# Resveratrol as a Probable Multiheaded Treatment Approach for COVID-19

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# Resveratrol as a Probable Multiheaded Treatment Approach for COVID-19

Roohollah Ahmadian, Hossein Biganeh, Yunes Panahi, Paul C. Guest, Tannaz Jamialahmadi, and Amirhossein Sahebkar

**Abstract**

The COVID-19 pandemic has plagued the world for more than 1 year now and has resulted in over 77 million cases and 1.7 million related deaths. While we await the rollout of the vaccines, new treatments are urgently needed to reduce the effects of this devastating virus. Here, we describe a number of preclinical studies which show promising effects of the polyphenol resveratrol.

**Keywords**

Resveratrol · COVID-19 · Herbal medicine

## 1 Introduction

SARS-CoV-2, the causative agent of COVID-19 disease, represents one of the leading causes of morbidity and mortality globally and is still spreading rapidly, even 1 year after its first identification in Wuhan, China. As there is no well-established drug therapy, testing of both existing and new compounds to combat this terrible disease has received considerable attention across the world [1]. One such approach is the use of natural products. Medicinal plants and their bioactive ingredients have been used comprehensively to treat human disorders and infections for thousands of years. Some phytochemicals and medicinal plants have been suggested to possess promising effects against COVID-19 disease [2]. Resveratrol (RSV), a senolytic phytoalexin clas-

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sified as a stilbenoid, can be produced by some species of plants after fungal or bacterial infections. Grape and peanut are major sources of RSV [3]. RSV has been shown to have diverse biological activities, which may provide a new means in our struggle with COVID-19 [4]. Herein, we provide an overview on the potential therapeutic effects of RSV against COVID-19 as well as the underlying mechanisms that could explain such protective effects.

## 2 Therapeutic Mechanisms Underlying the Efficacy of RSV in COVID-19

Evidence suggests that RSV could be beneficial in four contributory aspects of COVID-19 viral challenge: (1) protection of lung tissue as the most vulnerable part of the body in SARS-CoV-2 infection, (2) the host immune system response, (3) the coronavirus infectivity cycle, and (4) the ensuing effects of infection on the host.

Treatment with RSV was found to attenuate airflow limitations in several experimental models of respiratory disorders such as asthma and chronic obstructive pulmonary disease (COPD), and it has been investigated extensively in various lung injury conditions [5]. In an animal model of asthma, RSV was shown to reduce mucosal hypersecretion and eosinophilia along with anti-inflammatory effects [6]. Numerous mechanistic reports stated that after SARS-CoV-2 infection and creation of high levels of reactive oxygen species (ROS), extreme inflammation can cause considerable injuries to bronchial epithelial and endothelial cells [7]. In this manner, beneficial effects of RSV were found to be mediated by its antiapoptotic, anti-inflammatory, and antioxidant properties in alveolar spaces [5, 8].

One of the procedures for COVID-19 patients is to provide respiratory support by mechanical ventilation, especially in severe cases. High tidal volume mechanical ventilation by itself is a trigger for inflammation and cytokine release and can cause serious damages to both patients with and without lung disorders [9]. In vivo and in vitro studies carried out by Dong et al. demonstrated that RSV mitigated mitochondrial oxidative damage induced by an increase in the architectural chromatin-binding factor high-mobility group box 1 (HMGB1) induced by high tidal volume mechanical ventilation [10]. In another study on mechanically ventilated mice, despite no change observed in interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α levels by RSV, nuclear factor (NF)-κB DNA-binding activity was inhibited by pretreatment with this polyphenol [11]. Hypoxia-reoxygenation is another pulmonary-related disorder with the major contributing factors of oxidative stress and inflammation. Pretreatment of type II alveolar epithelial cell line with RSV led to reduction in IL-1β and IL-6 levels. In addition, amelioration of the anti-inflammatory factor IL-10 and surfactant proteins was also observed [12].

Viral infection at early stages may spontaneously be halted by the host immune response. Conversely, inappropriate response of the immune system can cause some deleterious and potentially long-term sequelae on different tissues. Due to this, evaluation of the patient's condition is vitally important to ensure the right decisions are made for amplification or attenuation of the immune system. An extreme immune response and its subsequent hyper-inflammation are called the "cytokine storm," phenomena which is an important factor in COVID-19 pathogenesis and severity [7]. Previous studies have shown elevated concentrations of pro-inflammatory cytokines like IL-6, TNF-α, IL-1β, monocyte chemoattractant protein 1 (MCP-1), and granulocyte-macrophage colony-stimulating factor (GM-CSF) in patients infected by SARS-CoV-2 [13]. This oversecretion of pro-inflammatory elements from type II pneumocytes, activated alveolar macrophages, infiltrated neutrophils, and T cells in a destructive cycle can cause acute respiratory distress syndrome (ARDS) and multi-organ failure [7]. In this light, the protective effects of RSV in disorders caused by autoimmune or inflammatory procedures are likely to be due to its anti-inflammatory properties [3]. Numerous in vivo and in vitro investigations have shown anti-inflammatory properties of

RSV to decrease several pro-inflammatory cytokines and modulate related intracellular signaling pathways [3, 14].

