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Antimetastatic effect of fucoidan against non-small cell lung cancer by suppressing non-receptor tyrosine kinase and extracellular signal-related kinase pathway

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Conflict of Interest
The authors declare no potential conflicts of interests.

ABSTRACT

BACKGROUND/OBJECTIVES: Fucoidan, a polysaccharide content in brown algae, has been reported to inhibit the growth of cancer cells. The present study aimed to investigate the suppression effects of fucoidan on A549 non-small cell lung cancer cells migration.
MATERIALS/METHODS: The anti-migratory activity of fucoidan in A549 cells was examined by wound healing assay and phalloidin-rhodamine staining in response to fucoidan (0–100 µg/mL) treatment for 48 h. Western blot analysis was performed to clarify the protein expressions relevant to migratory activity.
RESULTS: Fucoidan (25–100 µg/mL) significantly suppressed A549 cells migration together with reduced the intensity of phalloidin-rhodamine which detect filopodia and lamellipodia protrusions at 48 h of treatment. The protein expression indicated that fucoidan significantly suppressed the phosphorylation of focal adhesion kinase (FAK), Src, and extracellular signal-related kinase (ERK). In addition, the phosphorylation of p38 in A549 cells was found to be increased.
CONCLUSIONS: Our data conclude that fucoidan exhibits anti-migratory activities against lung cancer A549 cells mediated by inhibiting ERK1/2 and FAK-Src pathway.

Keywords: Fucoidan; non-small cell lung cancer; filopodia; metastasis

INTRODUCTION

Lung cancer has been presented as the most common concern of cancer-associated deaths for several yrs. Smoking history is one of the important risk factors and other complements such as lifestyle, environmental exposures, and genetic predisposition are also becoming the major risk factor in developing countries [1]. Non-small cell lung cancer (NSCLC) subtype is found approximately 85% of lung cancer cases [2]. Cell migration is involved in the metastasis and progression of tumor growth. Moreover, the cell migration process is driven by actin polymerization, generally, G-actin monomer, which is reversibly added at barbed ends of actin filaments to generate lamellipodia and filopodia (linear F-actin) extension [3,4].

Several proteins signaling is involved in the cancer development and progression. The non-receptor tyrosine kinases including focal adhesion kinase (FAK) and non-receptor tyrosine kinase (Src) have been activated in NSCLC [5-7]. Phosphorylation of FAK/Src complex can activate mitogen-activated protein kinases (MAPKs) and downstream proteins such as the Rho family of small guanosine triphosphatases (GTPases) which involve with Ras-related C3 botulinum toxin substrate 1 (Rac1), Ras homolog gene family member A (RhoA), and cell division control protein 42 (Cdc42), thereby trigger cell communication to contribute cell motility and cell survival [7,8].

Fucoidan is a natural polysaccharide molecule which is found in *Fucus vesiculosus*, Mozuku seaweed, *Cladosiphon okamuranus*, and many brown algae [9]. Several studies have reported that fucoidan exhibits various biological activities, including antioxidant, antibacterial, antiviral, anti-obesity, immune-modulating properties, and neuroprotection [10,11]. In addition, fucoidan demonstrated anti-cancer potential through different mechanisms. Fucoidan extracted from *Sargassum cinereum* has a potent anti-cancer effect on colon cancer adenocarcinoma [12]. Likewise, fucoidan from *F. vesiculosus* also intervenes cell cycle and induces cancer cell death through the apoptosis pathway [12,13]. Nevertheless, the underlying mechanism of fucoidan on NSCLC migration is still rarely understood. Thus, this study was to investigate the effects of fucoidan against A549 human lung cancer cell migration and also clarify its molecular mechanism.

MATERIALS AND METHODS

Reagents and cell culture
Fucoidan from *F. vesiculosus* was purchased from Sigma-Aldrich (St. Louis, MO, USA). 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was obtained from Thermo Fisher Scientific (Waltham, MA, USA). HaCaT human keratinocyte cell line (Cell Line Service, Heidelberg, Germany) and A549 human NSCLC cell line (American Type Culture Collection, Manassas, VA, USA) were maintained in Dulbecco's modified Eagle's medium containing 10% fetal bovine albumin (Gibco, Billings, MT, USA) and 1% antibiotics (Gibco) with 5% CO_2 and 37°C condition.

Cytotoxicity
The cytotoxicity effects of fucoidan against HaCaT and A549 cell lines were performed using MTT colorimetric assay. Briefly, 1×10^4 cells/well in a 96-well plate were incubated with fucoidan (0–500 μg/mL) for 24, 48, and 72 h. Formazan product was dissolved by dimethyl sulfoxide and then determined the absorbance at 570 nm by microplate spectrophotometer (BMG Labtech, Cary, NC, USA).

