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Resveratrol; an inflammasome inhibitor and a potential therapy for severe cases of COVID-19

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 126 million people worldwide and deaths exceed two million. Virological features of SARS-CoV-2, including its genomic sequence, have been identified but the mechanisms governing coronavirus disease 2019 (COVID-19) immunopathogenesis have remained uncertain. Severe COVID-19 is associated with a cytokine storm, chronic inflammation, neutrophilia, lymphocyte dysfunction, lymphopenia, reduction in T-lymphocytes and natural killer (NK) cells, disruption in viral clearance, and neutrophil/macrophage infiltration in the lungs. In many cases, patients develop acute lung injury (ALI), acute respiratory distress syndrome (ARDS), and/or multiple-organ dysfunction syndrome (MODS). Resveratrol reduces the expression of inflammasome activators such as thioredoxin-interacting protein (TXNIP) and nuclear factor erythroid 2 (NrF2) and increases that of the inflammasome inhibitor, i.e., NAD-dependent deacetylase sirtuin-1 (SIRT1). Resveratrol is able to inhibit the production of reactive oxygen species (ROS) and the activation of inducible nitric oxide synthases (iNOS). It affects signaling pathways including mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-κB) thereby further inhibiting inflammasomes. Because of its anti-inflammasome, anti-inflammatory, and anti-oxidant effects and considering the key role of inflammation and cytokine storm in disease severity and poor patient outcomes, it is concluded that resveratrol can be useful in the treatment of COVID-19. Given the persistence of the COVID-19 pandemic and the challenges of extensive vaccination in all countries, it is important to achieve more effective treatments to decrease the mortality rate and severity of severe injuries following COVID-19. Given all the effects reviewed in this article, resveratrol at a dose of up to 600 mg per day can be exploited as a potential adjunctive therapy for COVID-19 patients.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to the family of beta-coronaviruses, which induce acute respiratory syndrome (SARS) in the lower respiratory tract. Severe inflammation is a leading cause of mortality. The occurrence of a phenomenon called cytokine storm, along with acute respiratory distress syndrome (ARDS) and acute lung injury (ALI), are the main pathological complications in COVID-19 patients (1). Inflammasomes are molecular platforms, activated by infection or stress, to trigger the maturation of pro-inflammatory cytokines to engage innate immune defenses. Recently developed therapeutics target inflammasome activity in inflammatory diseases but the role of inflammasomes in the current COVID-19 crisis is ill-defined and the potential use of anti-inflammasome agents is not being avidly pursued. Structural models of mature peptides of SARS-CoV-2 show that the pathogen contains all the inflammasome-activating proteins (2). Resveratrol, a member of the family of polyphenols, called viniferine, is found in plants such as eucalyptus, iris, blackberries, peanuts, and grapes (3). Resveratrol is an antioxidant proven to be beneficial in some diseases (4). This review summarizes the diverse effects of resveratrol with a focus on inhibition of inflammasomes and suppression of inflammation under a variety of pathological conditions.

Key point

Our review study showed, resveratrol at a dose of up to 600 mg per day might be exploited as a potential adjunctive therapy for COVID-19 patients.

Anti-inflammatory effect of resveratrol

Resveratrol is able to inhibit cyclooxygenases,

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which also prevents the production of pro-inflammatory molecules by macrophages and inhibiting the expression of pro-inflammatory cytokines such as interleukin 6 (IL-6) and C-reactive protein (CRP). Moreover, resveratrol might also neutralize the formation of secondary inflammatory products such as reactive oxygen species (ROS) and other oxidative ones in a host (5). Besides, it was shown that resveratrol causes inducible nitric oxide synthases (iNOS) expression; thereby, it can be said that it has anti-hypertensive effects. This compound can further inhibit NF-κB by reducing H_2O_2 production, as well as inhibiting IkB kinase (IKK) and inhibiting phosphorylation or deacetylation of transcription factor p65 (6). However, some previous studies have suggested that the role of resveratrol might be mediated by other metabolic pathways including the stimulatory effect of resveratrol on adiponectin secretion (7). Adiponectin and leptin are among the hormones that have been confirmed to play significant roles in exacerbating metabolic inflammation. In addition, resveratrol can prevent obesity through the inhibition of the increased central leptin resistance. However, one of the salient features of resveratrol is its inhibitory role in inflammasomes.

