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MDCK 세포에서 인플루엔자 A 바이러스에 대한 현삼속 식물 3종 (현삼, 섬현삼, 토현삼)의 항바이러스 활성 비교

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Comparative Antiviral Activity of Three *Scrophularia* Species (*S. buergeriana*, *S. takesimensis*, and *S. koraiensis*) Against Influenza A Virus in MDCK Cells

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ABSTRACT

Background: Species of the genus *Scrophularia* have been traditionally used in East Asian medicine for anti-inflammatory and detoxifying purposes. However, comparative antiviral activity among different *Scrophularia* species remains insufficiently characterized.
Methods and Results: Extracts of *S. buergeriana*, *S. takesimensis*, and *S. koraiensis* were evaluated for cytotoxicity, antiviral activity against influenza A virus (A/PR/8/34, H1N1), and neuraminidase (NA) inhibitory effects. MDCK cells were used for cytotoxicity and cytopathic effect (CPE) reduction assays. Zanamivir was used as a positive control. All three extracts showed minimal cytotoxicity (> 93.40% cell viability) across concentrations of 3.13–300.00 ㎍/mL. In antiviral assays, all extracts inhibited viral replication in a dose-dependent manner. Among them, *S. buergeriana* showed the highest activity, reducing CPE by 22.36% at 200 ㎍/mL. In contrast, NA inhibition was generally weak; *S. takesimensis* showed the highest inhibition (16.38% at 300 ㎍/mL), whereas *S. buergeriana* showed no significant activity.
Conclusions: These results suggest that *Scrophularia* extracts exert antiviral effects through mechanisms other than NA inhibition, potentially involving intracellular viral replication pathways.

Key Words: *Scrophularia buergeriana*, *Scrophularia koraiensis*, *Scrophularia takesimensis*, Antiviral Activity, Influenza A Virus, MDCK Cells, Neuraminidase

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INTRODUCTION

Viral infections, particularly those caused by influenza A virus (IAV), remain a major global health burden due to their high transmissibility, rapid antigenic variation, and pandemic potential (Taubenberger and Morens, 2008; Iuliano *et al*., 2018). Influenza viruses are responsible for significant morbidity and mortality worldwide each year, especially in vulnerable populations such as the elderly and immunocompromised individuals (Iuliano *et al*., 2018). Although antiviral drugs, including neuraminidase (NA) inhibitors such as oseltamivir and zanamivir, are widely used, the emergence of drug-resistant viral strains has limited their long-term clinical efficacy (O'Hanlon and Shaw, 2019). Therefore, the development of alternative antiviral agents with novel mechanisms of action is urgently required.

Natural products derived from medicinal plants have attracted considerable attention as potential antiviral agents due to their chemical diversity, multi-target properties, and relatively low toxicity profiles (Lin *et al*., 2014; Newman and Cragg, 2020). Among these, Scrophulariae Radix, derived from the dried roots of *Scrophularia ningpoensis* or *Scrophularia buergeriana*, has been widely used in traditional East Asian medicine for the treatment of fever, inflammation, and toxin-related disorders (Jung *et al*., 2020; Seo *et al*., 2024).

Previous studies have demonstrated that *Scrophularia* species possess a wide range of pharmacological activities, including anti-inflammatory, antioxidant, neuroprotective, and immunomodulatory effects (Jeong *et al*., 2009; Lee *et al*., 2019; Shin *et al*., 2020). These biological activities are largely attributed to secondary metabolites such as iridoid glycosides and phenylpropanoids, which are known to regulate inflammatory signaling pathways and host immune responses (Pasdaran and Hamedi, 2017). In particular, harpagoside, a representative iridoid glycoside found in *Scrophularia* species, has been reported to exhibit anti-inflammatory and immunoregulatory activities that may contribute to antiviral defense mechanisms (Bermejo *et al*., 2002; Kaur *et al*., 2026).

