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Therapeutic potential of resveratrol against emerging respiratory viral infections

Simone Filardo *, Marisa Di Pietro, Paola Mastromarino, Rosa Sessa

Department of Public Health and Infectious Diseases, Microbiology Section, University of Rome "Sapienza", Rome, Italy

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ABSTRACT

Resveratrol has been widely studied for its therapeutic potential due to its antioxidant, anti-inflammatory and anti-microbial properties. In particular, resveratrol has shown promising antiviral activity against numerous viruses responsible for severe respiratory infections. Amongst these, influenza virus, respiratory syncytial virus and the emerging SARS-cov-2 are known to cause pneumonia, acute respiratory distress syndrome or multi-organ failure, especially, in vulnerable individuals like immunocompromised patients or the elderly, leading to a considerable economic burden worldwide. In this context, resveratrol may have potential value for its anti-inflammatory activity, since most of the severe virus-associated complications are related to the overactivation of the host-immune response, leading to lung damage.

Herein, we present an overview of the antiviral activity and potential mechanisms of resveratrol against the respiratory tract viruses considered as a public threat for their rapid transmission and high morbidity and mortality in the general population.

Contents

1. Introduction

Respiratory tract infections due to viral pathogens are recognized as a critical public health issue due to their substantial burden to individual health and economies, causing millions of deaths, each year, worldwide (Farrag, Hamed, Amer, & Almajhdi, 2019). Viral respiratory infections represent approximately 25% of total lower respiratory tract infections, although this might be heavy underestimated since these are underdiagnosed and often lead to bacterial superinfections (Dandachi & Rodriguez-Barradas, 2018). In this regard, there is a growing consensus on viruses as etiologic agents for both community and hospital-acquired pneumonia, affecting, most often, children, immunocompromised patients or elderly adults with underlying chronic diseases, such as chronic obstructive pulmonary disease or cardiovascular disorders (Dandachi & Rodriguez-Barradas, 2018). Currently, influenza viruses are still the most significant causes of lower respiratory tract

Abbreviations: ACE-2, angiotensin-converting enzyme-2; AHR, airway hyperresponsiveness; ARDS, acute respiratory distress syndrome; GSH, glutathione; HCoV, human coronavirus; hMPV, human metapneumovirus; HRV, human rhinovirus; ICAM-1, intercellular adhesion molecule-1; ICU, intensive care unit; IFN, interferon; IL, interleukin; IRF, interferon regulatory factor; MAPK, p38 mitogen-activated protein kinase; MERS-Cov, middle-east respiratory syndrome coronavirus; MIC, minimal inhibitory concentration; myD88, myeloid differentiation primary response 88; NF-κB, nuclear factor-κB; NK, natural killer; PKC, protein kinase C; RANTES, regulated on Activation Normal T Cell Expressed and Secreted; RNP, ribonucleoprotein; ROS, reactive oxygen species; RSV, respiratory syncytial virus; SARM, Sterile α and HEAT/Armadillo motif–containing protein; SARS-Cov, severe acute respiratory syndrome coronavirus; TBK1, TANK-binding kinase 1; TLR, toll-like receptor; TNFα, tumor necrosis factor-α; TRIF, TIR-domain-containing adapter inducing interferon-β.

* Corresponding author at: Department of Public Health and Infectious Diseases, Microbiology Section, University of Rome "Sapienza", P.le Aldo Moro, 5 00185 Rome, Italy.
E-mail address: simone.filardo@uniroma1.it (S. Filardo).

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infections, followed by other viral pathogens including respiratory syncytial virus (RSV), human coronaviruses (HCoV), rhinovirus (HRV) and metapneumovirus (hMPV) (Alimi, Lim, Lansbury, Leonardi-Bee, & Nguyen-Van-Tam, 2017; Dandachi & Rodriguez-Barradas, 2018). Specifically, infections from influenza viruses and RSV share the highest healthcare burden; seasonal influenza viruses, indeed, are one of the most common causes of severe viral pneumonia, leading to global estimates of 290,000 to 650,000 deaths every year, whereas RSV is considered as the most common etiologic agent of lower respiratory tract infections in children, resulting in nearly 3.2 million hospitalization and 60,000 deaths worldwide in children aged less than 5 years (Daoud, Laktineh, Macrander, Mushtaq, & Soubani, 2019; Obando-Pacheco et al., 2018). Moreover, hMPV has been recently recognized as the cause of a significant portion of respiratory illnesses in children (approximately 10–12%), leading to hospitalization at a rate of 1 out of 1000 in children under the age of 5 years, with the highest rate for children under the age of 2 years (2 out of 1000) (Russell, Penkert, Kim, & Hurwitz, 2020).

