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Anticancer and Antiviral Activity of Chlorine Dioxide by Its Induction of the Reactive Oxygen Species

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Anticancer and antiviral activity by inducing active oxygen production of chlorine dioxide

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Abstract Chlorine dioxide has been used for a disinfectant by exhibiting antimicrobial activity and is also potent to kill insect pests infesting stored grains. This study aimed to extend the usefulness of chlorine dioxide with respect to anticancer and antiviral activities. Cytotoxicity of chlorine dioxide was assessed against five different human cancer cell lines. Chlorine dioxide exhibited significant cytotoxicity against two breast cancer cell lines (MCF-7, MDA-MB-231) and three colorectal cancer cell lines (LoVo, HCT-116, SW-480). This cytotoxicity appeared to be associated with the capacity of chlorine dioxide to induce the production of reactive oxygen species (ROS). Compared to control insect cell lines, the cancer cell lines possessed much higher levels of ROS. On the other hand, a treatment of an antioxidant, vitamin E, significantly reduced the cytotoxicity, suggesting that the cytotoxicity was induced by high levels of ROS production. Chlorine dioxide exhibited antiviral activity against different viruses. A baculovirus, Autographa californica nuclear polyhedrosis virus (AcNPV), is a dsDNA insect virus and lost its viral activity to form polyhedral viral particles in response to chlorine dioxide. The antiviral activity against AcNPV was dependent on the incubation time with chlorine dioxide. Tobacco mosaic virus is a ssRNA plant virus and was reduced in its population after exposure to chlorine dioxide along with significant decrease of viral symptoms. These results indicate that chlorine dioxide possesses anticancer and antiviral activities probably due to its inducing activity of ROS production.

Keywords anticancer · antivirus · chlorine dioxide · reactive oxygen species

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Introduction

Chlorine dioxide (ClO2) is a type of chlorine oxide and is widely used as a disinfectant and bleaching agent for drinking water (Volk et al., 2002). In particular, chlorine oxide is relatively safe because it does not produce trihalomethane, which causes cancer, unlike chlorine used as a general disinfectant (Don, 1998), has high solubility in water, and can be formulated in liquid and gaseous states for various purposes. It is expanding the possibility of using it as a disinfectant for Chlorine dioxide has a broad antibacterial ability against pathogenic bacteria and viruses. That is, chlorine dioxide is food-contaminated pathogenic bacteria (Bang et al., 2014; Sun et al., 2014), oral-contaminated bacteria (Taneja et al., 2014; Aung et al., 2015), drinking water-contaminated bacteria (Vlad et al., 2014), and general tableware contaminating bacteria. (Nam et al., 2014) showed excellent antimicrobial ability. In particular, for bacteria that are resistant to various antibiotics, chlorine dioxide showed superior antibiotic ability compared to conventional sodium hypochlorite (NaClO) (Hinenoya et al., 2015). Chlorine dioxide also protects against Enterovirus 71 (EV71), which causes hand, foot and mouth disease.

It showed antiviral activity against various human pathogenic viruses including

By formulating chlorine dioxide in a gaseous state that can be treated with fumigation, it shows the pest control ability against sanitary pests that damage the living environment of humans and low-grain pests that damage storage. For bedbugs (Cimex lectularius, Cimex hemipterus) occurring in hospital facilities, it showed a fast-acting control effect on exposure to a relatively high concentration (about 1,000 ppm) of chlorine dioxide (Gibbs et al., 2012) For moth (Plodia interpunctella), it showed a complete control effect at a relatively low concentration (200 ppm) exposure (Kumar et al., 2015). The mechanism of action of chlorine dioxide, which exhibits antibacterial effects against various diseases and pests, has not yet been precisely elucidated. However, the high oxidative power of this compound implies a central mechanism of action for this antibiotic ability. Chlorine dioxide exposure oxidizes aromatic amino acids, leading to protein denaturation and, through this, loss of protein function (Ogata, 2007). For example, with respect to influenza virus, a cold virus, chlorine dioxide causes the virus to oxidize tryptophan at position 153, an amino acid important for binding to a receptor on the host, to N-formylkynurenine to lose its function (Ogata, 2012). In addition, it has been reported that chlorine dioxide has an action to directly change the nucleic acid of DNA or RNA (Jin et al., 2013). Recently, it was reported that chlorine dioxide induces a large amount of reactive oxygen species (ROS) in the treated insects, resulting in a high mortality rate of the treated insects (Kumar et al., 2015). ROS can affect a relatively wide variety of biomolecules. Therefore, it is expected that the ROS generating function of chlorine dioxide can be given to pathogens in more diverse areas. This study was designed to expand the useful range of applications based on the oxidizing power of chlorine dioxide. In terms of agricultural control of low-grain pests, this study was designed for medical application by verifying the anticancer effect of chlorine dioxide treatment, which is known to be relatively safe for normal cells (Nishikiori et al., 2008), on cancer cells. For this purpose, the cancer cells analyzed in this study were 2 types of breast cancer and 3 types of colorectal cancer, and the effect of chlorine dioxide treatment was verified on all 5 types of cancer cell lines. In addition, it was attempted to expand the scope of agricultural application by verifying whether chlorine dioxide could have an antiviral effect on insect viruses that damage sericulture and beekeeping farms and plant viruses that harm crops. Bacculovirus is a double-stranded DNA virus that specifically causes viral diseases in insects (Clem and Passarell, 2013). Tabaco mosaic virus (TMV) is a single-stranded RNA virus that causes the greatest damage to tobacco (Scholthof, 2004). This study investigated whether chlorine dioxide had a distinct antiviral function against these different viruses.