Wound healing assays
The wound healing assay was used to demonstrate the cell migration activity. A549 cells at 3×10^5 cells/well were seeded into a 6-well plate until 90–100% confluent cell monolayer. A straight scratch wound was made by sterilized tip (200 μL). Then, A549 cells were treated with fucoidan (10–100 μg/mL) for 0, 24, and 48 h. Then, the wound spaces were captured at 0, 24, and 48 h by phase contrast microscope (4× magnification, Olympus IX70 with DP50; Olympus, Tokyo, Japan) and evaluated the area using ImageJ software. The data was shown as a percentage of wound closure area compared with the control group (0 h exposure).

Phalloidin-rhodamine staining

The phalloidin-rhodamine fluorescent staining was conducted as previously described by Woonnoi *et al.* [14]. The cells were fixed and permeabilized with 4% paraformaldehyde and triton-X100 for 15 min after 48 h of fucoidan (25–100 μg/mL) treatment. Then, the fixed cells were blocked with 1% bovine serum albumin (BSA) for 1 h and stained with 5 μg/mL of phalloidin-rhodamine and Hoechst 33342 (10 μg/mL) for 40 min. The filopodia and lamellipodia formation was visualized by the fluorescence microscope (20× magnification, Olympus IX70 with DP50; Olympus).

Western blot analysis

After 48 h of fucoidan (25–100 μg/mL) treatment, A549 cells were lysed with lysis buffer containing protease inhibitor for cellular proteins extraction on ice for 30 min. The 75 μg of protein samples were separated on sodium dodecyl-sulfate polyacrylamide gel electrophoresis, subsequently transferred onto a polyvinylidene difluoride membrane. BSA (3% w/v) was used to block the non-specific protein of each membrane for 2 h. Then, specific primary antibodies against proteins: Akt (SC-81434, 1:1,000), pAkt (SC-514032, 1:1,000), extracellular signal-related kinase 1 and 2 (ERK1/2, ab36991, 1:1,000), pERK1/2 (ab50011, 1:1,000), p38 (ab31828, 1:1,000), p-p38 (ab4822, 1:1,000), FAK (SC-271126, 1:1,000), pFAK (SC-81493, 1:1,000), Src (ab109381, 1:1,000), pSrc (SC-81521, 1:1,000), Rac1 (ab155938, 1:1000), RhoA (ab54835, 1:1,000), Cdc42 (ab187643, 1:1,000), and actin (1:1,000; Invitrogen Life Technologies, Carlsbad, CA, USA) were incubated for overnight at 4 ºC. Subsequently, horseradish peroxidase secondary antibody (1:7,500; Invitrogen Life Technologies) was incubated for 2 h at room temperature. All protein bands were normalized with beta-actin and calculated by ImageJ software (National Institutes of Health, Bethesda, MD, USA).

Statistical analysis

All measurement data were presented as mean ± standard error of the mean. $P < 0.05$ was considered to be statistical significance and all data were analyzed by using one-way analysis of variance, followed by least significant difference *post hoc* test.

RESULTS

Effects of fucoidan on the viability of HaCaT and A549 cells

To determine the cytotoxicity effect of fucoidan in non-cancer and cancer cells, HaCaT cells were used to represent normal cells and A549 cells were used for the cancerous cells. In normal HaCaT cells, fucoidan at all concentrations did not affect the viability of HaCaT cells when treated for 24 h. In contrast, fucoidan at the concentration of 10–500 μg/mL significantly decreased HaCaT cell viability when treated for 48 and 72 h. However, the viability of cells is still higher than 90% which is safe for the normal cells (**Fig. 1A**). In A549 cancer cells, the administration of fucoidan at concentrations ranging from 10 to 250 μg/mL for 48 h significantly suppressed cell viability to less than 90% compared to the control (**Fig. 1B**). However, all concentrations of fucoidan did not change the A549 cell viability after 24 and 72 h of treatment with values higher than 90% when compared to the untreated group.

Inhibitory effects of fucoidan on cell migration and cytoskeleton actin stress fiber