More importantly, since the last century, newly emerging viral pathogens, originated from animal hosts and capable of great pathogenicity in humans following specific genomic mutations, have been the source of devastating pandemics and outbreaks worldwide (Bradley & Bryan, 2019). Amongst them, pandemic influenza viruses have occurred several times, from the first recorded "Spanish flu" pandemic in 1918, caused by an influenza A H1N1 subtype virus and affecting approximately 500 million people worldwide with over 50 million deaths, to the most recent 2009 influenza outbreak caused by a new H1N1 influenza A strain, with an estimated 17,000 fatalities from over 213 countries, and the highly pathogenic avian H7N9 virus of 2017, with roughly 1600 confirmed cases and over 600 deaths in the Asia-Pacific region (Kumar et al., 2018; Park, Park, Song, How, & Jung, 2019). In addition to influenza viruses, HCoV have also acquired relevance, in recent times, for the emergence of novel HCoV as the cause of severe lower respiratory tract infections and death, including the 2003 severe acute respiratory syndrome coronavirus (SARS-Cov), the 2012 middle-east respiratory syndrome coronavirus (MERS-Cov) and the 2020 SARS-Cov-2 (Lai, Shih, Ko, Tang, & Hsueh, 2020; Yin & Wunderink, 2018). In particular, the SARS-Cov caused a total of 8096 cases from 29 countries, with an estimated 774 deaths, while the MERS-Cov showed a higher mortality, leading to 2266 confirmed cases and 804 fatalities (Bradley & Bryan, 2019). Lastly, the SARS-Cov-2, up to 8th June 2020, has caused approximately 6,881,352 cases with 399,895 deaths from 216 countries (www.who.int/emergencies/diseases/novel-coronavirus-2019, accessed on 8th June 2020). Indeed, despite a high homology with SARS-cov, SARS-cov-2 possessed no cross-immunity as well as a higher reproduction index (2–3.5) and, hence, higher morbidity (Wang, Wang, Chen, & Qin, 2020).

The majority of deaths from lower respiratory tract infections caused by pandemic viruses are usually associated with risk factors including age less than 5 years or more than 65 years, immunosuppression, underlying chronic diseases, poverty and poor access to healthcare services, and, consequently, result in a heavy burden on public health systems due to infected patients, more frequently requiring hospitalization, ventilatory support and intensive care unit (ICU) treatment (Bradley & Bryan, 2019). This is particularly worrisome since few therapeutic strategies targeting these newly emerging pathogens and their severe complications are available, and, in view of this, there has been a growing interest for the development of novel anti-viral strategies. In this regard, stilbene derivatives, such as resveratrol, have acquired increasing importance due to their multiple antioxidant, anti-inflammatory and antiviral activities (Li et al., 2006; Lin et al., 2017).

Herein, we present an overview of the potential antiviral effects and mechanisms of resveratrol against the respiratory tract viruses considered as a public threat for their rapid transmission and high morbidity and mortality in the general population.

2. Clinical manifestations, pathogenesis and treatment of respiratory viral infections

2.1. Influenza virus

Influenza virus is one of the most common causes of severe viral pneumonia and is associated with a significant healthcare burden due to its fast transmission, high morbidity and mortality (Kumar et al., 2018; Paules & Subbarao, 2017). Influenza A and B viruses are known to cause epidemic (seasonal or interpandemic) influenza, whereas influenza A viruses can give rise to sporadic pandemics, due to different mechanisms of antigenic variation in the surface glycoproteins (Kumar et al., 2018; Paules & Subbarao, 2017). Influenza usually presents with symptoms of upper respiratory tract infection and it is mostly responsible for self-limiting diseases (Cavallazzi & Ramirez, 2018; Kumar et al., 2018). However, more frequently during influenza pandemics than seasonal influenza, it can cause severe lower respiratory diseases in susceptible populations, like older adults and patients with underlying chronic diseases, requiring hospitalization and in some cases ICU care, leading, eventually, to death (Daoud et al., 2019).

Influenza pathophysiology, especially in patients presenting pulmonary complications, is characterized by exacerbated airway inflammation caused by the host immune response recruited to handle the virus, as well as by virus-associated mechanisms (Kalil & Thomas, 2019; Sessa, Pietro, Filardo, & Turriziani, 2014). Furthermore, it is known that influenza virus exerts a direct cytopathic effect on the airway epithelium, leading to cell death *via* apoptosis or necrosis, aggravating, thus, the respiratory symptoms (Kalil & Thomas, 2019).

Currently, the approved treatments consist in two major classes of anti-influenza drugs: Matrix-2 ion channel inhibitors (*i.e.*, amantadine and rimantadine) and neuraminidase inhibitors (*i.e.*, oseltamivir and zanamivir) (Englund, 2002). Amantadine and rimantadine affect an early stage of influenza A virus replication (Lamb, 2020), whereas the neuraminidase inhibitors bind to the envelope neuraminidase of influenza A and B viruses during the budding step, preventing, hence, their release from infected cells (Davidson, 2018). Only neuraminidase inhibitors are left as effective options against the currently circulating viruses, given the emerging resistance to anti-influenza virus drugs, like the adamantane-resistance (Davidson, 2018; Dong et al., 2015).