Materials and Methods

cell culture. Two types of insect cells were used as control cells. The Sf9 cell line (IPLB-Sf21-AE) was derived from the pupal ovarian tissue of Spodoptera frugiperda, with 5% fetal bovine serum (FBS, Hyclone, Logan, UT, USA) and an antibiotic-antimycotic complex (Cat. No. 15240-062, Gibco, Grand Island, NY, USA) It was cultured in the added TC100 insect cell culture medium (Cat. No. LM505-01, Hyclone, USA). The High Five cell line (BTI-TN-5B1-4) originated from Trichoplusia ni and was derived from Express Five® SFM (Cat. No. 10486-025, Gibco) was grown in culture medium. Both cells were proliferated at 28o C using a 25 cm2 tissue culture flask (Cat. No. 156340, Nunc, Roskilde, Denmark) . MCF-7 (Korean Cell Line Bank (KCLB) as a cancer cell line) No. 30022) and MDA-MB-231 (KCLB No. 30026) are derived from human breast cancer. On the other hand, LoVo (KCLB No. 10229), HCT-116 (KCLB No. 10247), and SW-480 (KCLB No. 10228) are all derived from colorectal cancer. All these cells were cultured using Dulbecco's modified Eagle medium/F-12 (1:1, v/v) containing 10% FBS and antibiotics (100 U/mL penicillin, 100 µg/mL streptomycin). Cell culture was performed at 37o C and 5% CO2 conditions using a 75 cm2 tissue culture flask (Cat. No. 156499, Nunc) . chlorine dioxide. Chlorine dioxide used in this study was 800 ppm stock solution. This reagent was provided by Frugopam (Suwon, Korea). Cell activity assay. Cell activity was analyzed using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, Cat. No. M-2128, Sigma Aldrich Korea, Korea) dye. 10,000 cells/50 µL of cells to be treated were dispensed into each 96 well plate. Chlorine oxide was diluted to 10ÿ9 ÿ10ÿ3 M with each cell culture medium , added to the cell suspension at a volume of 100 µL each, and treated at 28o C for 48 h. After that, 20 µL of MTT (5 mg/mL) was added and treated at 28o C for 5 h. After that, 70 µL of 25% sodium dodecyl sulfate (pH 2.0) was added and left at room temperature for 16-18 h to dissolve the formed formagen. Then, the absorbance was measured at 570 nm. Reactive oxygen species (ROS) assay. Quantitative ROS analysis was performed using the OxiSelect Intracellular ROS Assay Kit (Cat. STA-342, Cell Biolabs Inc., San Diego, CA, USA) was used. After washing the different cultured cells twice (1,000 rpm, 10 min) with phosphate buffered saline (PBS), 1×2',7'-dichlorofluorescin diacetate (DCFH-DA) diluted with each cell culture solution (20× DCFH-DA stock, Part No. 234201) was added with 1 mL and reacted at 28o C for 60 minutes. Thereafter, the cells were washed twice with PBS in the above manner, and the same cell density (10,000 cells) was dispensed into each tube. After removing the supernatant, chlorine dioxide (0-200 ppm) solution (250 µL/well) diluted with each cell culture medium was added and reacted at 28o C for 90 minutes. The reacted cells were washed twice with PBS and suspended in 250 µL of cell culture solution. The same volume (250 µL) of 2× Cell Lysis Buffer (Part No. 234203) was added and reacted at room temperature for 5 minutes. Each 150 µL of cell lysate was transferred to a 96 well plate (Cat. No. 167008, Nunc) and fluorescence was measured under the conditions of 480 nm incident light and 530 nm output light. To check whether this fluorescence value correlates with the formed ROS, dilute 2',7'-dichlorofluorescein (DCF) standard solution (1 mM, Cat. No. 234202) with cell culture solution to a concentration of 0ÿ10 µM. , Each 75 µL of DCF standard solution was treated in 96 wells having the same cell density (10,000 cells), reacted at 28o C for 20 minutes, and the fluorescence value indicated by the above method was measured. Analysis of the effect of antioxidant vitamin E on chlorine dioxide cytotoxicity. A stock solution of vitamin E (ÿ-tocopherol, Cat. No. 258024, Sigma-Aldrich Korea) was prepared with dimethyl sulfoxide, and this w

