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Short Communication

Matairesinol Treatment Interferes with the Replication of Coronavirus

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The spread of a coronavirus infection can result in a pandemic, similar to the coronavirus disease 2019 pandemic. Such an infection also accounts for a considerable portion of common cold cases. Although coronavirus medicines are already available, alternative treatments are still required as the coronavirus can produce many variants. Matairesinol, a lignan family compound, is the constituent of cereals, such as rye. We used the human coronavirus OC43 to evaluate the antiviral activity of matairesinol. Matairesinol treatment interferes with coronavirus replication. This treatment decreases the expression of coronavirus protein and RNA as well as the number of coronavirus-induced plaque formations. Our experimental results collectively indicate that matairesinol treatment can potentially reduce coronavirus replication.

Keywords: Alternative medicine, Common cold, Coronavirus, Matairesinol

INTRODUCTION

Coronavirus can cause a serious pandemic like a recent COVID-19, and coronavirus also belongs to the causal virus of common colds (15%-30%) [1]. In addition, many animal problems can be caused by the infection of coronaviruses, including porcine epidemic diarrhea virus (PEDV) and feline infectious peritonitis virus (FIPV) [2,3]. Although the coronavirus vaccines and medicines were recently developed, alternative medicines will be required due to the potential appearance of new coronavirus variants that are resistant to the current medicines [4]. In addition, inexpensive natural products will be welcomed to treat the animal coronaviruses for pets and domestic animals.

Matairesinol (MT) belongs to the lignan family, and MT treatment showed anti-oxidative, anti-cancer, and anti-osteoclast activity [5]. MT treatment significantly reduced the viability of cancer cells such as breast and prostate cancer [6]. Recently, MT was reported to have antiviral effects against HBV; however, the detailed study was not fully performed [7]. Because MT is the constituent of cereals including rye, MT can be ingested by having various cereals [8-10]. Therefore, MT can be a potential alternative medicine for coronavirus-related diseases.

MATERIALS AND METHODS

1. Cell culture and coronavirus infection

The HCoV-OC43 virus was purchased from ATCC, and rhabdomyosarcoma (RD) cells were obtained from the Korean Cell Line Bank. RD cells were maintained in DMEM (Welgene) containing 10% fetal bovine serum (FBS; Thermo Fisher Scientific). RD cells were infected with coronavirus (HCoV-OC43) [11]. Cell viability was measured using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay [12]. MTT was purchased from USB Corp. RD cells were treated using MT (Cayman Chemical Co.).

2. Plaque formation assay

RD cells were prepared in a twelve-well plate one day before the assay to enumerate the virus titer. The collected samples were serially diluted 10-fold in MEM (2% FBS), added to the cell plates, and cultured for 1 hour at 33°C and 5% CO_2. Overlay medium (MEM containing 0.3% agarose) was added to each well, and the plate was incubated for four days. Finally, the cells were fixed with a 4% formaldehyde solution and stained with 0.25% crystal violet.

3. Western blotting

Western blotting was used to examine the level of coronavirus protein in cells and media, as described previously [11]. Briefly, infected cells and conditioned media were collected and resuspended in cell lysis buffer (150 mM NaCl, 50 mM HEPES [pH 7.5], and 1% NP40) containing a protease inhibitor cocktail (Roche). Cell lysates were resolved by SDS-PAGE and transferred to immune-blot PVDF membrane filters (Bio-Rad). Viral proteins were detected with a 1:10,000 dilution of primary HCoV-OC43 antibody using an ECL Western blotting substrate (DoGenBio). The images were acquired using the ChemiDoc Imaging System (Bio-Rad). The HCoV-OC43 antibody was purchased from Sigma-Aldrich.

4. Quantitative reverse transcription polymerase chain reaction

Quantitative reverse transcription polymerase chain reaction (qRT-PCR) was used to measure the level of coronavirus RNA in cells and media, as previously described [11]. Briefly, cells and media were harvested, and RNA was extracted using Trizol (Thermo Fisher Scientific) in accordance with the manufacturer's instructions. Then, it was subjected to RT-PCR using the StepOnePlus Real-Time PCR System (Thermo Fisher Scientific). Primer sequences were described in the previous publication [11].

