Columns indicated the relative expression level of STAT3 in nuclei of HeLa cells. (**G**) The immunoblots of PKCζ, Survivin, MMP2, MMP9, and GAPDH in SiHa cells. (**H**) The immunoblots of p-STAT3 and STAT3 in SiHa cells. (**I**) The immunoblots of STAT3 and Histone H3 in nuclei of SiHa cells. (**J**) Columns indicated the relative expression levels of PKCζ, Survivin, MMP2, MMP9, and GAPDH in SiHa cells. (**K**) Columns indicated the phosphorylation level of STAT3 in SiHa cells. (**L**) Columns indicated the relative expression level of STAT3 in nuclei of SiHa cells.

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Conclusions

Taken together, data collected in the present study revealed the potent suppressive effects of baicalin on proliferation, invasion, and metastasis of human cervical cancer cells. These results indicated baicalin could be possibly employed as an anti-cancer agent in cervical cancer patients. Moreover, inhibition of the PKCζ/STAT3 signaling activation was supposed as the underlying mechanism of the anti-cancer activity of baicalin. However, our results were *in vitro*, thus they were very limited and preliminary. More sophisticated *in vivo* investigation and clinical trials in the future are needed to collect more solid evidence.

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