It was diluted with the culture solution. Each reaction solution consisted of 50 µL of cell suspension (10,000 cells), 50 µL of chlorine dioxide (final concentration: 3.9×10ÿ6 M), and 50 µL of vitamin E solution and incubated at 28o C for 48 hours. . Thereafter, cell activity was analyzed using the MTT assay. Antiviral bioassay for baculovirus of chlorine dioxide. For the baculovirus, Autographa californica nuclear polyhedrosis virus (AcNPV) was used (Jung et al., 2006). This virus was propagated using the Sf9 cell line. The concentration of AcNPV was 5×107 pfu/mL, and chlorine dioxide was treated to 200 ppm in this virus solution. The treated solution was reacted at room temperature for 0-24 hours. The treated virus solution was inoculated into Sf9 cells to confirm the formation of nuclear polygons at 28o C for 3 days. The number of nuclear polygons was expressed as the density of nuclear polygons present in 100 randomly selected cells. Each treatment was repeated with 3 cell reactions. Antiviral bioassay for TMV of chlorine dioxide. The antiviral effect of chlorine dioxide on TMV was confirmed. Tobacco used in the experiment was Nicotiana tabacum cv. N. tabacum cv. forming a local lesion with NC 82. Tobacco with 6-8 leaves was used as Xanthi-NC cultivar. For TMV, the same variety was inoculated with the strain kept in the laboratory, and leaves with symptoms were used. 2 g of leaves showing symptoms of TMV were ground in 5 mL of sterile water and used as an inoculum. After mixing 500 µL of this virus solution and 500 µL of chlorine dioxide solution, it was incubated for a certain period of time (0, 12, 24, 48 h) at room temperature (23±2o C) and inoculated into tobacco leaves. In TMV infection, N. tabacum cv. After sprinkling carborundum on the second lower leaf of NC82 cultivar, the TMV juice diluted for each concentration was inoculated using a sterile cotton swab. The carborundum on the surface of the inoculated tobacco leaves was washed with running water and placed on a plant growth stage at 25o C to observe symptoms. To check the change in virus concentration, 10 days after inoculation, the same amount of leaves for each treatment group were recovered using a Cork borer (diameter 6 mm), and the control effect on TMV was evaluated by the DAS-ELISA method (Jeon et al., 2008). Confirmed. Absorbance was measured at 405 nm using an ELISA reader (Gen5, BioTek, USA). Each treatment was repeated 3 times. N. tabacum cv. forming localized lesions. The Xanthi-NC cultivar was inoculated with TMV juice in the upper 2nd, 3rd and 4th lobe. In the same leaf, half was inoculated with TMV juice diluted by concentration, and half was inoculated through the half leaf method in which TMV juice diluted in sterile water was inoculated. Three days after inoculation, the leaves were cut into 3×3 cm sizes, and the number of lesions formed in the leaves was visually inspected and compared with the number of lesions in the untreated group to calculate the control value.

