Bardoxolone and bardoxolone methyl, two Nrf2 activators in clinical trials, inhibit SARS-CoV-2 replication and its 3C-like protease

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Fig. 1 Inhibition activity of bardoxolone methyl and bardoxolone. a) SARS-CoV-2 3CLpro inhibition activity of bardoxolone methyl and bardoxolone. Various concentrations of bardoxolone methyl and bardoxolone were pre-incubated with SARS-CoV-2 3CLpro for 30 min at room temperature before the addition of pNA-substrate. b) Anti-SARS-CoV-2 activity and cytotoxicity of bardoxolone methyl and bardoxolone in Vero cells or Calu-3 cells. Cells were infected with SARS-CoV-2 at MOI of 0.01 (Vero cell line) and 1 (Calu-3 cell line) in the treatment of different doses of bardoxolone methyl and bardoxolone for 48 h. The viral yield in the cell supernatant was then quantified by qRT-PCR. The cytotoxicity of the compounds at different concentrations was measured by CCK-8 assays. The EC50 and CC50 were calculated by nonlinear regression analysis using Origin 2018 software. The selective indexes (SI) were calculated as the ratio of CC50 to EC50. c) Immunofluorescence microscopy of virus infection upon treatment of bardoxolone methyl. Virus infection and drug treatment were performed as mentioned above. At 48 h post infection, the infected Vero cells were fixed, and then probed with mouse sera against the SARS-CoV-2 nucleoprotein as the primary antibody and Alexa 488-labeled goat anti-mouse IgG as the secondary antibody, respectively. The nuclei were stained with DAPI dye. Bars, 500 μm.
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Conceptualization: L.L. and Q.S.; experimental studies: Q.S., F.Y., H.L., C.L., R.L., B.H., and L.Z.; docking studies: H.L.; writing: Q.S., H.L., F.Y., and L.L.; supervision: L.L. and W.T.

ADDITIONAL INFORMATION
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