In Korea, *Scrophularia koraiensis* (To-Hyun-Sam) has traditionally been used as an antipyretic and anti-inflammatory agent, whereas *Scrophularia takesimensis* (Seom-Hyun-Sam), an endemic species restricted to Ulleung-do Island, remains insufficiently studied with respect to its biological activity (Nam *et al*., 2020). Although *S. buergeriana* has been relatively well characterized, comparative studies evaluating antiviral activities among different *Scrophularia* species are still limited.

Given the reported pharmacological properties of *Scrophularia* species and their potential immunomodulatory effects, it is hypothesized that these plants may exert antiviral activity against influenza virus infection. However, the antiviral efficacy and underlying mechanisms of *S. buergeriana*, *S. takesimensis*, and *S. koraiensis* have not yet been systematically investigated.

Therefore, in the present study, we compared the cytotoxicity, antiviral activity against IAV (H1N1), and NA inhibitory effects of extracts from three *Scrophularia* species. This study aimed to identify species-specific differences in antiviral efficacy and to provide a scientific basis for their potential use as natural antiviral agents.

MATERIALS AND METHODS

1. Plant materials and extraction

Three *Scrophularia* species—*S. buergeriana*, *S. takesimensis*, and *S. koraiensis*—were used in this study. Fresh plant materials were collected from cultivated plants in the experimental field of the National Institute of Horticultural and Herbal Science (Eumseong-gun, Chungcheongbuk-do, Korea) on March 21, 2017. Species identification was performed based on morphological characteristics, including leaf and stem features (Fig. 1), in accordance with the taxonomic keys described in the Flora of Korea (Choi *et al*., 2018) and previous taxonomic studies of the genus *Scrophularia* (Han *et al*., 2009; Jang and Oh, 2013). Voucher specimens were deposited at the Korean Herbarium of Standard Herbal Resources (Index Herbariorum code: KIOM), Korea Institute of Oriental Medicine, under accession numbers 2-18-0144 (*S. buergeriana*), 2-18-0145 (*S. koraiensis*), and 2-18-0146 (*S. takesimensis*). After taxonomic identification, the roots of the identified plants were dried and used as experimental materials. *S. buergeriana* (778.14 g), *S. koraiensis* (69.15 g), and *S. takesimensis* (92.50 g) were extracted with 70% ethanol (v/v) at a solvent-to-sample ratio of 10:1 (v/w). Each sample was refluxed for 2 h and this extraction procedure was repeated twice times to ensure complete extraction. The combined extracts were filtered through filter paper and evaporated in vacuo. The powders of the 70% ethanol extract for *S. buergeriana*, *S. koraiensis*, and *S. takesimensis* were 363.83 g (46.76% of yield, w/w), 30.40 g (43.96% of yield, w/w), and 53.91 g (58.28% of yield, w/w), respectively. The dried extracts were dissolved in dimethyl sulfoxide (DMSO) and diluted to the

