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MINIREVIEW

Potential therapeutic effects of Resveratrol against SARS-CoV-2

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Summary. – Novel Coronavirus COVID-19 or Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as well as Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), are human pathogens. Current pandemics of SARS-CoV-2 represents a major health problem worldwide, with over four million cases and more than 300,000 deaths in the world. Development of effective therapy thus became an emergency. This report aims to highlight Resveratrol as possible therapeutic candidate in SARS-CoV-2 infection. The antiviral efficacy of Resveratrol was demonstrated for several viruses, including coronavirus. Resveratrol was shown to mitigate the major pathways involved in the pathogenesis of SARS-CoV-2, including regulation of the renin-angiotensin system (RAS) and expression of angiotensin-converting enzyme 2 (ACE2), stimulation of immune system and downregulation of pro-inflammatory cytokines release. It was also reported to promote SIRT1 and p53 signaling pathways and increase cytotoxic T lymphocytes (CTLs) and natural killer (NK) immune cells. In addition, Resveratrol was demonstrated to be a stimulator of fetal hemoglobin and a potent antioxidant, by trapping reactive oxygen species (ROS). According to these reports, Resveratrol could be proposed as potential therapeutics in the treatment of SARS-CoV-2.

Keywords: SARS-CoV-2; Resveratrol; antiviral activity; immune response; ACE2; oxidative stress; HbF

Introduction

SARS-CoV-2 is a novel coronavirus, which appeared firstly in Wuhan, China, in December 2019 (Zhu *et al*., 2020). The World Health Organization (WHO) reported on 24 May 2020 five million cases of SARS-CoV-2 infection and more than 300,000 deaths worldwide (WHO). This virus causes high fever, dry cough, headache, muscle pain and pneumonia leading to acute respiratory distress syndrome (ARDS). SARS-CoV-2 is covered with spike surface glycoprotein, which binds to host cells via the receptor angiotensin-converting enzyme 2 (ACE2). Attachment of SARS-CoV-2 to ACE2 would induce a decrease in ACE2 activity, resulting in inflammatory damages and severe form of the disease (Lan *et al*., 2020).

SARS-CoV-2 infection induces aggressive inflammation initiated by functional exhaustion of immune system with reduction of total number of NK and CD8+ T cells and increased serum levels of pro-inflammatory cytokines (Cao, 2020). It was also demonstrated to be responsible for oxidative stress by causing consumption of nicotinamide adenine dinucleotide (NAD) and accumulation of reactive oxygen species (ROS), which induce pro-inflammatory response (Kouhpayeh *et al*., 2020). Moreover, SARS-CoV-2

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Abbreviations: ACE2 = angiotensin-converting enzyme-2; CTLs = cytotoxic T lymphocytes; HbF = fetal hemoglobin; MERS-CoV = Middle-East respiratory syndrome virus; NAD = nicotinamide adenine dinucleotide; NK cells = natural killer cells; RAS = renin–angiotensin system; ROS = reactive oxygen species; SARS-CoV = Severe acute respiratory syndrome coronavirus; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; SIRT1 = sirtuin 1

was reported to attack the heme on the 1-beta chain of hemoglobin, leading to the deterioration of porphyrin. The transport of oxygen and carbon dioxide is thus damaged, resulting in accumulation of poisonous metabolites and development of inflammation in the lung cells (Wenzhong *et al*., 2020).

Resveratrol (3,4,5-trihydroxy-trans-stilbene) is natural compound belonging to the family of stilbene. This polyphenol is produced in various plants, especially in grapes (*Vitis vinifera* L.), berries, peanuts, as an antibiotic in response to various stimuli such as stress (Berman *et al*., 2017).

Resveratrol has been the subject of more than 4,000 studies for its anti-aging, anti-oxidant, anti-inflammatory, anti-viral and cardio-protecting properties (Malaguarnera, 2019) and has been currently tested in clinical trial as potential anticancer treatment (Ko *et al*., 2017). This report aims to highlight the antiviral and potential therapeutic effect of Resveratrol against SARS-CoV-2.