In the wound healing assay, fucoidan was found to inhibit the migration of A549 lung cancer cells (**Fig. 2A**). At 24 h of treatment, the area of wound gradually increased to 71.46, 69.84, 77.67, and 75.82% after treatment with fucoidan at 10, 25, 50, and 100 μg/mL, respectively
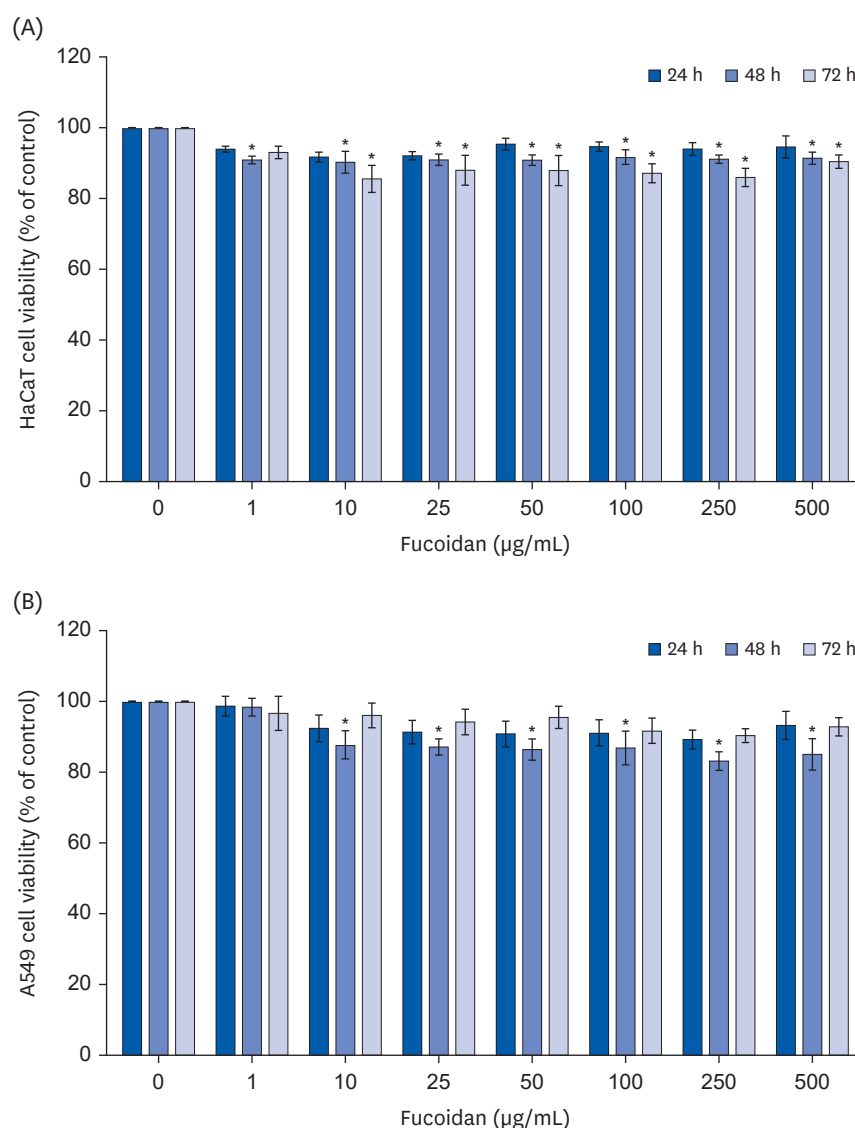
Fig. 1. Effects of fucoidan on the cytotoxicity in HaCaT (A) and A549 (B) cells. Both cells were incubated with fucoidan (0–500 μg/mL) for 24, 48, and 72 h. The cytotoxicity effect was determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay. The data were shown as mean ± standard error of the mean (n = 4).
[*]P < 0.05 was considered for statistical significance when compared with the untreated control.