Effect of resveratrol on inflammasome in lung diseases

Resveratrol has several anti-inflammatory properties in many lung diseases (8). As reported earlier, nickel is a common environmental pollutant that can disrupt the lungs. Furthermore, this chemical element can increase the expression of inflammatory cytokines including IL-1β, TNF-α, IL-6, and IL-8. In addition, it was shown to activate p38 mitogen-activated protein kinase (MAPK), NF-κB, and NLR family pyrin domain containing 3 (NLRP3), while resveratrol can reverse these effects (9). Correspondingly, the inhalation of suspended fine particulate matter (PM2.5) can cause pneumonia and fibrosis. Besides, PM2.5 exposure activates autophagy and NLRP3 inflammasome in lungs. Therefore, the treatment with resveratrol can inhibit the PM-induced pneumonia and fibrosis, suppress autophagy, and activate NLRP3 inflammasome (10). Additionally, resveratrol reduces the prevalence of pneumonia caused by *Staphylococcus aureus* by inhibiting NLRP3 inflammasome. It can significantly minimize mortality resulted from *S. aureus* in rats as well as the lower levels of cytokines in rats infected by *S. aureus* (11). Accordingly, resveratrol therapy can moderate the pathological damage of lungs and pulmonary edema, as well as moderating neutrophil infiltration caused by lipopolysaccharides (LPS). Furthermore, resveratrol reverses the increased IL-1β and IL-18 caused by LPS in bronchoalveolar lavage fluids. Therefore, its injection not only suppresses NF-κB (p65) nuclear translocation, NF-κB activity, and ROS production in the LPS-exposed rats, but it also inhibits thioredoxin-interacting protein (TXNIP) expression and TXNIP-NLRP3 interaction in the lung tissues. At the same time, resveratrol augments NAD-dependent deacetylase sirtuin-1 (SIRT1) in LPS-exposed rats (12).

The effect of resveratrol on inflammasome in cardiovascular diseases

Resveratrol downgrades vascular inflammation by inhibiting the inflammasome activation in vitamin D2-treated rats with hypercholesterolemia. In the present study, the administration of resveratrol in rats reduced their vascular histopathological changes, von Willebrand factor levels, and serum IL-1β levels. It also lowered the expression levels of mRNA and the proteins of NLRP3 inflammasome, caspase-1, and apoptosis-associated speck-like a protein containing CARD (ASC) (13). A study had previously evaluated the effect of resveratrol modulation on the inflammatory responses caused by myocardial ischemia and reperfusion (I/R) in rats. By administrating resveratrol with different concentrations, the pathology and morphology had significantly improved. In addition, resveratrol had decreased both mRNA and protein levels of NLRP3 and CASP-1 and had significantly modulated IL-1β and IL-18 activations as well (14). This compound has also protected the body against chronic intermittent hypoxia (CIH)-induced myocardial injury by targeting nuclear factor erythroid 2 (NrF2) as well as blocking NLRP3 inflammasome activation. Moreover, CIH-impaired cardiac structure and function along with the increased oxidative stress, endoplasmic reticulum (ER) stress, and NLRP3 induction in the heart had been evaluated. Accordingly, these effects had been attenuated following the administration of resveratrol (15). It was indicated that resveratrol could prevent cardiac injury induced by pulmonary embolism (PE), and reduce PE-induced cardiac injury by suppressing the inflammasome activation (16).

The effect of resveratrol on inflammasome in brain injuries

Resveratrol was found to reduce brain injury I/R in rats by the inhibition of the NLRP3 inflammasome activation and the induction of SIRT1-dependent autophagy. Brain injury following I/R could increase the activities of NLRP3 inflammasome, CASP-1, IL-1β, and IL-18. Thereafter, in this study, the treatment with resveratrol had further minimized I/R injury by NLRP3 inflammasome activity and also increased autophagy. (17). Furthermore, it was demonstrated that resveratrol protects the brain against sepsis-associated encephalopathy (SAE), which is known as cerebral dysfunction associated with sepsis (18), and inhibits NLRP3/IL-1β axis in microglia. Correspondingly, the given compound can also inhibit early brain injury (EBI) after experimental subarachnoid hemorrhage (SAH) via the inhibition of the NLRP3 inflammasome activation. Moreover, resveratrol has some beneficial effects on traumatic brain injury (TBI) and SAH (18). In this regard, a study has investigated the neuroprotective

effects of resveratrol and the basic mechanisms associated with the control effect of this compound, on NLRP3 inflammasome in TBI. It was also shown that resveratrol pre-treatment could prevent the activations of NLRP3 and CASP-1 and also reduce the productions of inflammatory cytokines and ROS. Ischemic injury increases the TXNIP expression in rats as well. On the other hand, resveratrol prevents TXNIP expression and protects the brain from ischemic injury (19).