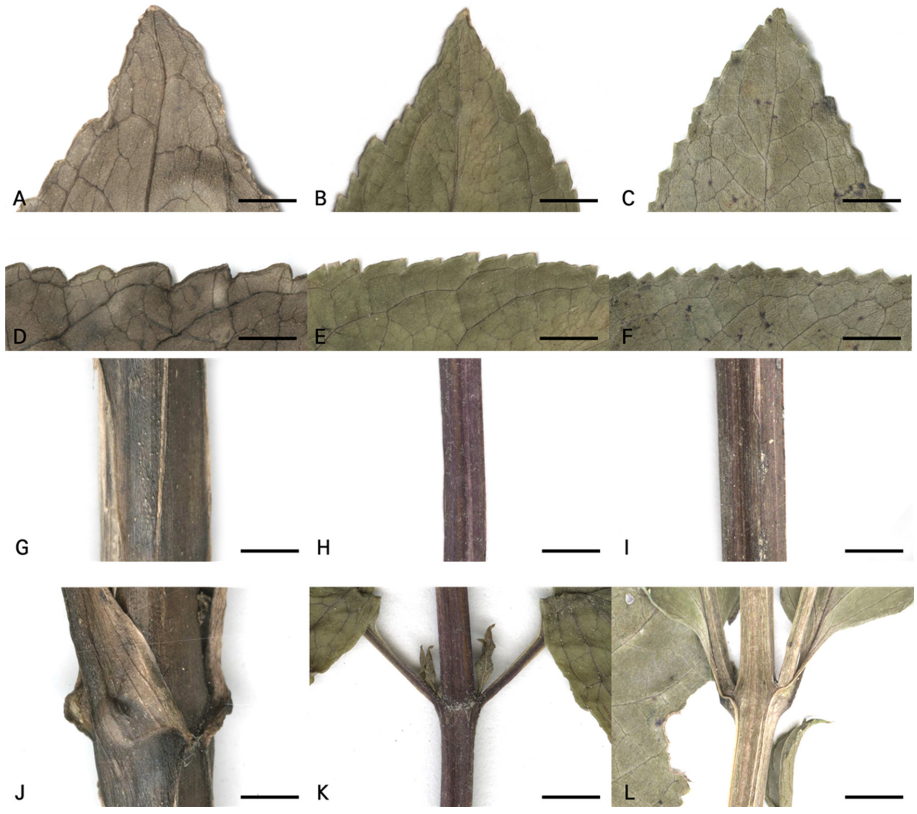

Fig. 1. Comparative leaf and stem morphology of three *Scrophularia* species. A–C, leaf apex; D–F, leaf margin; G–I, stem internode; J–L, stem node. A, D, G, J, *S. takesimensis*; B, E, H, K, *S. koraiensis*; C, F, I, L, *S. buergeriana*; A representative individual (n = 1) is shown for each species, and all images are at the same magnification. Scale bar = 0.5 cm.

desired concentrations prior to use.

2. Cell culture and virus

Madin–Darby canine kidney (MDCK) cells (ATCC CCL-34, Manassas, VA, USA) were maintained in EMEM supplemented with 10% FBS, 100 U/mL penicillin, and 100 μg/mL streptomycin at 37°C in 5% CO_2. Influenza A/PR/8/34 (H1N1) virus (ATCC VR-1469) used for antiviral assays. The virus was propagated in MDCK cells in the presence of 2 μg/mL TPCK-treated trypsin and stored at −80°C until use.

3. Cytotoxicity assay

The cytotoxic effects of extracts from three *Scrophularia* species were evaluated in MDCK cells. Cells were seeded in 96-well plates and cultured until reaching approximately 90% confluency. The cells were then treated with various concentrations (3.13–300 μg/mL) of each extract for 48 h. Cell viability was determined using an MTT assay, and the results were expressed as a percentage relative to untreated control cells.

4. Antiviral activity assay (cytopathic effect reduction)

The antiviral activity of extracts from three *Scrophularia* species against IAV was evaluated using a cytopathic effect (CPE) reduction assay. MDCK cells were infected with IAV at a multiplicity of infection (MOI) of 0.0005 for 1 h with rocking. After removal of inoculum, EMEM containing 2 μg/mL TPCK-treated trypsin and each extract was added at varying concentrations (3.13–300 μg/mL) for 48 h. CPE reduction assays were independently performed three times as biological replicates, and each independent experiment included triplicate technical wells for each treatment group. After 48 h, cell viability was determined using an MTT assay. Normal control refers to uninfected and untreated MDCK cells, whereas virus control refers to IAV-infected MDCK cells without extract or zanamivir treatment. Zanamivir (5 μM) was used as a positive control. CPE reduction rate was calculated using the following formula:

CPE reduction rate (%) = [(OD of extracts-treated infected cells − OD of virus control) / (OD of normal control − OD of virus control)] × 100.