5. Statistical analysis

The results of western blotting, qRT-PCR, and MTT assay were evaluated by a two-tailed Student's t-test using Excel software (Microsoft). Statistical significance was set as $p < 0.05$.

RESULTS

1. Matairesinol treatment inhibits coronavirus-induced plaque formation

We examined whether MT treatment inhibits coronavirus replication. First, we examined the cytotoxicity of MT. RD cells were treated with various concentrations of MT, and cell viability was evaluated using an MTT assay. RD cells showed no cytotoxic effect up to 10 μM (Fig. 1A). Next, we examined whether MT treatment alleviates coronavirus-induced plaque formation. As reported, we observed the plaque formation when RD cells were infected with the coronavirus. However, MT treatment decreases coronavirus-induced plaque formation (Fig. 1B). These results suggest that MT treatment alleviates the coronavirus-induced

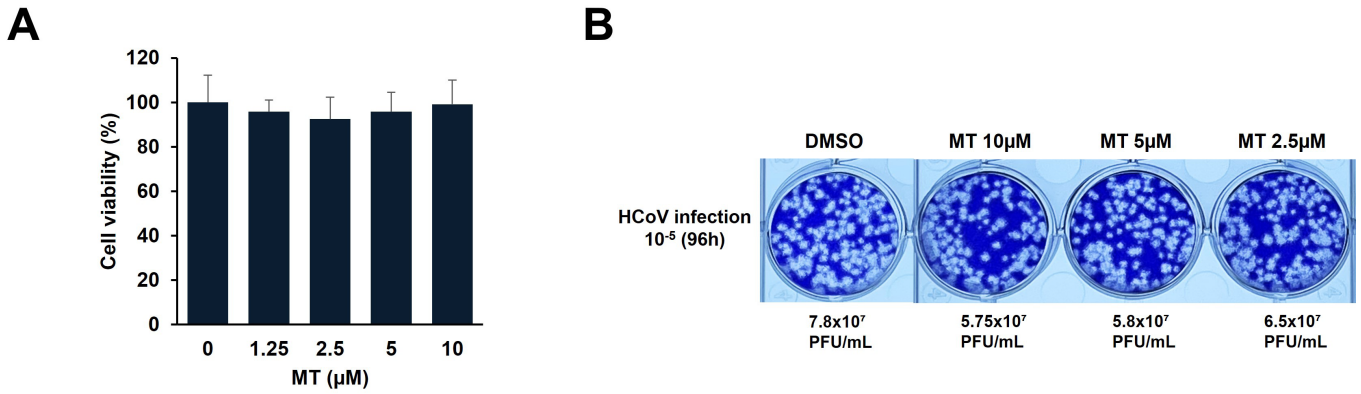

Fig. 1. Matairesinol (MT) treatment interferes with coronavirus-induced plaque formation. (A) Rhabdomyosarcoma cells were treated with the indicated concentration of MT and incubated for 24 h to examine the cytotoxic effect of MT. (B) MT treatment reduced coronavirus-induced plaque formation. DMSO: dimethyl sulfoxide, PFU: plaque forming unit.

