Short Communication

Resveratrol Oligosaccharides (Gluco-Oligosaccharides) Effectively Inhibit SARS-CoV-2 Infection: Glycoside (Polysaccharide) Approach for Treatment of COVID-19

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Abstract

To examine the anti-SARS-CoV-2 effects of resveratrol oligosaccharides, human MRC5 lung cells, which had been infected with SARS-CoV-2, were incubated with different concentrations of resveratrol oligosaccharides. These suppressed the cell death induced by SARS-CoV-2 infection, more efficiently, at 0.1% concentration, than resveratrol itself. Resveratrol oligosaccharides effectively inhibited SARS-CoV-2 infection in the 5% to 10% concentration range, which indicates that these compounds could be useful anti-SARS-CoV-2 agents.

Keywords

antiviral effects, anti-SARS-CoV-2 compounds, polyphenol, resveratrol, oligosaccharides

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Resveratrol is a polyphenol that is present in many fruits, including grape berries of *Vitis vinifera*.[1] There have been many studies of resveratrol demonstrating its capacity to prevent versatile conditions, including cardiovascular diseases and cancer, and to control bacterial and viral infections.[2-6] It has also been reported for its ability to abolish the effects of oxidative stress in cultured cells.[6] The biological activity of resveratrol as an antiproliferative and antiviral drug in cultured fibroblasts has been shown. There have been other studies showing that this compound inhibits the proliferation of different viruses such as herpes simplex, varicella-zoster and influenza A.[7] Its toxicity at high concentrations has been found, but, on the other hand, at sub-cytotoxic concentrations, resveratrol can effectively inhibit the synthesis of polyomavirus DNA.[7] The transfer of the virus from the endoplasmic reticulum to the nucleus may be hindered, thus inhibiting the production of viral DNA, due to the damage caused by resveratrol to the plasma membrane.

Cultured plant cells can be used to transform organic molecules to more useful compounds by carrying out hydrolysis, oxidation, reduction, esterification, isomerization, and glycosylation reactions.[8] Glycosylation of biological active compounds can enhance water solubility, physicochemical stability, intestinal absorption, and biological half-life.[8] The fact that many secondary metabolites accumulate in the form of glycosides in plants suggests that such cells would contain glucosyltransferases, which catalyze the conjugation of an aglycone and a glucosyl donor molecule.

In this study, we investigated the antiviral effects of resveratrol oligosaccharides for SARS-CoV-2 in comparison with resveratrol itself. For this, human MRC5 lung cells infected with SARS-CoV-2 were incubated with various concentrations of resveratrol oligosaccharides. The incubation of MRC5 cells with SARS-CoV-2 was carried out for 1 hours. After the incubation was stopped, formazan was extracted with MTT, which consists of 4 mM HCl in isopropanol, and its absorbance measured at 570 nm. Resveratrol oligosaccharides at 5% and 10% effectively decreased the infection of the MRC5 cells by

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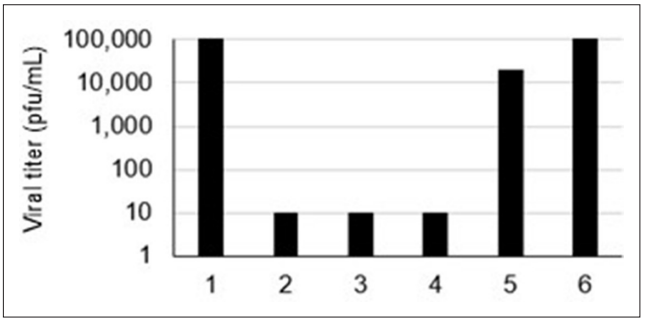

Figure 1. Antiviral activity of resveratrol oligosaccharides (gluco-oligosaccharides) against SARS-CoV-2 infection. 1: Acidic water (pH = 2.287); 2: 10% resveratrol oligosaccharides; 3: 5% resveratrol oligosaccharides; 4: 0.1% resveratrol oligosaccharides; 5: 0.1% resveratrol; 6: control (0.2% PBS/DMEM).

SARS-CoV-2 (Figure 1). This result indicated that these compounds efficiently inhibited the cell death induced by SARS-CoV-2 infection in the 5% to 10% concentration range. Resveratrol oligosaccharides also inhibited SARS-CoV-2 infection at a concentration of 0.1%, more than that of resveratrol itself. The antiviral activity of resveratrol oligosaccharides was as strong as that of birchbark extracts.[7] These results suggest that resveratrol oligosaccharides are potent anti-SARS-CoV-2 compounds.

Inhibition of human cytomegalovirus replication by resveratrol has been shown.[9] At least 50-fold higher concentrations of this compound were required to produce cyto-toxicity against either growing or stationary human embryonic lung fibroblasts. Studies of the mechanism of action indicated that resveratrol blocked virus-induced activation of the epidermal growth factor receptor and phosphatidylinositol-3-kinase signal transduction, as well as NF-kappaB and Sp1 transcription factor activation shortly following infection.[9]

Viral titer (pfu/mL) was calculated as (Number of infected cells × Positive rate)/(Dilution rate ×Volume)

Human cytomegalovirus DNA replication was decreased to undetectable levels by treatment with this compound, as were the second phases of virus-induced phosphatidylinositol-3-kinase signaling and transcription factor activation. This compound lost substantial antiviral activity when its addition was delayed until 4 hours pre-infection. Studies of compound reversibility and preincubation were inconsistent with a virucidal mechanism of action, showing that resveratrol likely operated during attachment and entry.[9]

Further studies on the mechanism of the antiviral effects of resveratrol oligosaccharides for SARS-CoV-2 infection are now in progress in our laboratory.

Experimental

General

MRC5 cells, which had been induced from the human lung tissue, were purchased from VisGene Ltd. (Ibaraki-shi, Osaka 567-0047, Japan).

MTT Assay

In vitro cytotoxicity was evaluated by the MTT assay after 1 hours of viral exposure. MRC5 cells were seeded in a 96-well plate with PBS in DMEM. After incubation at 37 °C in 5% CO_2 for 0.5 hours, different concentrations of resveratrol oligosaccharides were added to each well. After incubation of cells with virus, 5 mg/mL MTT solution was added to each well and the plate was incubated for 1 hours. Formed formazan crystals were dissolved in 10% (w/v) SDS with 0.02 n HCl, and were incubated. The absorbance of each well was measured at 570 nm. The experiment was independently performed. Viral titer was calculated as follows.

Viral titer (pfu/mL) = (Number of infected cells × Positive rate)/(Dilution rate ×Volume)

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Declaration of Conflicting Interests

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