compared with the control (69.43%). After 48 h of fucoidan treatment (10, 25, 50, and 100 μg/mL), the percent of wound area were significantly increased to 50.31, 56.97, 60.83, and 59.60, respectively when compared with control (40.80%) (**Fig. 2B**). Thus, fucoidan (10–100 μg/mL) significantly suppressed (P < 0.05) the A549 lung cancer cell migration which demonstrated by wound healing assay (**Fig. 2A and B**). According to the actin cytoskeleton, phalloidin-rhodamine staining was performed to evaluate cytoskeleton actin stress fiber including filopodia and lamellipodia. The present finding demonstrated that fucoidan at 25, 50, and 100 μg/mL decreased the fluorescence intensity which was related to suppressing the formation of filopodia and lamellipodia protrusions in the A549 lung cancer cells compared to the untreated group (**Fig. 2C**).
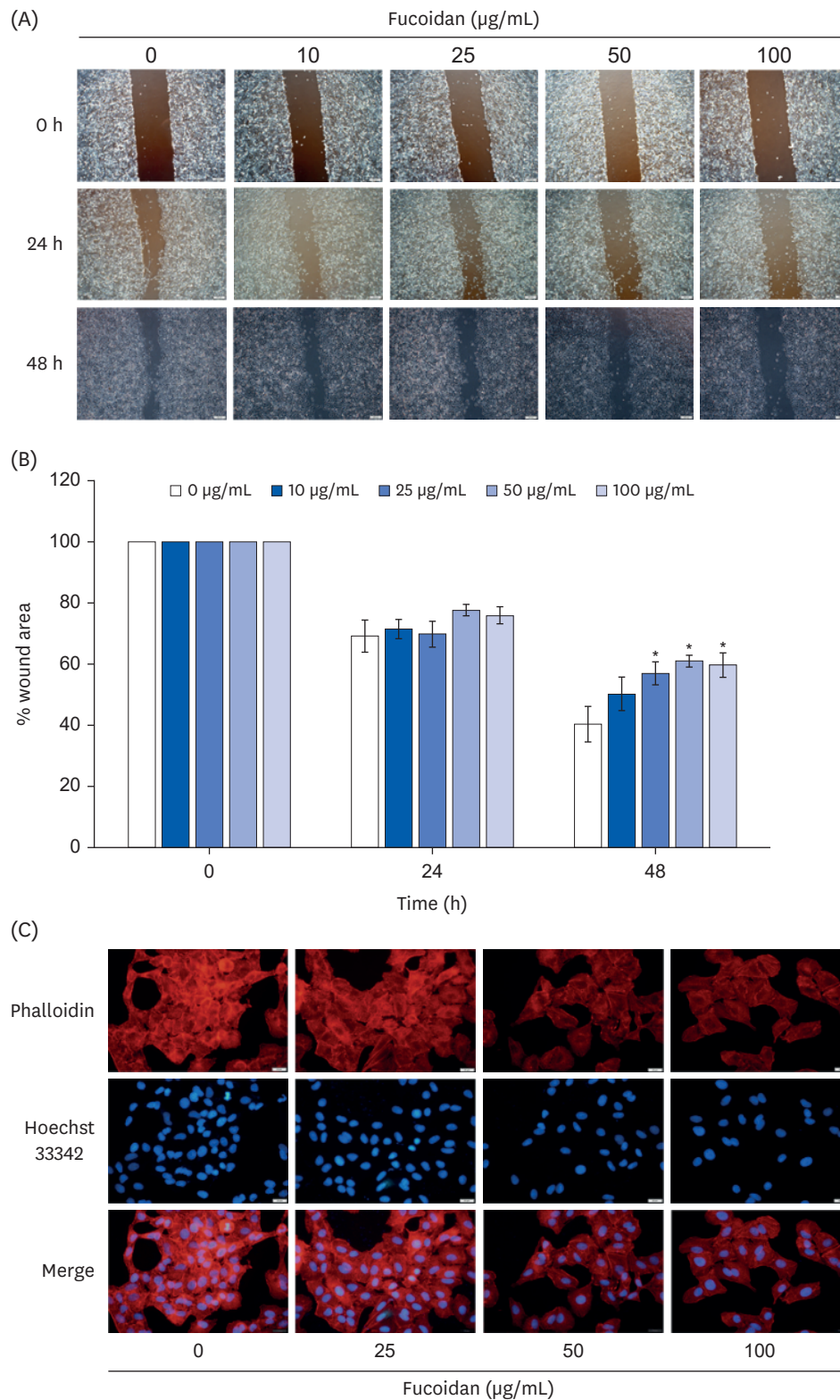