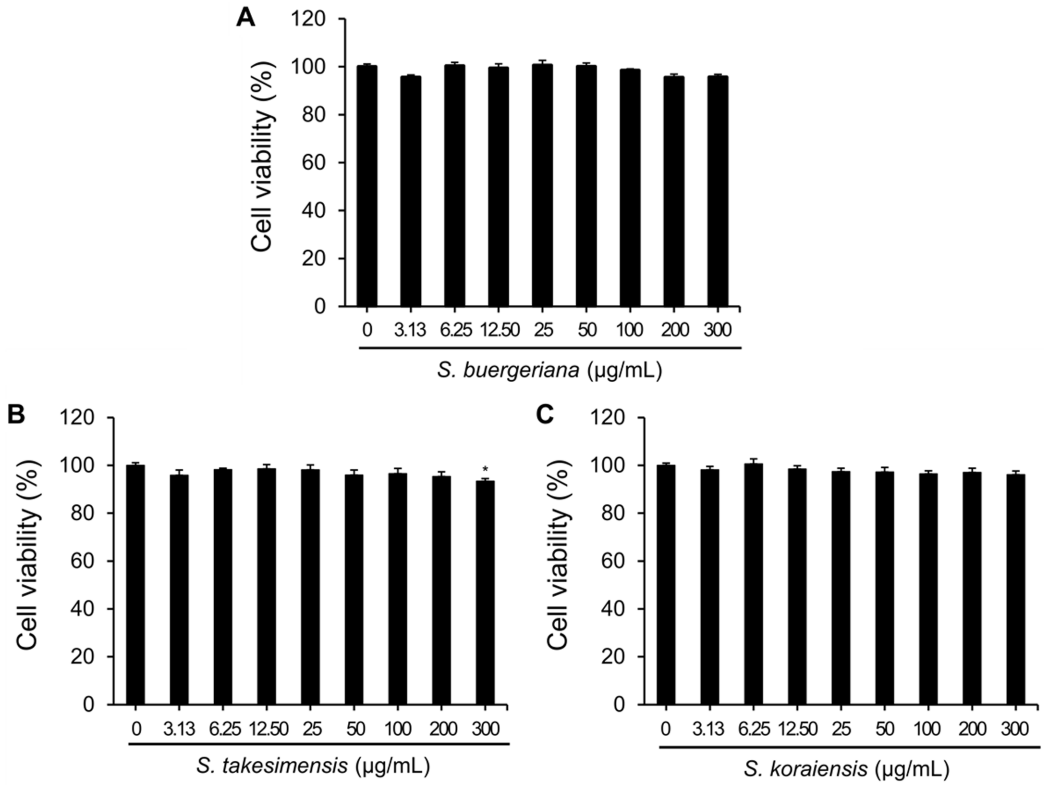

Fig. 2. Effect of ethanol extracts of the three *Scrophularia* species on cell viability. A, S. *buergeriana*; B, S. *takesimensis*; C, S. *koraiensis*. MDCK cells were treated with various concentrations (3.13–300 μg/mL) for 48 h. Cell viability was assessed using the MTT assay and is presented as relative cell viability compared with untreated control. Data are presented as the mean ± SEM. Statistical significance was analyzed using one-way ANOVA followed by Tukey's multiple comparisons test. * $p < 0.05$ vs. control.

5. Neuraminidase inhibition assay

NA inhibitory activity was measured using the NA-Star™ influenza NA inhibitor resistance detection kit (Applied Biosystems, CA, USA). Extracts were tested at concentrations ranging from 3.13 to 300 μg/mL. The enzymatic activity of NA was quantified by measuring chemiluminescence intensity, and inhibition was expressed as a percentage relative to the untreated virus control. Zanamivir was used as a reference NA inhibitor.

6. Statistical analysis

Prior to one-way ANOVA, the normality of data distribution was assessed using the Shapiro–Wilk test, and the homogeneity of variance was evaluated using the Levene's test. All datasets satisfied the assumptions of normality and homogeneity of variance, and one-way ANOVA followed by Tukey's multiple comparison test was subsequently performed. Statistical analyses were performed using SigmaPlot 10.0 software (Systat Software Inc., San Jose, CA, USA). A value of $p < 0.05$ was considered statistically significant.

RESULTS

1. Comparative leaf and stem morphology of *Scrophularia* species

Comparative analysis of leaf and stem morphology revealed clear diagnostic differences among the three *Scrophularia* species. Distinction is possible based on leaf shape, apex form, margin characteristics, stem pubescence, and calyx morphology.

