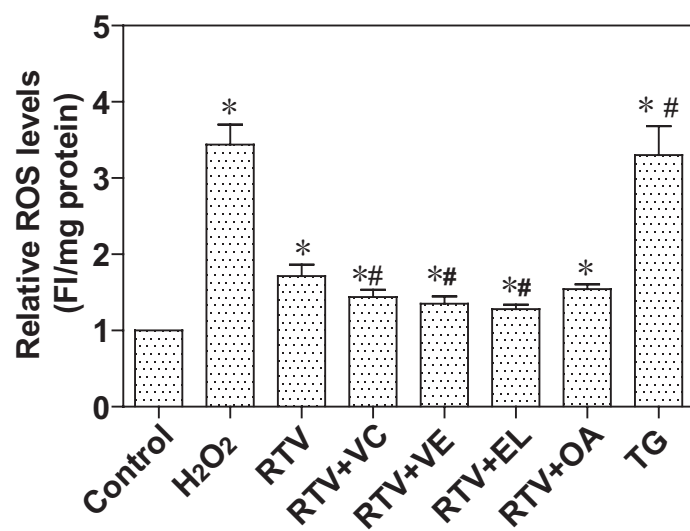
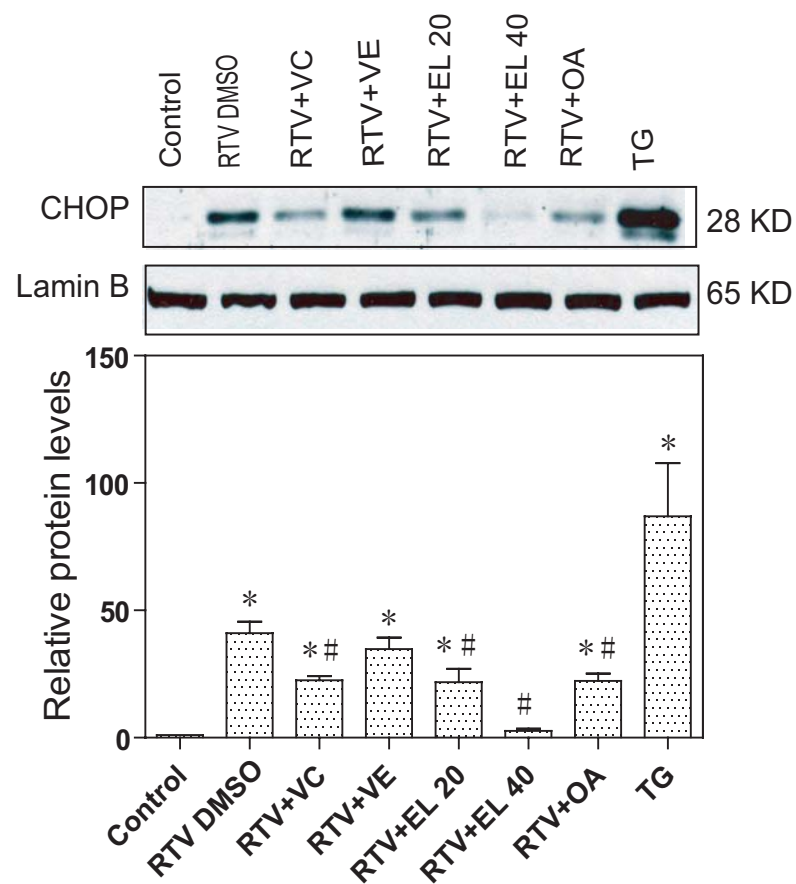