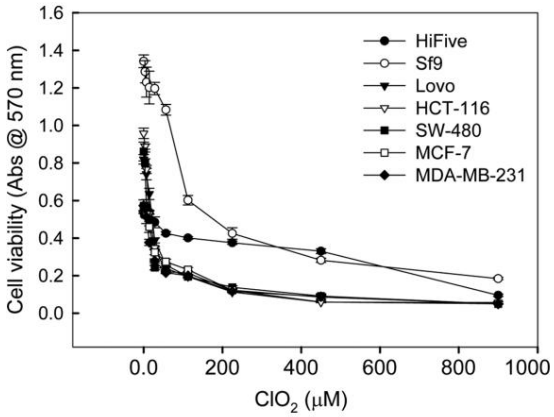

Fig. 1 Susceptibility of cancer cell lines to chlorine dioxide (ClO2). Controls are two insect cell lines: Sf9 and High Five ('HiFive'). Treatments include MCF-7 and MDA-MB-231 for breast cancer cell lines and Lovo, HCT-116, SW-480 for colorectal cancer lines. Cell survival was measured by MTT assay. Each treatment was measured 8 times (8 wells) per replication and replicated two times.

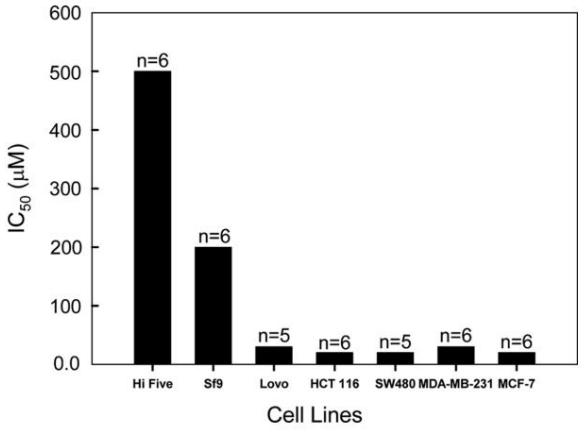

Fig. 2 Median inhibition concentrations (IC50s) of chlorine dioxide (ClO2) against cancer cell lines. Controls are two insect cell lines: Sf9 and High Five ('HiFive'). Treatments include MCF-7 and MDA-MB-231 for breast cancer cell lines and Lovo, HCT-116, SW-480 for colorectal cancer lines. Cell survival was measured by MTT assay. IC50s were calculated based on the absorbance values obtained from the MTT assays using Graphpad Prism 5.00.288 program (http://whatpulse.org/app/ graphpad-prism-5-00-288).

result

Cytotoxicity of chlorine dioxide to cancer cells. The cytotoxicity of chlorine dioxide against two human breast cancer cell lines and three colorectal cancers was analyzed (Fig. 1). As the concentration of exposure to chlorine dioxide increased, the activity of these cancer cells decreased. As a control, insect cells also showed sensitivity to chlorine dioxide. However, the cancer cell lines showed significantly higher sensitivity than the control group. The median inhibitory concentration (IC50) for chlorine dioxide was calculated (Fig. 2). The cancer cell lines showed an IC50 of less than about 10 ppm , while the control cell groups all showed an IC50 of 100 ppm or more. That is, cancer cell lines are more sensitive to chlorine dioxide than normal cells.

It was found to exhibit more than 10-fold sensitivity to

In order to identify the cause of the sensitivity of cancer cell lines to chlorine dioxide, the cytotoxic effect of intracellular reactive oxygen species was analyzed. First, as a result of treating these cells with vitamin E, an antioxidant, the cytotoxicity caused by chlorine dioxide was slowed (Fig. 3). This meant that chlorine dioxide-induced cytotoxicity to cancer cell lines was caused by reactive oxygen species. Before exposure to chlorine dioxide, there was a difference in the amount of intracellular free radicals between these cells. All cancer cell lines had higher ROS than the control cell group. As a result of exposure to chlorine dioxide, the amount of free radicals generated was greatly increased, and compared to the control, all cancer cell lines generated significantly higher amounts of active oxygen.

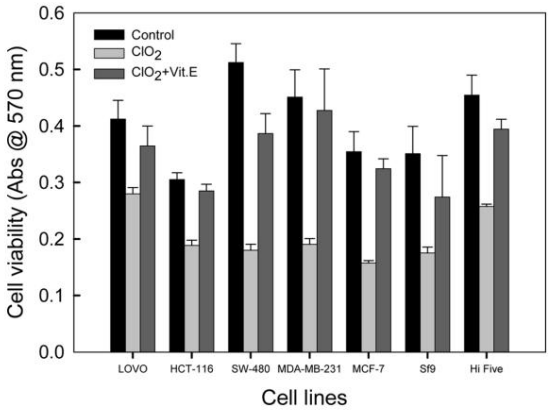

Fig. 3 Rescue effect of vitamin E on cancer cells in response to 3.9 x 10-6 M of chlorine dioxide (ClO2). Controls are two insect cell lines: Sf9 and High Five ('HiFive'). Treatments include MCF-7 and MDA-MB-231 for breast cancer cell lines and Lovo, HCT-116, SW-480 for colorectal cancer lines. Cell survival was measured by MTT assay. Each treatment was measured 8 times (8 wells) per replication and replicated two times.