The effect of resveratrol on inflammasome in kidney failure

Resveratrol-loaded nanoparticles (Res-NPs) conjugated with anti-kidney injury molecule (KIM-1) antibodies are exploited as a potential drug delivery system during chronic kidney disease (CKD). Therefore, the anti-KIM-1 antibodies have been linked to Res-NPs and then analyzed for their safety and efficacy. Res-NPs have a low toxicity, which also induces autophagy. Hence, they may also be considered as a solution to prevent CKD through the attenuation of NLRP3 inflammasome and the induction of autophagy (20). In this regard, the injection of resveratrol can reduce glomerular proliferation, glomerulosclerosis, and glomerulonephritis in a rat model of progressive immunoglobulin A (IgA) nephropathy. These findings are associated with the decreased renal mononuclear leukocyte infiltration, the lowered renal superoxide anion levels, and the inhibited renal NLRP3 inflammasome activation (21). Accordingly, a study had previously evaluated the protective effect of resveratrol on the rat model of contrast-induced nephropathy (CIN). In this study, the resveratrol treatment had further reduced both injury and apoptosis processes and also inhibited inflammasome pathway in the CIN rat model (22). As it was observed, resveratrol can inhibit TXNIP binding to NLRP3 in diabetic rats exposed to renal I/R injury. Under the conditions of hyperglycemia and exposure to hypoxia-reoxygenation (H/R) for one time, human kidney 2 (HK-2) cells can also lead to the stimulation of TXNIP expression with the increased NLRP3 expression, as well as the higher productions of ROS, CASP-1, and IL-1β, and the exacerbation of HK-2 cell apoptosis. Correspondingly, all these changes can be moderated with resveratrol treatment (23).

The effect of resveratrol on inflammasome in liver failure

The liver is one of the organs that seems to be damaged by unbridled inflammation caused by SARS-CoV-2 (24). In a study, pro-inflammatory markers had been assessed in the liver of aged male rats and the effect of resveratrol on these inflammatory markers was then evaluated. As a result, resveratrol had reduced IL-1β and TNF-α levels in these aged rats. The mRNA levels of NALP-3, ASC, CASP-1, COX-2, and NALP-1 had further displayed an age-dependent increase that was reversed by resveratrol (25). Resveratrol also regulates NAD bioavailability and SIRT1-related metabolism, which are associated with aging, metabolic syndrome, and non-alcoholic fatty liver diseases. In another study, glucose control had been disrupted and subsequently, serum and liver triglyceride (TG) levels had augmented after four weeks of the treatment with resveratrol in high-fat-diet rat models. Thereafter, resveratrol injections had significantly improved glucose control as well as TG contents of the serum and the liver. These improvements had been accompanied by some changes in SIRT1 and NLRP3 pathways (26).

Other studies on the effect of resveratrol on inflammasome

Psoriasis is a chronic immune-mediated inflammatory disease of the skin. Although the activation of absent in melanoma 2 (AIM2) inflammasome is important for immune defense, it can lead to some inflammatory and autoimmune diseases like psoriasis. Consequently, the EFLA®945 containing resveratrol can limit the activation of AIM2 inflammasome. In a rat model, the EFLA®945 had reduced inflammatory responses caused by psoriasis, including CASP-1 activation, IL-1β secretion, and IL-17 production (27). The IL-1β production following the NLRP3 activation due to the monocyte/macrophage treatment with monosodium urate (MSU) was also shown to be responsible for the pathogenesis of gouty arthritis. In a rat model, resveratrol had further reduced recurrent attacks of MSU-induced arthritis. The given compound had similarly suppressed IL-1β secretion by primary human monocytes stimulated with MSU crystals (28). In this regard, a previous study had investigated the potential impact of SIRT1 on the radiation-induced IL-1β expression in mesenchymal stem cells (MSCs). Accordingly, radiation had significantly increased IL-1β mRNA and protein levels, and pre-treatment with resveratrol, as a SIRT1 activator, had also inhibited the radiation-induced IL-1β expression in a dose-dependent manner (29). Moreover, the effects of metformin and resveratrol on ROS production, mitochondrial fission, ER stress, TXNIP/NLRP3 activation, inflammation, and apoptosis had been also investigated in high glucose-exposed adipose tissues. It was found that metformin and resveratrol could protect mitochondrial fission by the inhibition of the dynamin-like protein 1 activity as well as the prevention of the NLRP3 inflammasome activation (30). Resveratrol can also inhibit the accumulation of acetylated α-tubulin due to causing mitochondrial damage in macrophages resulted from the NLRP3 activation, and prevent their subsequent exposures to ER, which can consequently lead to the insufficient accumulation of ASC in mitochondria and NLRP3 in ER (31). A study examined the role of pyrophosphate crystals and resveratrol in the inflammatory process produced by MSU and calcium pyrophosphate. As a result, cell treatment was effective on reducing IL-1β mRNA expression, while it had no effect on NLRP3 gene expression (32). Another study had further evaluated the