S. takesimensis can be differentiated by its ovate leaves with an acute apex (Fig. 1A) and serrate margins that are largely devoid of spinose teeth (Fig. 1D). The stems are glabrous (Fig. 1G), and the calyx is characteristically semicircular with a rounded apex (Fig. 1J).

S. koraiensis possesses predominantly lanceolate, occasionally ovate, leaves with a pronounced acuminate apex (Fig. 1B). The margins are serrate with spinose teeth (Fig. 1E). The stems show sparse pubescence composed of non-glandular trichomes

(Fig. 1H), while the calyx is lanceolate, tapering to an acute or attenuate apex (Fig. 1K).

S. buergeriana exhibits ovate leaf blades with an acute apex (Fig. 1C) and serrate margins bearing distinct spinose teeth (Fig. 1F). Its stems are glabrous (Fig. 1I), and the calyx is ovate with a blunt (obtuse) apex (Fig. 1L).

2. Cytotoxic effects on MDCK cell

Treatment with *Scrophularia* extracts did not induce significant cytotoxicity in MDCK cells at the tested concentrations. All three species of extracts showed high cell viability (> 93.40%) across the tested concentration range, indicating minimal cytotoxicity. Subsequent antiviral assays were performed at concentrations determined to be minimally toxic.

3. Antiviral activity against influenza A virus

Antiviral activity was assessed using a post-infection treatment protocol, with uninfected/untreated cells serving as normal controls and infected/untreated cells as virus controls. The CPEs were observed in IAV-infected/untreated cells, whereas no morphological changes were detected in the control groups.

All three extracts significantly improved cell viability in virus-infected MDCK cells when compared with the untreated control group, indicating that they exert protective effects against virus-induced cytotoxicity. Furthermore, the magnitude of this antiviral effect increased in a dose-dependent manner, meaning that higher concentrations of the extracts resulted in greater improvements in cell survival (Fig. 3). However, representative microscopic images showing virus-induced morphological changes and extract-mediated cellular protection were not obtained. This lack of morphological evidence is a limitation of the present study.

When comparing the efficacy among the tested species, the extract derived from *S. buergeriana* demonstrated the most potent antiviral activity. This was followed by *S. koraiensis*, which showed moderate effectiveness. In contrast, *S. takesimensis* exhibited the least antiviral activity among the three, although it still provided a measurable protective effect