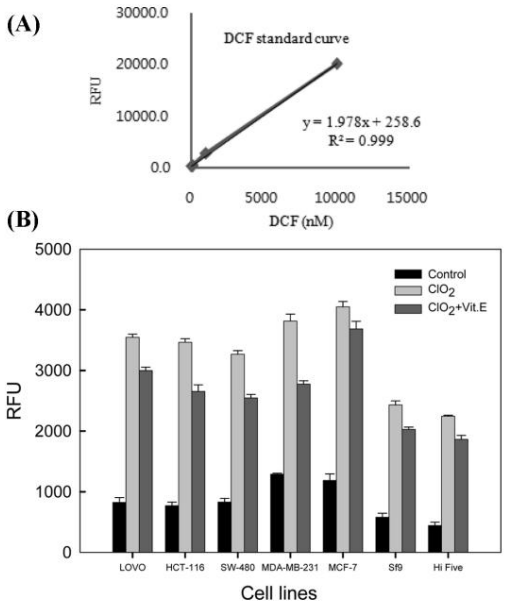

Fig. 4 Up-regulation of reactive oxygen species (ROS) production in response to chlorine dioxide (ClO2) in cancer cell lines. Controls are two insect cell lines: Sf9 and High Five ('HiFive'). Treatments include MCF-7 and MDA-MB-231 for breast cancer cell lines and Lovo, HCT-116, SW 480 for colorectal cancer lines. ROS in the cells oxidized DCFH-DA into a fluorescent DCF. (A) A linear relationship between DCF amount and relative fluorescence unit (RFU) (B) Change in ROS amount in response to ClO2 with or without vitamin E. Each treatment was replicated three times.

Antiviral effect of chlorine dioxide on AcNPV. The antiviral effect of chlorine dioxide on AcNPV, a type of baculovirus that causes viral disease in insects, was analyzed (Fig. 5). In the preliminary exposure experiment, as the concentration of chlorine dioxide (0-800 ppm) was increased, the polymorph formation rate of AcNPV in Sf9 cells decreased. As the reaction time was increased at a constant AcNPV concentration (80 ppm) that can give antiviral effect, the polymorph formation rate in Sf9 cells decreased.

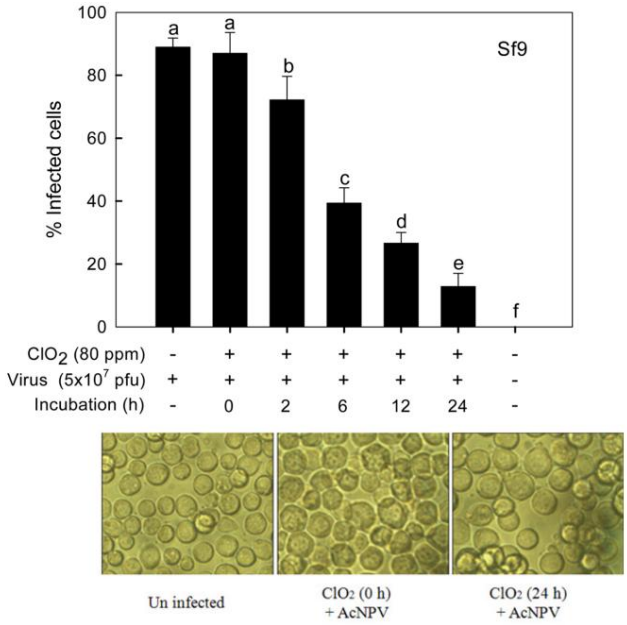

Fig. 5 Antiviral effect of chlorine dioxide (ClO2) on polyhedrin formation of AcNPV. After incubation of AcNPV (5×107 pfu/mL) with a final concentration of 20 ppm ClO2, the virus sample was overlaid on Sf9 cells and incubated for 3 days at 28o C. Virus activity was assessed by counting polyhedra formed in the cells. Each treatment was replicated three times.