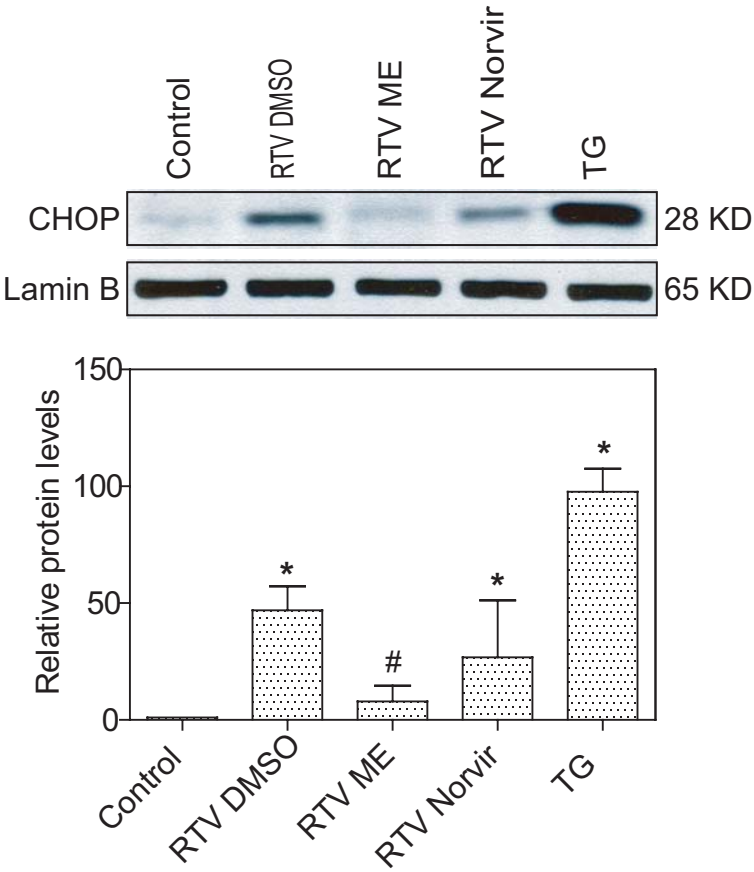
Online Figure 1



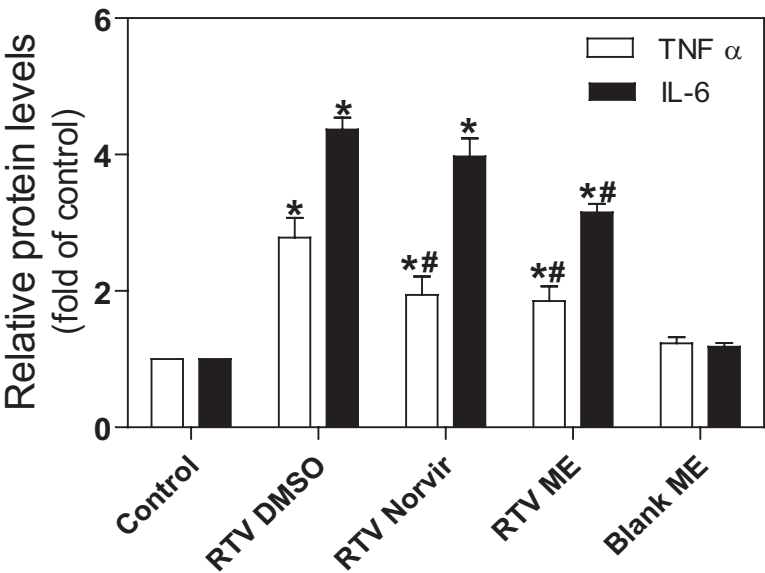
Online Figure 2



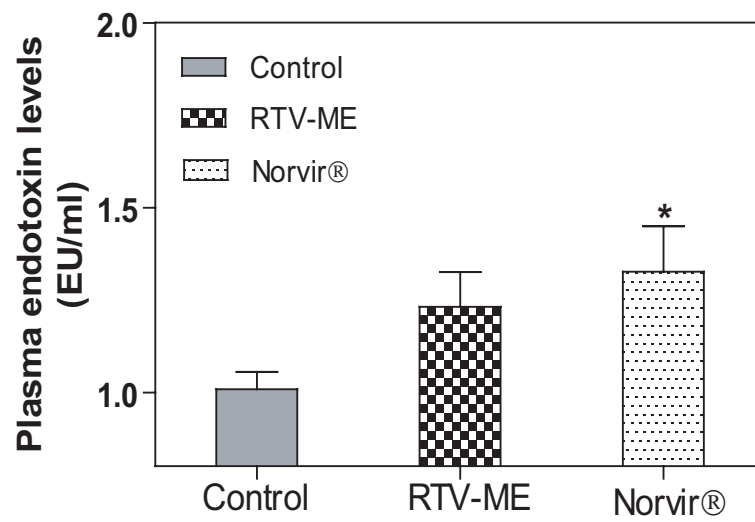
Online Figure 3



Online Figure 4



Online Figure 5



ONLINE SUPPLEMENTAL FIGURE LEGENDS

Figure 1. Effect of antioxidants on ritonavir-induced ROS production in macrophages.

Mouse Raw264.7 cells were treated with vehicle control (DMSO), positive control (H₂O₂, 10 μ M), thapsigargin (TG, a known ER stress inducer, 100 nM), ritonavir (RTV, 15 μ M), RTV with vitamin C (VC 15 μ g/ml) or, vitamin E (VE 20 μ g/ml), or ethyl linoleate (EL, 20 μ g/ml) or oleic acid (OA, 10 μ g/ml) for 4h. The intracellular ROS levels were measured as described in “Methods”. Values are mean \pm SD of 3 independent experiments and analyzed using one-way ANOVA. Statistical significance relative to control, * p < 0.05 or relative to RTV, # p <0.05.

Figure 2. Effect of antioxidants on ritonavir-induced UPR activation in macrophages.

Representative immunoblots against CHOP and lamin B from the nuclear extracts of mouse raw264.7 cells treated with ritonavir (RTV, 15 μ M) in the absence or presence of individual antioxidant, vitamin C (VC 15 μ g/ml) or, vitamin E (VE 20 μ g/ml), or ethyl linoleate (EL, 20 μ g/ml or 40 μ g/ml) or oleic acid (OA, 10 μ g/ml) for 4 h. Lamin B was used as a loading control of nuclear protein. Relative protein levels of CHOP from three independent experiments. Statistical significance relative to control, * p < 0.05 or relative to RTV, # p <0.05.