Resveratrol was described as potent antiviral compound against influenza virus, enterovirus (Campagna *et al*., 2010) and two species of *Coronavirus:* Severe acute respiratory syndrome virus (SARS-CoV) and Middle-East respiratory syndrome virus (MERS-CoV) (Lin *et al*., 2017). Its antiviral- properties would reside in NF-κB inhibition (Holmes-McNary *et al*., 2000) and activation of both SIRT1 and p53 signaling pathways (Shih *et al*., 2002). Interestingly, Resveratrol was also found to stimulate immune system by activation of CD8+ T lymphocytes and NK cells, and regulation of CD4+ suppressive T cells (Svajger *et al*., 2012). This stimulation is mainly related to anti-oxidative and anti-inflammatory properties of Resveratrol (Berman *et al*., 2017). In addition, Resveratrol could play an important role in regulation of the renin-angiotensin system (RAS) and activation of ACE2 (Moran *et al*., 2017).

On the other hand, Resveratrol could stimulate the expression of γ-globin genes and the production of fetal hemoglobin (HbF) in erythroid precursors, leading to increased capacity of hemoglobin to transport oxygen in erythrocytes (Fibach *et al*., 2012).

Given the urgency to find preventive or curative treatment strategy for SARS-CoV-2 in order to limit the spread of the virus, we attempt in this report to summarize the different molecular mechanisms involved in antiviral activities of Resveratrol and highlight its potential therapeutic effects against SARS-CoV-2.

Antiviral and anti-inflammatory properties of Resveratrol

Currently, the SARS-CoV-2 pandemic has still no effective remedial drugs or vaccine available. Resveratrol has been shown to affect a wide variety of viruses *in vitro* and *in vivo*, including influenza virus (Palamara *et al*., 2005), herpes simplex virus (HSV) (Docherty *et al*., 1999), as well as enterovirus (Wang *et al*., 2004). Interestingly, a strong antiviral activity of Resveratrol has been demonstrated against the coronaviruses SARS-CoV (Li *et al*., 2006) and MERS-CoV (Lin *et al*., 2017). The possible antiviral mechanism of Resveratrol seems not to lie in particle inactivation but in the decrease of the translation of late viral proteins (Yusuf *et al*., 2015). Resveratrol was shown to reduce the inflammation caused by MERS-CoV infection by inhibiting the NF-κB pathway and regulating the production of pro-inflammatory cytokines (Jakus *et al*., 2013). On the other hand, Resveratrol has been reported to stimulate the activation of p53-mediated apoptosis (Lin *et al*., 2002) and promote SIRT1 signaling (Chao *et al*., 2017), two pathways playing a key role in the antiviral activity.

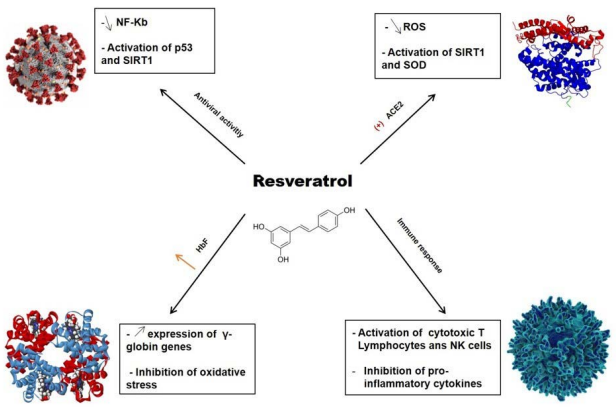

Fig. 1

The major pathways affected by Resveratrol
Antiviral activity, (2) Stimulation of immune system, (3) Activation of ACE2, (4) Production of fetal hemoglobin (Towler, P. *et al*., J. Biol. Chem. 279, 17996–18007, 2004; Modélisation en 3D du coronavirus SARS-CoV-2. Wikipedia; Haemoglobin-3D-ribbons.Wikipedia; K45300522 www.fotosearch.com).

Resveratrol regulates immune system

SARS-CoV-2 viral infection is regulated by the immune system, in particular by cytotoxic T lymphocytes (CTLs) and NK cells (Zheng *et al*., 2020). Uncontrolled immune responses and reduction of CTLs and NK were correlated with disease progression. Recent study demonstrated that upregulation of NKG2A expression on NK cells and CTLs in most patients infected with SARS-CoV-2 leads to increased release of pro-inflammatory cytokines (Fu *et al*., 2020). Pro-inflammatory cytokines such as IL-1β, IFN-γ, IL-6, and TNF-α are important mediators of inflammation

and their stimulation is associated with lung inflammation observed in SARS-CoV-2 infection (Conti *et al*., 2020), Interestingly, several *in-vitro*, preclinical and clinical studies were performed to prove very effective properties of Resveratrol against harmful pro-inflammatory cytokine accumulation (Rafe *et al*., 2019). Indeed, Resveratrol proved to play an important role in the regulation of immune response and demonstrated strong inhibitory effect on the pro-inflammatory cytokines as IFN-γ, TNF-α and IL-1β, (Zang *et al*., 2011; Limagne, 2016). Resveratrol was also shown to modulate immune system function by increasing the cytotoxic activity of both CTLs and NK cells, resulting in attenuation of inflammatory responses (Falchetti *et al*., 2001).