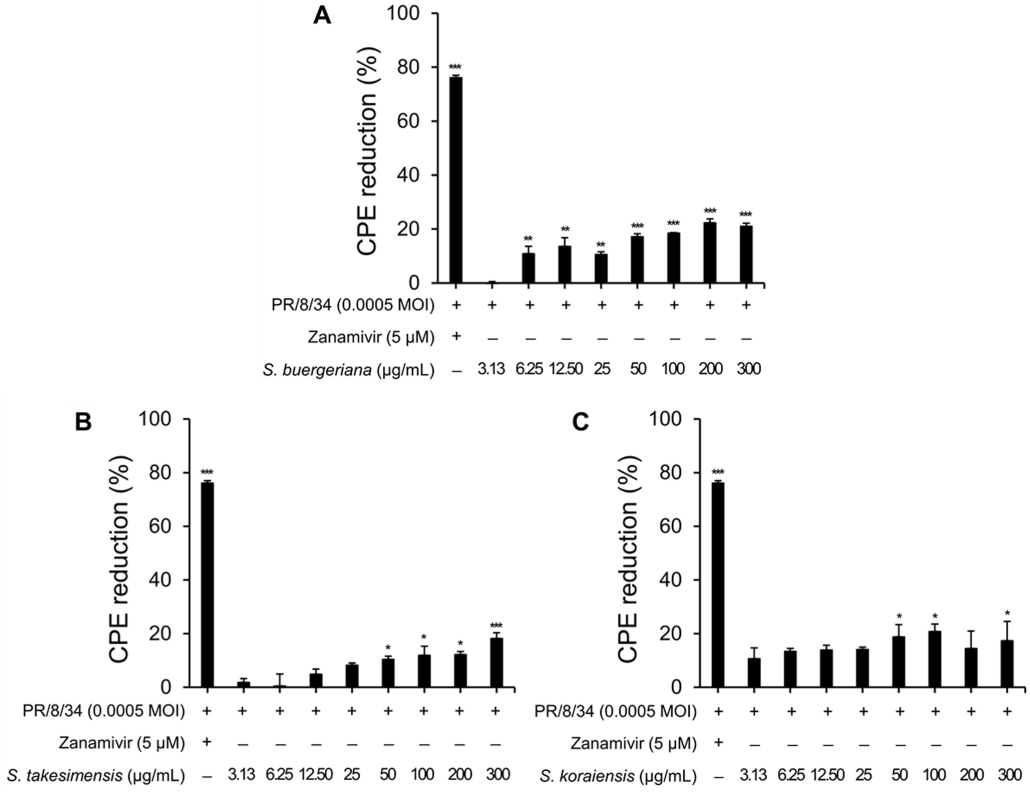

Fig. 3. Anti-influenza effects of ethanol extracts of the three *Scrophularia* species in MDCK cells. A, *S. buergeriana*; B, *S. takesimensis*; C, *S. koraiensis*. MDCK cells were infected with A/PR/8/34 at an MOI of 0.0005 and treated with the indicated concentrations of each extract. At 48 hpi, IAV-induced cytopathic effects (CPE) under different treatments were evaluated using an MTT assay. Data are presented as the mean ± SEM. Statistical significance was analyzed using one-way ANOVA followed by Tukey's multiple comparisons test. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ vs. virus control.