Antiviral effect of chlorine dioxide on TMV. The antiviral effect of chlorine dioxide on plant viruses was confirmed (Fig. 6). The antiviral effect of chlorine dioxide on TMV was highest at 400 ppm. After treatment with TMV at 400 ppm of chlorine dioxide for 48 hours, tobacco inoculation showed an effect of 84.9% reduction in virus density, and 54.1% of virus suppression effect in the treatment group at 200 ppm for 48 hours (Fig. 6A). . N. tabacum cv. forming localized lesions. The control effect on the Xanthi-NC variety was confirmed (Fig. 6B). As the concentration of chlorine dioxide treatment increased, the symptoms of TMV were significantly reduced ($F = 591.69$; $df = 2, 39$; $p < 0.0001$), but the time to react with chlorine dioxide before inoculating tobacco leaves with the virus had no significant effect. ($F = 1.96$; $df = 9, 39$; $P = 0.0733$) (Fig. 6B).

Review

Chlorine dioxide is known to exhibit high toxicity to various microorganisms by changing the structure of lipids and proteins constituting biological membranes with high oxidizing power (Huang et al., 1997; Gordon and Rosenblatt, 2005). In particular, it has been reported that chlorine dioxide in vivo induces the generation of active oxygen and exhibits an insecticidal effect (Kumar et al., 2015). This study focused on identifying the anticancer and antiviral effects of chlorine dioxide toxicity. For several cancer cell lines, chlorine dioxide treatment exhibited high cytotoxicity. For two types of breast cancer cell lines and three types of colorectal cancer cell lines, chlorine dioxide gave more than 10 times higher cytotoxicity than normal control cells. This cytotoxicity seems to be due to the reactive oxygen species produced by chlorine dioxide. because it is an antioxidant

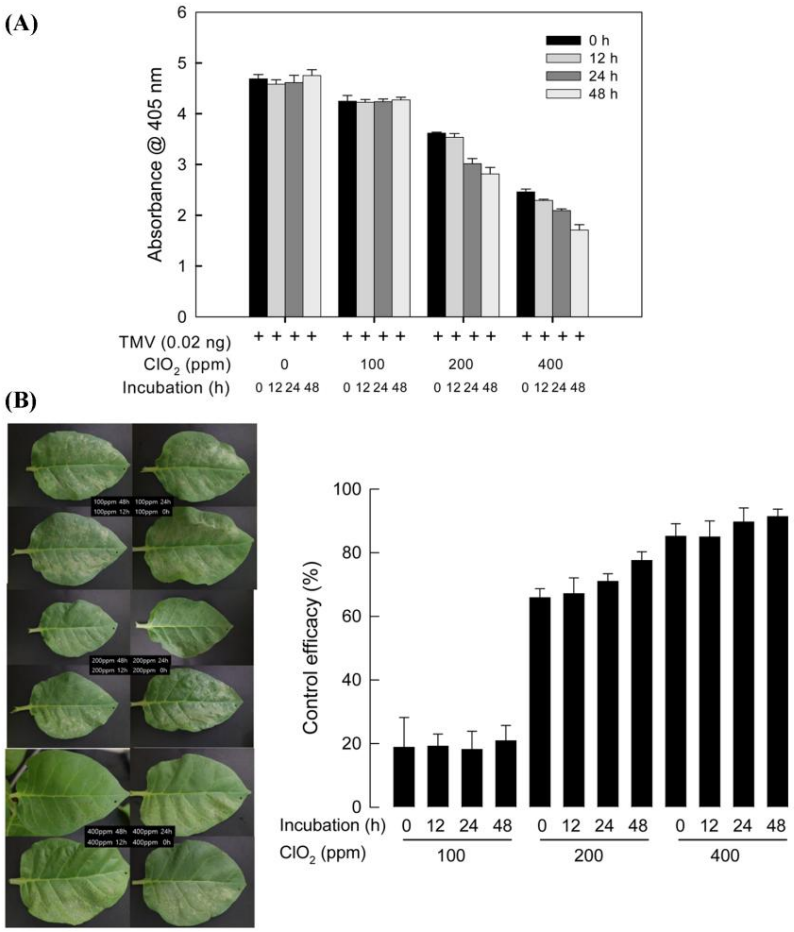

Fig. 6 Antiviral effect of chlorine dioxide (ClO2) on TMV. (A) ELISA test using a method described by Jeon et al. (2008). Each treatment was replicated three times. (B) TMV symptom on tobacco leaves. Each leaf was halved into control (virus+PBS, lower half) and treatment (virus+ClO2, upper half).