Figure 3. Effect of ritonavir SMEDDS on UPR activation in macrophages.

Representative immunoblots against CHOP and lamin B from the nuclear extracts of mouse RAW264.7 cells treated with vehicle control (DMSO), ritonavir in DMSO (RTV DMSO, 15 μ M), ritonavir SMEDDS (RTV ME, 15 μ M) or Norvir® (15 μ M), or TG (25 nM) for 4 h. Lamin B was used as a loading control of nuclear protein. Relative protein levels of CHOP from three independent experiments were analyzed. Statistical significance relative to control,

* $p < 0.05$ or relative to RTV DMSO, # $p < 0.05$.

Figure 4. Effect of ritonavir SMEDDS on TNF- α and IL-6 expression in macrophages.

Mouse Raw264.7 cells were treated with 15 μ M of ritonavir in DMSO, ritonavir SMEDDS or Norvir® or the same amount of vehicle control for 24 h. The TNF- α and IL-6 levels in medium were determined by ELISA as described in “Methods”. The total amounts of TNF- α and IL-6 in media were normalized to the total protein amounts of the viable cells. Relative protein levels of TNF- α and IL-6 from three independent experiments were analyzed. Statistical significance relative to control, * $p < 0.05$ or relative to RTV DMSO, # $p < 0.05$.

Figure 5. Effect of ritonavir SMEDDS and Norvir® on gut microbial translocation *in vivo*. Wild type C57BL/6 mice were treated with control solution (PBS), ritonavir SMEDDS (RTV ME) or Norvir® (50 mg/kg) for 4 weeks. The plasma endotoxin levels were determined using LAL Endotoxin Assay Kit (from GeneScript). Statistical significance relative to control (n=5), * $p < 0.05$.