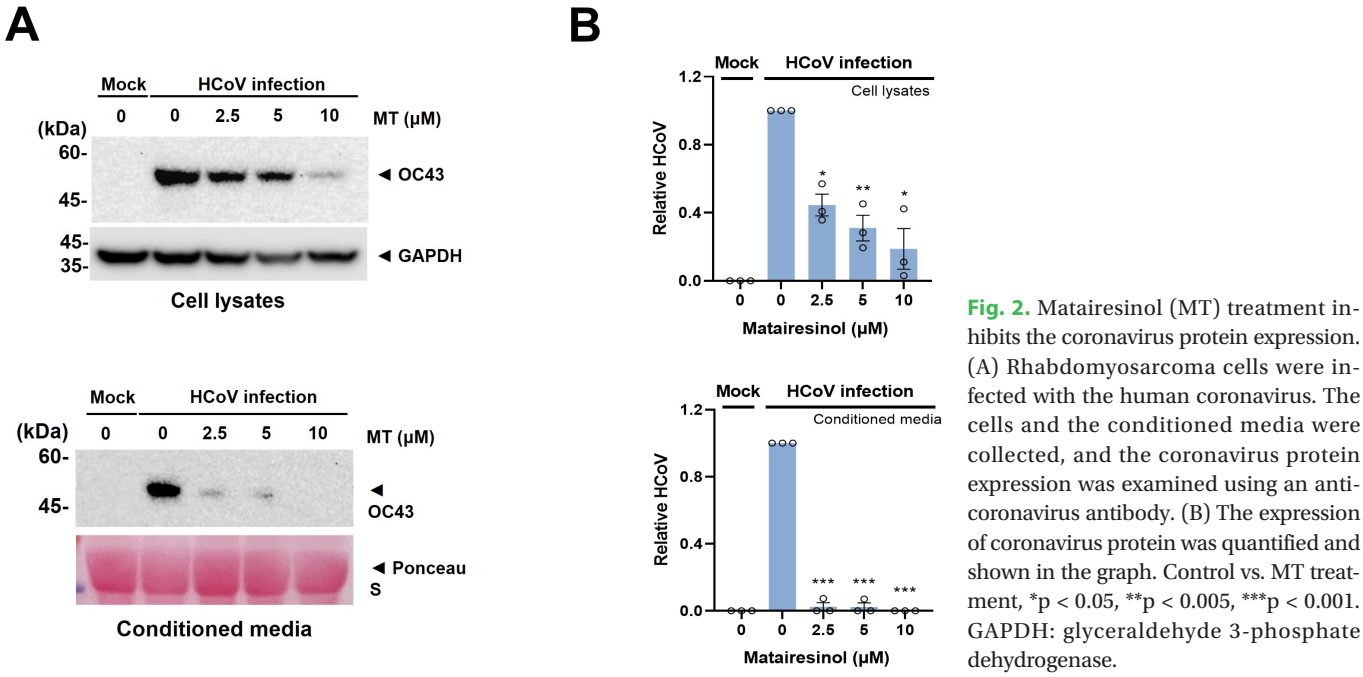

Fig. 2. Matairesinol (MT) treatment inhibits the coronavirus protein expression. (A) Rhabdomyosarcoma cells were infected with the human coronavirus. The cells and the conditioned media were collected, and the coronavirus protein expression was examined using an anti-coronavirus antibody. (B) The expression of coronavirus protein was quantified and shown in the graph. Control vs. MT treatment, *p < 0.05, **p < 0.005, ***p < 0.001. GAPDH: glyceraldehyde 3-phosphate dehydrogenase.

plaque formation.

2. Matairesinol treatment interferes with the release of coronavirus

Next, we examined whether MT treatment interferes with coronavirus replication. RD cells were infected with coronavirus, and we examined whether MT treatment decreases the expression of coronavirus protein by Western blot assay. We observed a significant decrease of coronavirus protein in the cell lysates, and MT treatment also decreases the expression of coronavirus protein in the conditioned media (Fig. 2). Because coronavirus proteins in the conditioned media were mainly from the coronavirus particles, which were released into the media, these results indicate that MT treatment decreases the release of coronavirus into the media.

3. Matairesinol treatment inhibits the replication of coronavirus

Because the level of coronavirus protein was decreased in the conditioned media by MT treatment, we hypothesized that MT treatment inhibits coronavirus replication. We used qRT-PCR to evaluate the level of the coronavirus genome. We prepared the total RNA from the infected cells and conditioned media and evaluated the RNA levels of the membrane (M), nucleocapsid (N), and RNA-dependent RNA-polymerase (RdRp). The level of coronavirus RNA was significantly decreased by MT treatment (Fig. 3). These re-