Fig. 2. Effects of fucoidan on the migration in A549 lung cancer cells. (A) The wound area was imaged by a phase contrast microscope (200 μm scale bar). (B) The percentage of wound area (compared with the control) was evaluated using ImageJ software. (C) Phalloidin-rhodamine staining for cytoskeleton protrusion was visualized by a fluorescence microscopy (20 μm scale bar). All data were expressed as mean ± standard error of the mean (n = 5).
*$P < 0.05$ was considered for statistical significance when compared with the untreated control.
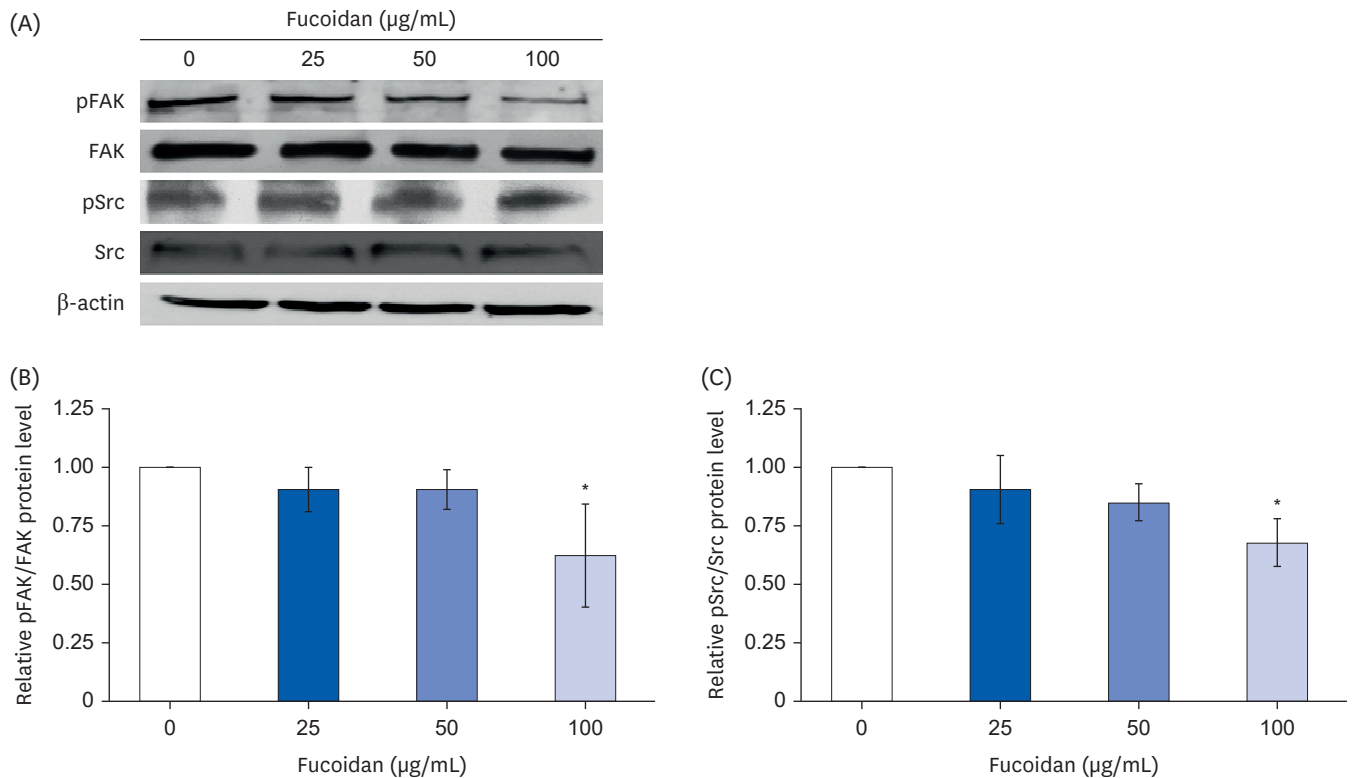
Fig. 3. Effects of fucoidan on the expression of FAK and Src signaling pathway. A549 cells were incubated with fucoidan (0–100 μg/mL) for 48 h. (A) Protein expression was evaluated by western blotting and normalized with β-actin. (B) Relative pFAK/FAK protein expression. (C) Relative pSrc/Src protein expression. All data were expressed as mean ± standard error of the mean (n = 4).
FAK, focal adhesion kinase.
$^*P < 0.05$ was considered for statistical significance when compared with the untreated control.