Activated neutrophils by neutrophil extracellular trap (NET) formation in this inflamed environment are one of the main factors in alveolar capillary permeation [15]. In an isolated neutrophil model, RSV attenuated neutrophil activities in a dose-dependent manner by inhibiting phosphorylation of Src family kinases [16]. Furthermore, Vargas et al. hypothesized that treatment via RSV could cleave DNA in NETs and improve cell survival [15].

A considerable decrease of the increased IL-1β and IL-18 was confirmed by RSV treatment due to its NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome-attenuating activities [17]. In a cellular context, NLRP3 inflammasome inactivation causes an inhibitory effect on neutrophil infiltration and ARDS progression [7, 17].

The progressive cycle of cytokine and ROS production to activate cells which can generate more ROS and release further chemokines finally ends in uncontrollable systemic inflammation [7]. Cytokine gene expression is predominantly regulated by the NF-κB pathway [5]. Thus, suppressing SARS-CoV-2-induced NF-κB signaling would be a potential strategy to counteract the associated destructive effects. Convergent evidence from cellular and animal experiments suggest that RSV could act as an agent for NF-κB inhibition and modulation [3, 18].

Two of the main pathways for cytokine release after lipopolysaccharide (LPS)-induced lung injury are NF-κB and mitogen-activated protein (MAPK) signaling, although corticosteroid treatment effects are restricted to the NF-κB pathway. On the other hand, evidence has shown that RSV modulates both of these signal transduction pathways [19]. Furthermore, Bhakti et al. [20] showed that RSV can reinforce dexamethasone anti-inflammatory properties in acute lung inflammation by a significant decrease in TNF-α and IL-8 concentrations in comparison to control group. Dexamethasone (2.5 mg/kg) combined with RSV (50 mg/kg) caused a significant reduction in neutrophil counts and lung edema. This combination impeded matrix metallopeptidase 9 (MMP-9) and myeloperoxidase activity as important factors involved in pulmonary neutrophil infiltration [20]. Despite widespread studies on anti-inflammatory activities of RSV, a systematic review and meta-analysis of clinical trials showed a significant decrease in C-reactive protein (CRP) but no significant effects on IL-6 or TNF-α reduction [21].

Studies have reported interruptive properties of RSV in the life cycle of various respiratory viruses [22]. Significant antiviral properties have been observed in influenza, respiratory syncytial, varicella zoster, Epstein-Barr, and herpes simplex virus models by RSV [23]. A recent in vitro study showed that RSV exhibited anti-MERS-CoV activity [24]. Although MERS-CoV is only about 50% similar at the phylogenetic level to SARS-CoV-2 and MERS-CoV entry into host cells occurs via binding to dipeptidyl peptidase (DPP)-4 receptors versus angiotensin-converting enzyme (ACE)-2 receptors in the case of SARS-CoV-2, Lin et al. found that RSV inhibited MERS-CoV at the level of viral replication [22, 24]. Using in silico approach, two studies demonstrated the binding affinity of RSV itself and its derivatives to an RNA-dependent RNA polymerase and papain-like protease which are essential in the virus life cycle [1, 25]. Computational analysis revealed that the RSV dimer, δ-viniferin, inhibited the 3C-like protease and RNA-dependent RNA polymerase enzymes [1]. In addition, a recent computational docking study found that RSV can theoretically bind to the ACE-2 and spike complex, which is essential for viral entry, with superior affinity to chloroquine as positive control [4]. A schematic showing the potential protective mechanisms of RSV in COVID-19 patients is shown in Fig. 1.

Some studies have reported complications related to COVID-19 are thromboembolism and lung tissue fibrosis. A recent retrospective study [26] analyzed chest computed tomography (CT) images of COVID-19 patients and showed that a high prevalence of pulmonary embolism was associated with poor prognosis. Major etiological factors related to pulmonary thromboembolism are ROS production and the cytokine storm