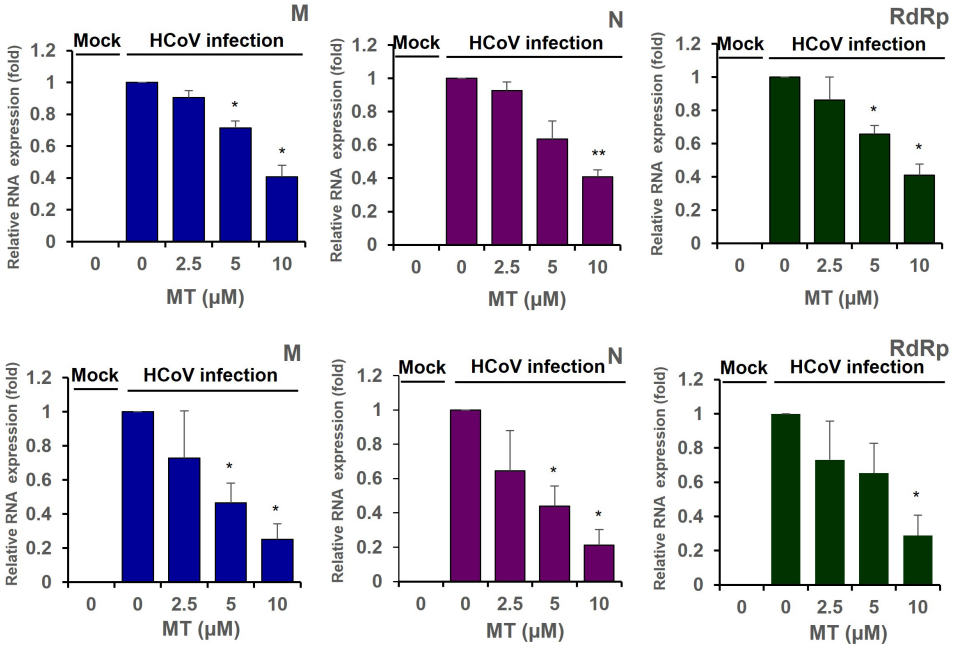

Fig. 3. Metairesinol (MT) treatment decreases the level of coronavirus RNA. Rhabdomyosarcoma cells were infected with human coronavirus and treated with MT. Expression of coronavirus genes (M, N, and RdRp) were evaluated by using quantitative reverse transcription polymerase chain reaction. Control vs. MT treatment, *p < 0.05, **p < 0.005. M: membrane, N: nucleocapsid, RdRp: RNA-dependent RNA-polymerase.

sults are consistent with the Western blot data (Fig. 2).

DISCUSSION

Recently, the coronavirus caused a severe pandemic, COVID-19. Now, effective vaccines are available. However, RNA viruses, including coronavirus, can produce many variants that can evade the vaccine-induced immune system. Therefore, alternative medicines and natural products will be valuable to respond to the new coronavirus. Here, we demonstrated that MT, classified as a lignan, has an anti-viral effect against coronavirus. We used HCoV-OC43, a model virus system for COVID-19, because HCoV-OC43 and SARS-CoV-2 belong to beta coronavirus family [11]. We showed that MT treatment blocks coronavirus protein expression and viral RNA expression, indicating that MT treatment inhibits coronavirus replication.

In this report, we used a micromolar concentration of MT, which is relatively high compared with other natural compounds [13]. Therefore, the availability of MT in the blood can be limited, and it would be difficult to get enough concentration in the blood and respiratory organs. However, MT can be effective in the digestive organs. As reported, a natural product like EGCG can exist in a higher concentration in the intestines than in other organs [13]. Moreover, SARS-CoV-2 can infect the lungs and intestines mainly because these organs express ACE-2, a cellular receptor for SARS-CoV-2 [14]. The infection of SARS-CoV-2 to the digestive organs results in diarrhea and other digestive problems [15]. Therefore, MT can be effective in reducing coronavirus-related digestive problems. Here, we showed the in vitro study with MT, and further study, including animal study, will be required to study the pharmacological use of MT.

NOTES

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- **Authors' contributions:** J.P., J.S., and K.W.Y. participated in conceptualization. K.W.Y., S.L., J.S., and C.L. participated in conducting the experiments. S.L. and J.P. participated in curated the data. J.P. wrote the original draft of the manuscript. J.P. and S.L. participated in writing, review & editing.
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