effect of dialysis solutions containing high glucose on mitochondrial ROS and NLRP3 activations in human polymorphonuclear cells. In this regard, the exposure of polymorphonuclear cells to dialysis solutions led to ROS production, which could subsequently activate NLRP3 and then result in IL-1B secretion. It had also induced mitophagy/autophagy, and then the resveratrol treatment had weakened this effect (33). In intestinal ischemia-reperfusion (IIR) injury, pre-treatment with resveratrol can reduce the activation of mast cells (MCs) and NLRP3 inflammasome. Consequently, it can suppress IIR injury by stabilizing MC and inhibiting their degranulation, as observed along with the inhibition of inflammatory bowel disease (IBD), the decreased NLRP3, and intestinal epithelial cell (EC) apoptosis (34). Table 1 shows different effects of resveratrol on different pathological conditions.

Conclusion

COVID-19 in comorbidity with multi-organ failure can cause disorders in various organs and systems of the body such as lungs, heart, liver, kidneys, blood circulation and neural network. Some of the extra-pulmonary presentations caused by COVID-19 infection include blood agglutination, loss of smell and taste, conjunctivitis, hepatic failure, acute renal failure, rashes and acute encephalitis, which are attributed to SARS-CoV-2. There are multiple causes for death from COVID-19, the most important of which is spread of infection to different organs such as RBC (thromboembolism), immune cell, gastrointestinal tract, endothelium, brain, kidney, liver and heart via the angiotensin converting enzyme 2 receptor, depending on the viral load. The present study was conducted to fight against the inflammation by impeding the inflammasomes

Table 1. Direct/indirect effects of resveratrol on inflammation and various other diseases

Diseases	Model	Outcome	Mechanisms	Ref
Traumatic brain injury	Rat	TBI and inflammatory response might be reduced by RSV through an inhibition in NLRP3 activation and a decrease in ROS formation	SIRT1-dependent manner may be suggested in the RSV impact on ROS formation and NLRP3 inflammasome	(35)
Intestinal ischemia-reperfusion	Rat	IIR injury was improved by RSV	Prevention of mast cell degranulation and their stabilization, resulting in the inhibition of NLRP3 inflammasome and induction of apoptosis	(34)
Early brain injury	Rat	EBI could be controlled by RSV	An inhibition in NLRP3 inflammasome signaling	(18)
Hepatic metaflammation	Male C57BL/6 J	Pro-inflammatory markers were decreased by RSV	A change in the activation of NLRP3 inflammasome and SIRT1 pathway	(26)
Ischemic acute kidney injury in diabetes	Rat HK-2 cells	The formation of IL-18 and IL-1β and the expression level of cleaved caspase-1 were dropped and TXNIP-NLRP3 binding was inhibited significantly following the administration of RSV	The activation of NLRP3 mediated by TXNIP via oxidative stress	(23)
Pneumonia *Staphylococcus aureus*	Murine model	The risk of pneumonia caused by S. aureus in mice was reduced significantly by RSV	The NLRP3 inflammasome inhibition	(11)
Peritoneal inflammatory injury	Peritoneal mesothelial cells	Autophagy/mitophagy was induced by RSV through the activation of AMPK signaling pathway	The activation of NLRP3 inflammasome via mitochondrial ROS	(33)
Liver	Old male C57BL/6J	The meta-inflammation in the liver was attenuated by RSV in old mice	Reversing the COX-2 and NALP-3 inflammasome components	(25)
Chronic intermittent hypoxia	Rat	RSV can inhibit mTNA/TTP/ NLRP3 mRNA signaling by activating AMPK.	Impeding the activation of NLRP3 inflammasome and targeting Nrf2	(15)
Sepsis-associated encephalopathy	Mice BV2 cell lines	The spatial memory recovery by RSV in SAE-induced mice	Blocking NLRP3/IL-1β axis present in microglia	(36)
Monocytic cell line	THP-1	The crystal-induced inflammation was impeded by PD and RSV	The inhibition of NO and ROS formation and the reduction of IL-1 mRNA expression	(32)
Spinal cord injury	Rats BV2 microglia	Neuroprotective potential was observed for polydatin in the induced SCI rats	Blocking the production of iNOS and the activation of NLRP3 inflammasome in the microglia	(37)
CKD	Murine model	CKD might be controlled by RSV-loaded NPs	Reduction of NLRP3 inflammasome and induction of autophagy	(20)
Toxicity of nickel	BEAS-2B	Ni-induced cytotoxicity on BEAS-2B cells can be prevented by RSV	The inhibition of NLRP3 inflammasome activation and NF-kB and p38 MAPK signaling	(9)
Progressive IgA nephropathy	Mouse, J774A.1	NLRP3 inflammasome was inactivated by RSV	The establishment of mitochondrial integrity and by the enhancement of autophagy	(21)