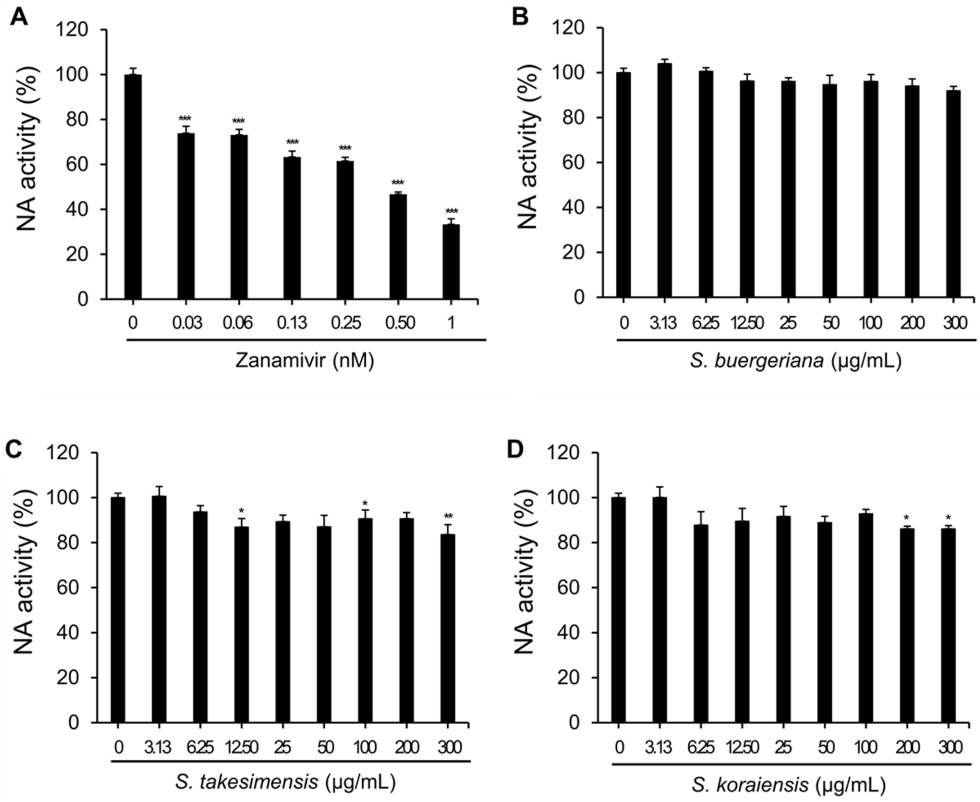

Fig. 4. Inhibitory activity of ethanol extracts of the three *Scrophularia* species on neuraminidase from influenza A viruses. A, Zanamivir; B, *S. buergeriana*; C, *S. takesimensis*; D, *S. koraiensis*. Neuraminidase inhibitory activity was assessed using the NA-Star™ kit according to the manufacturer's instructions. Each extract (3.13–300 μg/mL) or zanamivir (0.03–1 nM; positive control) was reacted with A/PR/8/34 for 30 minutes. Data are presented as the mean ± SEM. Statistical significance was analyzed using one-way ANOVA followed by Tukey's multiple comparisons test. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ vs. virus control.

compared to the untreated control.

Moreover, chemiluminescence-based NA inhibition assays showed little inhibitory activity for each extract against influenza viruses. While *S. takesimensis* and *S. koraiensis* showed weak dose-dependent inhibition, *S. buergeriana* did not exhibit significant inhibitory activity (Fig. 4).

DISCUSSION

IAV infection remains a global health concern, and currently available antiviral drugs primarily target viral proteins such as NA. However, the widespread emergence of drug-resistant viral strains has reduced the effectiveness of conventional antiviral therapies (Moscona, 2005). Therefore, natural products with alternative mechanisms of action have been increasingly explored as complementary or alternative antiviral strategies (Musarra-Pizzo *et al*., 2021).

In the present study, ethanol extracts from three *Scrophularia* species (*S. buergeriana, S. koraiensis,* and *S. takesimensis*) exhibited antiviral activity against IAV in MDCK cells without significant cytotoxicity. Notably, all extracts showed dose-dependent inhibition of virus-induced CPE, suggesting their potential as natural antiviral agents. Among the three, *S. buergeriana* exhibited the strongest activity, with a 22.36% CPE reduction at 200 μg/mL, followed by *S. koraiensis* and *S. takesimensis*, which showed moderate and weaker protection, respectively. This potency order contrasts with the NA inhibition results: *S. takesimensis* and *S. koraiensis* demonstrated weak but measurable dose-dependent NA inhibition, whereas *S. buergeriana* showed no detectable NA inhibition.

NA plays a critical role in viral release from infected cells, and its inhibition is a well-established antiviral strategy (Colman, 1994). The species-specific pattern of NA inhibitory activity observed in this study may be related to differences in harpagoside content among the three species. A previous study using HPLC/MS quantification reported harpagoside contents of 1.94

± 0.24, 6.47 ± 0.02, and 5.50 ± 0.02 ㎎/g in *S. buergeriana*, *S. koraiensis*, and *S. takesimensis*, respectively (Nam *et al*., 2020). The two species with higher harpagoside content (*S. koraiensis* and *S. takesimensis*) exhibited weak NA inhibitory activity, whereas *S. buergeriana*, with the lowest harpagoside level, showed no inhibition. This raises the possibility that harpagoside or co-occurring iridoid glycosides may contribute, at least in part, to the NA-inhibitory activity of *Scrophularia* extracts. However, harpagoside itself has not been established as an NA inhibitor, and the actual NA inhibitory constituents remain to be identified. Direct compound-level validation, including testing of isolated harpagoside against NA activity, is warranted to confirm this association. Conversely, the more potent CPE-reducing activity of *S. buergeriana* despite its low harpagoside content suggests that its overall antiviral effect is likely driven by other constituents, such as phenylpropanoid glycosides, acting through NA-independent mechanisms.