Inhibitory effects of fucoidan on A549 cells migration through FAK-Src signaling

The western blot analysis was performed to determine the effects of fucoidan on inhibiting proteins involving cell migration. As shown in **Fig. 3**, fucoidan at 100 μg/mL significantly downregulated the phosphorylation of FAK (**Fig. 3A and B**) and Src (**Fig. 3A and C**) when compared with the control. Taken together, our finding suggested that fucoidan inhibited lung cancer cell migration through the FAK-Src signaling.

Effects of fucoidan on ERK1/2, p38MAPK and Akt pathway

ERK1/2, p38MAPK, and Akt pathways were determined in response to fucoidan treatment in A549 lung cancer cells. Our results found that fucoidan at all concentrations did not interfere with the Akt signaling pathway (**Fig. 4A and B**). As presented in **Fig. 4A and C**, western blotting demonstrated that fucoidan at 50–100 μg/mL significantly upregulated p38 phosphorylation compared with the control group while did not change their total protein levels. Additionally, fucoidan at 100 μg/mL significantly reduced the phosphorylation of ERK1/2 compared with the control group (**Fig. 4A and D**).

Effects of fucoidan on Rho GTPases family

Cell migration and cytoskeleton protrusion were also regulated by downstream signaling in the Rho GTPases family. As presented in **Fig. 5A and B**, our results demonstrated that 100 μg/mL fucoidan significantly downregulated Rac1 (relative level was 0.62 folds compared to the untreated group). However, both Cdc42 (**Fig. 5A and C**) and RhoA (**Fig. 5A and D**) were not affected by fucoidan treatment.
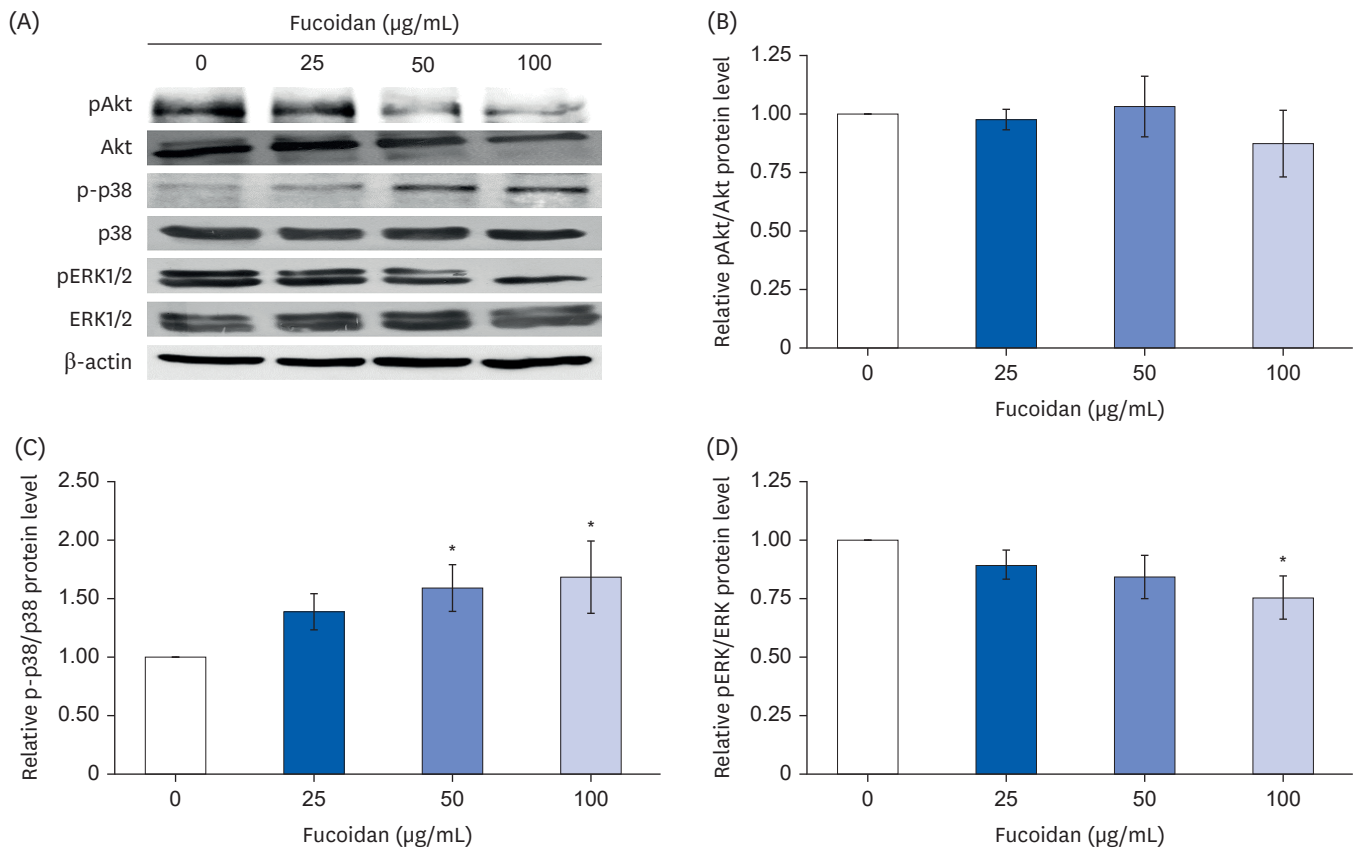
Fig. 4. Effects of fucoidan on the expression of Akt, ERK1/2, and p38MAPK pathway. A549 cells were incubated with fucoidan (0–100 μg/mL) for 48 h. (A) Protein expression was evaluated by western blotting and normalized with β-actin. (B) Relative pAkt/Akt protein expression. (C) Relative p-p38/p38 protein expression. (D) Relative pERK/ERK protein expression. All data were expressed as mean ± standard error of the mean (n = 4).
ERK1/2, extracellular signal-related kinase 1 and 2; MAPK, mitogen-activated protein kinase.
*$P < 0.05$ was considered for statistical significance when compared with the untreated control.