Treatment with vitamin E is supported by a reduction in these cytotoxic effects. In addition, as a result of measuring intracellular reactive oxygen species, all cancer cell lines maintained high reactive oxygen species, and the production of such active oxygen increased according to the chlorine dioxide treatment, showing a significantly higher active oxygen content than the control group. This highly elevated active oxygen is thought to have been provided as the main cause of inducing high cytotoxicity to cancer cells. Various non-surgical cancer treatments include strategies to induce cell death or apoptosis by increasing the level of free radicals in cancer cells (Yang et al., 2014). Cancer cells maintain relatively high ROS levels (Sullivan and Chandel, 2014). Antioxidant enzyme expression is induced by using NF E2-related factor 2 (Nrf2) transcription factor to defend cancer cells against these high free radicals (Thimmulappa et al., 2002; Hayes et al., 2010). Therefore, the inactivation of this transcription factor causes cancer cells to become more sensitive to reactive oxygen species (Choi et al., 2014). Chlorine dioxide treatment has the potential to modify the protein involved in the Nrf2 signaling process due to its high oxidative power as well as the generation of reactive oxygen species. To understand the response of cancer cells showing high sensitivity to chlorine dioxide, it is necessary to analyze the effect of chlorine dioxide on the defense system of free radicals derived from Nrf2. This study is based on the It is reported for the first time that the cytotoxicity to cancer cells in cattle is due to the increase of reactive oxygen species.

Chlorine dioxide with high oxidizing power showed antiviral effect against two different types of viruses. Bacculovirus is an entomopathogenic virus with a dsDNA genome that expresses a nuclear polyhedron to form an inclusion body structure including a large number of virions, and can be microscopically examined with an optical microscope. This study revealed that the activity of this virus was inhibited with increasing chlorine dioxide treatment time. In addition, TMV, which is a phytopathogenic ssRNA virus, also showed activity inhibition against chlorine dioxide. As mentioned above, chlorine dioxide exerted an antiviral mechanism against various human pathogenic viruses. The antiviral mechanism of chlorine dioxide has been found to modify viral envelope proteins or directly affect nucleic acids (Ogata, 2012; Jin et al., 2013). TMV single plant virus alone causes an economic loss of $1 billion annually worldwide (Wu et al., 1995). Therefore, this study shows the applicability of chlorine dioxide as a control factor that exerts antiviral effects against two types of viruses that cause major damage to the agricultural industry.

green

Chlorine dioxide is used as a disinfectant due to its high antibiotic effect, and it is also showing an insecticidal effect against low-grain pests. This study verified whether this substance could exhibit anticancer and antiviral activity in order to broaden the useful effect of chlorine dioxide. The cytotoxicity of chlorine dioxide was analyzed for five cancer cell lines appearing in the human body. Chlorine dioxide showed high cytotoxicity against both breast cancer type 2 cell lines (MCF-7, MDA-MB-231) and colorectal cancer type 3 cell lines (LoVo, HCT-116, SW-480). This cytotoxicity is due to the reactive oxygen-induced effect of chlorine dioxide. All cancer cell lines treated with chlorine dioxide formed high intracellular free radicals. As a control, it had much higher free radicals compared to the general insect cell line. On the other hand, treatment with the antioxidant vitamin E significantly reduced this cytotoxicity, demonstrating that the high cytotoxicity to cancer cells was caused by free radicals. In addition, chlorine dioxide showed antiviral activity against different viruses. Autographa californica nuclear polyhedrosis virus (AcNPV), an entomopathogenic virus and a type of baculovirus with a double-stranded DNA genome, loses its activity upon exposure to chlorine dioxide, significantly slowing its ability to form nuclear polyhedra. The antiviral effect of chlorine dioxide on AcNPV increased in proportion to the reaction time. Tobacco mosaic virus, which is a phytopathogenic virus and has a single-stranded RNA genome, has a reduced viral content following exposure to chlorine dioxide and a lower pathogenicity against tobacco. Therefore, in this study, it was found that chlorine dioxide has anticancer and antiviral activity, which is due to the high induction of free radicals by this material.

Keywords chlorine dioxide, antiviral, anticancer, active oxygen

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