In this study, *S. buergeriana* exhibited the strongest antiviral activity among the tested species, achieving the highest reduction in CPE despite showing no significant NA inhibitory activity. This finding suggests that the antiviral mechanism of *S. buergeriana* is likely independent of NA inhibition. Since the antiviral effects of *Scrophularia* extracts could not be fully explained by direct NA inhibition alone, alternative mechanisms may be involved. Antiviral effects may occur at various stages of the viral life cycle, including viral attachment and entry, intracellular genome replication, viral RNA polymerase activity, viral protein synthesis, virion assembly, and viral release, as well as through modulation of host antiviral signaling pathways (Ponticelli *et al*., 2023; Arumugam *et al*., 2025). The pharmacological activities of *Scrophularia* species are known to be associated with bioactive secondary metabolites, particularly iridoid glycosides such as harpagoside and various phenylpropanoids (De Santos Galíndez *et al*., 2002). These compounds have been reported to exhibit anti-inflammatory, antioxidant, and immunomodulatory effects (Chaibeddra *et al*., 2020; Thabet *et al*., 2022), which may contribute to antiviral activity by enhancing host defense mechanisms. For instance, iridoid glycosides have been shown to regulate NF-κB signaling pathways and cytokine production, which are closely involved in antiviral immune responses (Mihaylova *et al*., 2025). In addition, a recent study on 8-O-(E-*p*-methoxycinnamoyl)harpagide (MCH), an iridoid glycoside isolated from *S. buergeriana* roots, reported that MCH inhibited IAV infection in human lung epithelial cells by lowering intracellular Ca^{2+} and mitochondrial Ca^{2+}/ROS levels, restoring mitochondrial membrane potential, and suppressing viral proteins such as M1, M2, PA, and NS1 (Kwon *et al*., 2021). The discrepancy between antiviral activity and NA inhibition observed in this study, together with previous evidence that plant extracts can show pronounced antiviral effects despite weak inhibition of viral enzymes, suggests that CPE reduction may involve alternative targets such as viral RNA polymerase or host cell pathways (Lin *et al*., 2014), rather than NA inhibition alone. However, viral RNA quantification by qRT-PCR and viral protein expression analysis by western blotting or immunofluorescence were not performed in the present study. Further studies, including viral RNA and protein assays and time-of-addition experiments, are required to clarify the precise antiviral mechanisms of the *Scrophularia* extracts.

Another important finding of this study is the low cytotoxicity of all three *Scrophularia* extracts in MDCK cells. The maintenance of high cell viability (> 93.40%) across a wide concentration range suggests a favorable safety profile, which is a critical factor in the development of antiviral agents. Natural compounds with low toxicity and multi-target effects are particularly attractive candidates for further drug development (Newman and Cragg, 2020).

Despite these promising findings, several limitations should be considered. First, although zanamivir was included as a positive control, a direct quantitative comparison of antiviral potency (e.g., IC_{50} values) between the *Scrophularia* extracts and zanamivir was not performed, limiting objective assessment of their relative efficacy. Second, the exact molecular mechanisms underlying the antiviral effects were not elucidated and require further investigation using molecular and biochemical approaches. Third, *in vivo* validation is needed to confirm the therapeutic potential of these extracts.

It should also be noted that the harpagoside content values discussed above were derived from a previously published study (Nam *et al*., 2020) rather than from direct phytochemical analysis of the extracts used in the present study. Since the chemical composition of plant materials can vary depending on cultivation conditions, harvest timing, and processing methods, the extracts used in this study were not subjected to direct chemical characterization (e.g., HPLC-based quantification of harpagoside or other marker compounds). This lack of direct phytochemical analysis is a limitation of the present study, and future studies should include quantitative analysis of the bioactive constituents in the same extract batches used for antiviral

evaluation.

This study is the first to compare antiviral activity among three Korean *Scrophularia* species against IAV. All extracts showed dose-dependent, low-toxicity protective effects, with *S. buergeriana* demonstrating the strongest activity despite minimal NA inhibition, suggesting an NA-independent mechanism distinct from conventional antivirals such as zanamivir. However, the absence of mechanistic data (viral RNA/protein assays), reliance on a single viral strain, and lack of *in vivo* validation limit these conclusions. Future studies should focus on isolating the active constituents (e.g., harpagoside and related iridoids), elucidating their mechanism of action, and validating efficacy *in vivo* to establish *Scrophularia* species as viable natural antiviral candidates.

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