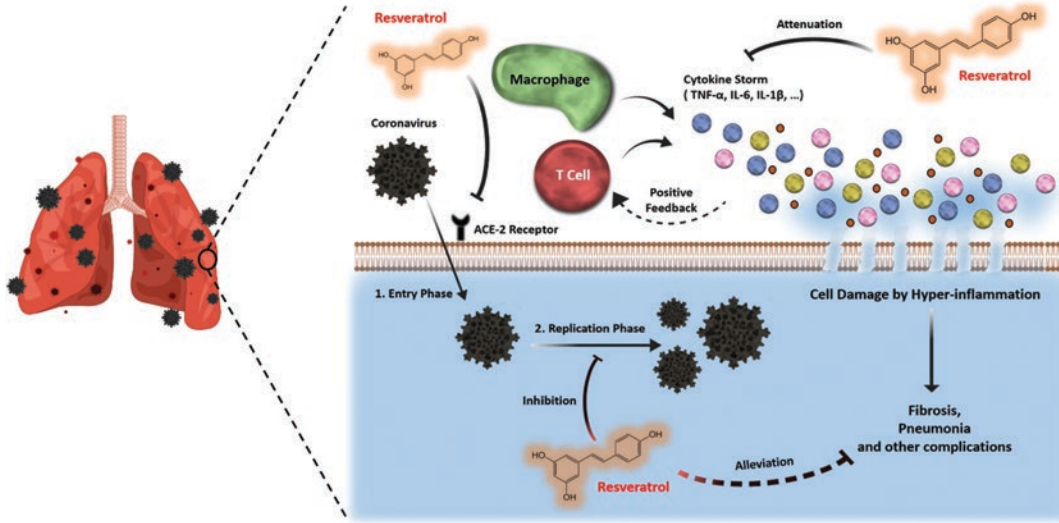


**Fig. 1** Holistic scheme of resveratrol's potential effects against COVID-19

which can activate platelets. The interaction between these activated platelets and neutrophils results in the maintenance of the hyper-inflammatory and pro-coagulant status in the lung tissue [7]. In an animal study, it was shown that intraperitoneal pretreatment with RSV (10 mg/kg) decreased monocyte chemoattractant protein-1 (MCP-1) expression and MAPK phosphorylation in an acute pulmonary thromboembolism-induced pulmonary artery hypertension model [27]. Another study showed that oral administration of a RSV hybrid with furoxan had antithrombic effects in a mouse pulmonary thromboembolism model [28].

Another pathological consequence of infection via SARS-CoV-2 and its subsequent cytokine release syndrome is pulmonary fibrosis. Transforming growth factor-β 1 (TGF-β1) plays a pivotal role in this pathologic status which finally causes gross collagen deposition in lung tissue [29]. In in vivo models of LPS- and bleomycin-induced pulmonary fibrosis, RSV was found to exert its anti-fibrotic properties by TGF-β suppression along with attenuation in the Smad signaling pathway [30, 31].

In ARDS patients, excessive heme may contribute to a pro-inflammatory and pro-fibrotic condition, as found in COVID-19 cases [32]. RSV, via its capacity to increase intracellular heme oxygenase enzymes [33], could be beneficial in attenuating complications related to NLRP3 inflammasome activation, platelet hyperactivity, and hyper-inflammatory syndrome [32].

## 3 Delivery of RSV to the Lung

All of these beneficial effects on pulmonary system and antiviral properties of RSV are dependent on its concentration. Due to RSV poor bioavailability, several nanoparticulate drug delivery systems have been applied to enhance its solubility and potency. In a recent study, beneficial effects of RSV encapsulated in lipid nanoparticles were demonstrated. LPS-induced elevation of inflammatory markers like IL-6, macrophage inflammatory protein-1 alpha (MIP-1α), and MCP-1 was suppressed efficiently. Furthermore, in contrast to RSV alone or empty lipid nanoparticles, RSV loaded in lipid core nanoparticles reduced histological changes and leukocyte gathering in the bronchoalveolar fluid in a mouse model [34].

To provide suitable localized concentrations of antiviral agents for respiratory infections, inhalation-based formulations have been suggested [35]. Therefore, another instrumental strategy for RSV administration to COVID-19 patients is via

a pulmonary drug delivery approach. Co-delivery of RSV and budesonide microparticles via inhalation led to a significant decrease in TNF-α and IL-6 levels in rat alveolar macrophage cells [19]. Using a vibrational atomization spray-drying method, polymeric microparticles of RSV were prepared to achieve deep lung displacement for pulmonary arterial hypertension by Dimer et al. [36]. In an in vitro study, an inhalable dry powder of RSV significantly inhibited IL-8 expression in the Calu-3 lung epithelial cell line [37]. Generally, nanoformulations and respirable forms of RSV could provide better stability and bioavailability properties for patients with active respiratory infection and inflammation.

## 4 Conclusion

In conclusion, what we know about RSV in this field is largely based upon cellular, animal, and computational studies that investigated how it could be beneficial. However, the findings taken together suggest that RSV may provide a novel treatment strategy to reduce the effects of the devastating SARS-CoV-2 virus at the level of individual patients and on societies worldwide. These findings warrant the testing of RSV in further preclinical and clinical studies of COVID-19 and other pathogens.

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