DISCUSSION

Since the incidence lung cancer remains the leading cause of death and chemotherapeutic agents cause patient's undesired effects, natural active products have been continually interested in pharmacological treatments [13]. Many natural polysaccharides from plant sources have been reported to possess anti-cancer properties, for example, *Ganoderma lucidum* (known as Lingzhi mushroom) inhibited the metastatic of human lung and breast carcinoma [15]. Seaweed polysaccharides from *Ulva prolifera* demonstrated an antioxidant property on lung cancer cells [16]. Fucoidan is the main polysaccharide component isolated from brown algae [9]. In this study, we determined the anti-migratory effects of fucoidan in A549 lung cancer cell lines. Previous studies reported the non-cytotoxicity effect of fucoidan on normal cells [17,18], which was similar to our current studies demonstrated by MTT colorimetric assay. In this study, we noted that fucoidan has a potent anti-cancer activity. This result is in agreement with previous studies, which reported that fucoidan exerts anticancer action in many cancer cell types [12,13]. Furthermore, our studies displayed that fucoidan could inhibit the migration and cytoskeleton protrusions (filopodia and lamellipodia) in NSCLC A549 cells. Sung *et al.* [19] reported that fucoidan treatment inhibited bladder cancer cell migration and suppressed stress fibers aggregation including filopodial protrusion in bladder cancer
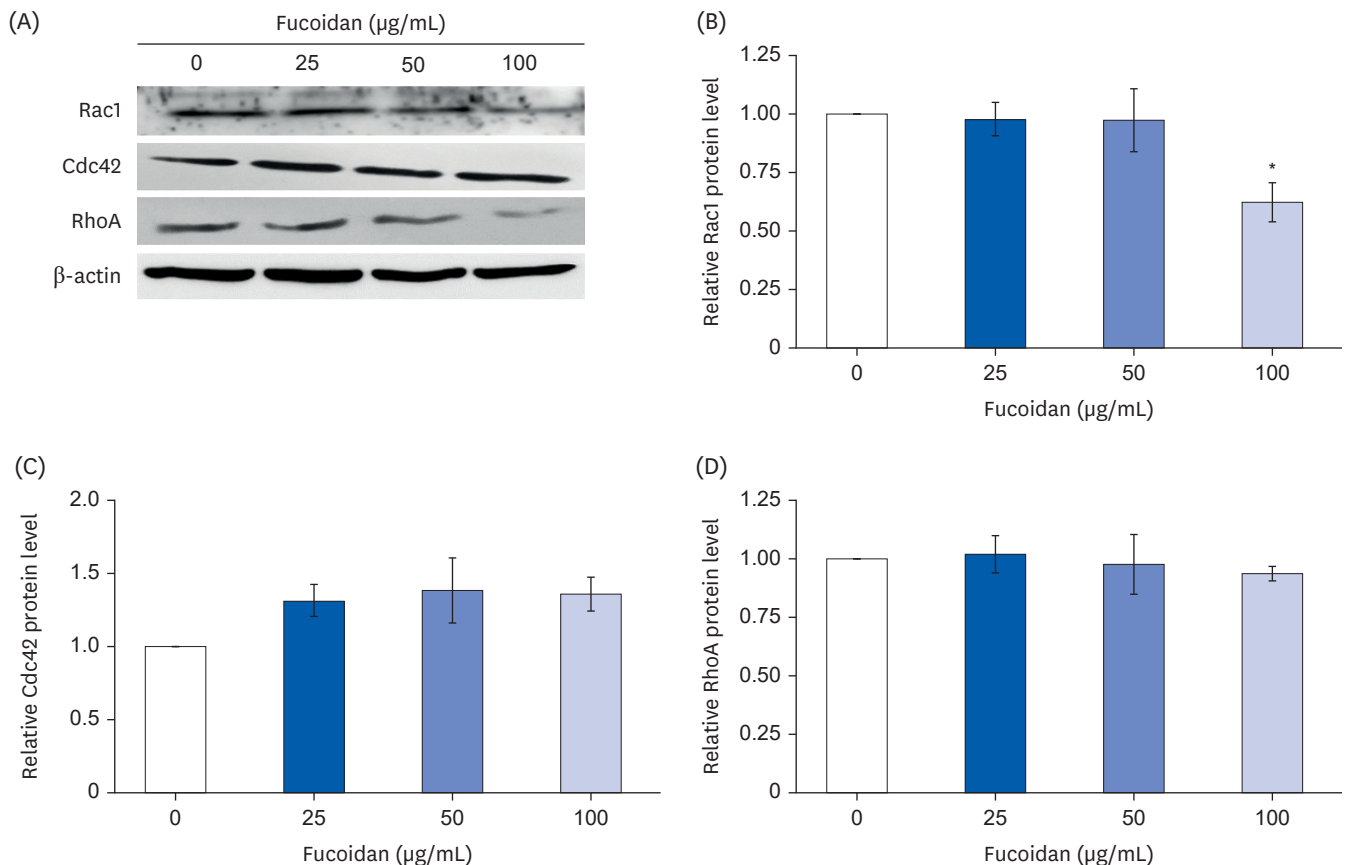
Fig. 5. Effects of fucoidan on the expression of Rac1, Cdc42, and RhoA signaling pathway. A549 cells were incubated with fucoidan (0–100 μg/mL) for 48 h. (A) Protein expression was evaluated by western blotting and normalized with β-actin. (B) Relative Rac1 protein expression. (C) Relative Cdc42 protein expression. (D) Relative RhoA protein expression. All data were expressed as mean ± standard error of the mean (n = 4).
Rac1, Ras-related C3 botulinum toxin substrate 1; Cdc42, cell division control protein 42; RhoA, Ras homolog gene family member A.
*$P < 0.05$ was considered for statistical significance when compared with the untreated control.

T24 and 5637 cells. In addition, fucoidan also inhibited cancer cell migration in many cancer cell types including HepG2-SR, CRPCa, and mCRPCa cells [20,21].