Table 1. Continued

Diseases	Model	Outcome	Mechanisms	Ref
Contrast-induced nephropathy	Rat model	Apoptosis and injury processes were reduced by RSV	Blocking inflammasome activation in rat model of CIN	(22)
Nephrotoxicity	HK-2 cells	The Cd-mediated activation of NRLP3 inflammasome and its pyroptosis and the IRE-1alpha/XBP-1s pathway was inhibited	The mediation of deacetylating XBP-1s to preserve SIRT1 activity versus pyroptosis induced by Cd	(38)
Gouty arthritis	Murine model	MSU-induced peritonitis was improved by RSV in mice	The mediation of p38 and Syk to influence adversely pro-IL-1β formation, as well as the inhibition of ASC oligomerization.	(28)
Vascular injury	Rat	A therapeutic activity was found for RSV against the vascular injury	Impeding the activation of inflammasome	(13)
Lung inflammation and fibrosis	C57BL/6J mice BEAS-2B cells	Fibrosis and inflammation of lung were improved by RSV.	Impeding the activation of NLRP3 inflammasome related to autophagy	(10)
Myocardial ischemia/ reperfusion	Rat	RSV exhibited cardio-protective activity to reduce the inflammation	Impeding the NLRP-3 inflammasome activation	(14)
Radiation injury	MSCs	The inflammation induced by ionizing irradiation was impeded by RSV in MSCs.	The induction of SIRT1 and the restriction of NLRP-3 inflammasome	(29)
Cerebral ischemia/ reperfusion (I/R)	Rat	Cerebral I/R damage was improved by RSV	The activity of SIRT1-dependent autophagy caused an inhibition in NLRP3 inflammasome activation	(17)
Human acute monocytic leukemia	THP-1 cells	Anti-inflammatory potentials were seen for cis-RSV, in accompanied with related pathways in human macrophages	The inhibition of non-canonical and canonical inflammasomes	(39)
Acute lung injury	Mice	Lung injury induced by LPS was inhibited by RSV	Prevention of NLRP3 inflammasome	(12)

observed in different disorders, such as pulmonary edema, fibrosis, pneumonia, cardiac damage, chronic intermittent hypoxia, myocardial ischemia and reperfusion, TBI, SAH, EBI, SAE, CIN, CKD, IBD, IIR, psoriasis and liver failure. Findings can be useful in the COVID-19 epidemic to reach several effective food supplements, anti-coronavirus treatments and therapeutic adjuncts. Moreover, we found that resveratrol can influence and inhibit the hyper-activation of diverse inflammasome regulators, such as ASC, p38, Syk, Nrf2, TXNIP and SIRT1. The resveratrol can employ various pathways, in particular the inhibition of NLRP3 inflammasome, to improve the conditions, such as inhibited ionizing irradiation, fibrosis, abolished lung inflammation, spatial memory, meta-inflammation, pneumonia, lung inflammation, sepsis-related encephalopathy, IBD, IIR and psoriasis. It can be claimed that resveratrol is a promising candidate to manage the severe form of COVID-19 infection. However, there is further need for clinical trials to reach a definitive conclusion in this area. Given the persistence of the COVID-19 pandemic and the challenges of widespread vaccination in all countries, it is essential to achieve more effective treatments to reduce the mortality rate and severity of severe injuries following COVID-19. Given all the effects reviewed in this article, resveratrol at a dose of up to 600 mg per day can be exploited as a potential adjunctive therapy for COVID-19 patients.

Authors' contribution

AA, ASB and MMS were the principal investigators of the study. SHH, AKH, STG and MMS were included in preparing the concept and design. MMS, ASB and AA revised the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. Authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. This article does not contain any studies with human participants or animals performed by any of the authors.

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