Resveratrol regulates the renin-angiotensin system and enhances ACE2 function

Recent studies demonstrated the important role of RAS signaling pathway and particularly ACE2 receptor in the entry of SARS-CoV-2 (Hoffmann *et al*., 2020). ACE2 is expressed in various organs such as the heart, the kidneys, blood vessels and lungs and it function is to convert angiotensin II (which is the main effector molecule responsible for pro-inflammatory activity in the vascular wall) in angiotensin 1–7 (Patel *et al.,* 2016). This latter compound has opposite activity to angiotensin II (Moriguchi *et al*., 1995). Consequently, the fixation of SARS-CoV-2 in ACE2 receptor results in reduction of ACE2 activity, leading to dysfunction of the RAS and excessive production of pro-inflammatory and pro-oxidant agents causing acute lung injury (Kuba *et al*., 2006). Resveratrol is known to have many beneficial cardiovascular properties mainly through activation of the sirtuin 1 (SIRT1) (Zordoky *et al*., 2015). Involved in several cellular processes, SIRT1 plays a protective role in stress response, inflammation and apoptosis regulation (Alcendor *et al*., 2007). In addition, previous studies demonstrated that activation of SIRT1 and Superoxide Dismutase (SOD) by Resveratrol was associated with increase of ACE2 function and decrease of key markers of inflammation (Clarke *et al*., 2014; Moran *et al*., 2017). Therefore, the upregulation of ACE2 by Resveratrol could play an important role in SARS-CoV-2 infection and prevent severe form of the disease.

Antioxidant activity of Resveratrol

Infection with SARS-CoV-2 results in production of ROS, which induce oxidative stress, resulting in reduction of antioxidant defense and release of pro-inflammatory cytokines (Roche *et al*., 2020). Depletion of NAD leads also to inhibition of protective protein SIRT1, inducing alteration of immune cell system and accumulation of ROS (Kume *et al*., 2007). Worsening of oxidative stress results in destructive effects on lipids, proteins and nucleic acids, triggers of a number of human diseases (Rada *et al*., 2008). Previous reports demonstrated the antioxidant potential and the protective properties of Resveratrol against oxidative stress and aging. Indeed, Resveratrol was demonstrated to scavenge the ROS and increase the expression of antioxidant proteins such as SIRT1. Activation of SIRT1 increases NAD levels and improves mitochondrial function, resulting in regulation of inflammatory diseases and dysfunctional physiological processes (Leonard *et al*., 2003).

Resveratrol stimulates HbF production

More recently it was reported that ORF1ab, ORF10, and ORF3a proteins of SARS-CoV-2 have the ability to attack hemoglobin's heme (Wenzhong *et al*., 2020), causing destruction of porphyrin and inability of erythrocytes to capture and distribute oxygen effectively (Chowdhury *et al*., 2017). As reported in experimental animal models and clinical studies in thalassemia patients, Resveratrol enhances the expression of γ-globin genes and could be a potent antioxidant and HbF stimulator, leading to improvement of oxygen-binding capacity of hemoglobin. Consequently, increasing production of HbF by Resveratrol would be proposed as an interesting approach for treating diseases affecting oxygen transport (Fibach *et al*., 2012).

Conclusion

In summary, the current report aims to analyze the potential therapeutic efficiency of Resveratrol against SARS-CoV-2. Although the anti-viral properties of Resveratrol in infection with different viruses have already been shown, this report reports for the first time the potential role of the Resveratrol in mitigating the major effects of SARS-CoV-2. Indeed, Resveratrol was reported to down-regulate the main signaling pathways of inflammation by increasing activity of both SIRT1 and p53, two proteins involved in anti-viral activities. It was also shown to boost immune system through activation of CTLs and NK cells and regulation of pro-inflammatory cytokines as IL-1β, IFN-γ and TNF-α. Furthermore, Resveratrol was demonstrated to activate ACE2 and reduce oxidative stress causing lung injury in SARS-CoV-2 infection. Regarding these findings, this report suggests that Resveratrol could be used as therapeutic agent or adjuvant against SARS-CoV-2.

Nevertheless, in order to validate this report, pre-clinical and clinical studies using Resveratrol must be conducted.

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