Several signaling molecules such as MAPKs, Akt, Src, and FAK have been reported to control cell migration in both normal and cancer cells [22,23]. Consequently, the inhibition of MAPKs, Akt, Src, and FAK signaling pathway involves in the treatment of lung cancer. The activation of FAK-Src signaling molecules is a major regulator to control the survival, proliferation, and migration signaling pathway that was reported to be increased and overactivated in various cancer cell types [8]. In this study, 100 μg/mL of fucoidan treatment to A549 cells for 48 h suppressed the phosphorylated FAK and phosphorylated Src. The inhibition of FAK-Src signaling was consistent with the inhibitory effects of fucoidan on lung cancer cell migration and cytoskeleton protrusion. Remarkably, fucoidan suppressed the pivotal upstream signaling of FAK and Src proteins. Additionally, the downregulation in the pFAK/FAK and pSrc/Src ratio implied that fucoidan might inactivate the FAK and Src protein. As FAK-Src is the main upstream regulator of cancer migration, FAK-Src suppression may inhibit A549 lung cancer metastasis. Several studies revealed that FAK-Src activation contributes to the stimulation of other signaling pathways such as MAPKs and Akt that control the survival, proliferation, and migration of cells [8]. The ERK1/2 and p38MAPK pathways are associated with the proliferation and migration of human cancers.

Hyperphosphorylation of ERK1/2 can induce cancer cell metastasis [13]. In addition, the p38 protein has been noted as a regulator of cell stress and cell death. The up-regulation of the p38 protein exhibited anti-cancer activity in lung cancer cells through the induction of cell apoptosis [24]. In response to fucoidan treatment, the expression of pERK/ERK was remarkably downregulated, whereas p-p38/p38 was significantly increased, which was correlated with the inhibition of migration and cytoskeleton protrusion in A549 cells. Our results indicate that fucoidan decreased the cellular pERK level and increased the induction of p-p38 caused by inhibiting FAK-Src signaling. Evidence from previous studies, fucoidan showed anti-metastatic potential via ERK1/2 and Akt downregulation [17]. However, we found that the highest concentration of fucoidan did not alter the phosphorylation of Akt levels, which is inconsistent with the previous report by Lee *et al.* [17]. According to this result, it might be from the difference in the concentration, time of incubation, and cancer cell types. The activation of upstream signaling molecules including FAK, Src, MAPKs, and Akt has been stated as the primary regulator in the migration and cytoskeleton protrusions of the cell by activating the downstream effectors, for example, Rac1, Cdc42, and RhoA [8]. Rho GTPases family including Rac1, RhoA, and Cdc42 plays an important role in the regulation of cell motility by increasing the filopodia and lamellipodium formation [25]. Moreover, an increase of cytoskeleton protrusions including stress fiber, lamellipodia, and filopodia have been recognized in cancer cells metastasis [26]. In the present study, fucoidan at 100 μg/mL could suppress the expression of Rac1 protein in A549 cells. However, the fucoidan did not have any effects on RhoA and Cdc42 levels in A549 cells. Remarkably, fucoidan exhibited a strong inhibitory effect on cancer cell migration that correlated with the changes in migratory-related protein expression in NSCLC cells.

This study suggests that fucoidan exhibits anti-cancer properties targeting the inhibition of tumor cell motility. Furthermore, fucoidan inhibits lung cancer cell migration by suppressing FAK, Src, and ERK1/2 pathways. In addition, Rac1 was inhibited in response to fucoidan treatment which is associated with suppressing cytoskeleton protrusion (**Fig. 6**). Therefore, these findings may offer fucoidan as a promising compound for anti-metastatic cancer drug development.
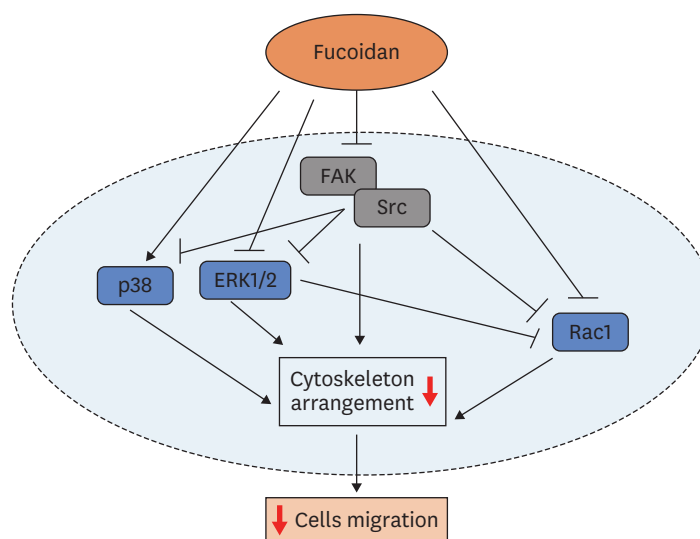

Fig. 6. The mechanism of fucoidan against lung cancer migration.
FAK, focal adhesion kinase; ERK1/2, extracellular signal-related kinase 1 and 2.

ACKNOWLEDGMENTS

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