2.2. Respiratory syncytial virus

RSV is responsible for acute respiratory tract diseases whose clinical manifestations vary greatly with age and underlying health conditions (Kodama, Nace, & Jump, 2017). RSV infections are associated with a significant morbidity in children less than 5 years of age, contributing to airway hyperresponsiveness (AHR), although they are also responsible for infections in adults, with a similar morbidity and mortality to those of seasonal influenza (Haber, 2018; Kodama et al., 2017). Early childhood RSV infections have also been suggested to cause long-term respiratory sequelae, including asthma and AHR, even 30 years after the original infection (Rossi & Colin, 2017).

RSV elicits a strong cellular and humoral immune response (Russell, Unger, Walton, & Schwarze, 2017). The first is marked by a strong systemic and, especially, pulmonary, IL-8 mediated neutrophil response, leading to lung inflammation and tissue damage (Russel et al., 2017), although the resulting humoral immunity is incomplete and does not warrant a protection against the re-infection (Russell et al., 2017). The second is characterized by the production of several Th1 and Th2 cytokines as well as chemokines (Hijano et al., 2019; Russell et al., 2017). The levels of Th1 cytokines, especially IFNγ, were demonstrated to negatively correlate with disease severity, whereas increased Th2 cytokine levels, especially IL-6, were associated with patients with bronchiolitis or pneumonia requiring hospitalization (Bohmwald et al., 2019; Hijano et al., 2019; Russell et al., 2017; Vázquez et al., 2019).

To date, as the only treatment option, a monoclonal antibody against its F-protein (Palivizumab) has indeed proven effective in reducing RSV hospitalization rates in high-risk infants by inhibiting the entry of the virus into the cell and preventing the formation of syncytia in the lung (Resch, 2017).

2.3. Novel human coronaviruses

Human coronaviruses have been well-known human pathogens for decades, although their clinical importance, epidemic and pandemic possibilities were not recognized until the emergence of SARS-cov and MERS-cov outbreaks, as well as the still ongoing, at the time of writing, SARS-cov-2 pandemic (Bradley & Bryan, 2019; Lai et al., 2020; Yin & Wunderink, 2018). SARS-cov and MERS-cov originated from the direct contact with intermediary host animals, like civets and camels, respectively (Bradley & Bryan, 2019; Yin & Wunderink, 2018). Differently, phylogenetic analysis revealed that SARS-cov-2 was closely related to bat-derived SARS-like coronaviruses, while being relatively distant from the previous SARS-cov (79% similarity) and MERS-cov (50% similarity) (Lai et al., 2020).

Disease severity in patients infected with SARS-cov or MERS-cov range from flu-like manifestations to ARDS, with nefarious outcomes mostly occurring in patients with underlying chronic medical conditions (Bradley & Bryan, 2019; Yin & Wunderink, 2018). On a similar note, the adverse outcomes of SARS-cov-2 infection are more likely to affect older people with underlying comorbidities, leading to major complications including bilateral interstitial pneumonia, ARDS, acute cardiac injury and secondary super-infections (Liu et al., 2020).

As for the pathogenesis of the disease, significant differences exist between SARS-cov and MERS-cov (Li et al., 2003; Meyerholz, Lambertz, & McCray Jr., 2016). Specifically, SARS-cov was shown to recognize the angiotensin-converting enzyme (ACE)-2, expressed on the alveolar and bronchial epithelial cells, whereas MERS-cov was demonstrated to bind to dipeptidyl peptidase-4, a multifunctional cell-surface protein mainly expressed in the alveolar epithelium (Li et al., 2003; Meyerholz et al., 2016). Following the internalization of viral particles, a delay in the induction of host immune responses, like the production of IFNs and other pro-inflammatory cytokines, such as IL-1β, IL-6 and IL-8, was observed for both infections (Lau et al., 2013; Menachery et al., 2014; Yin & Wunderink, 2018).

As for SARS-cov-2, at the moment of writing, the potential cellular and molecular pathogenetic mechanisms responsible for the different manifestations of the disease are still unexplored. However, recent evidence showed that the spike glycoproteins of SARS-cov-2 recognized human ACE-2 to enter cells, possessing structural similarity and sequence conservation to those of the previous SARS-cov (Walls et al., 2020). These findings suggest that the virus, by infecting the nasal and larynx epithelium, reaches the lungs through the respiratory tract and, in some cases, might enter the peripheral blood targeting all organs that express ACE-2, such as heart, kidneys and the gastrointestinal tract, aggravating, thus, the patient's conditions (Lin, Lu, Cao, & Li, 2020).

2.4. Human rhinovirus and metapneumovirus

HRV, in recent years, has been increasingly recognized as a lower respiratory tract pathogen, especially in vulnerable populations such as infants, the elderly and asthmatic or immunocompromised patients (Jacobs, Lamson, St George, & Walsh, 2013; Vandini, Biagi, Fischer, & Lanari, 2019). The airway epithelium is the primary site of infection and most serotypes enter the host cell *via* intercellular adhesion molecule (ICAM)-1, compromising the epithelial barrier's function (Vandini et al., 2019). Following HRV infection of airway epithelial cells, viral antigens are recognized by several pattern recognition receptors, like toll-like receptor (TLR)3 and retinoic acid-inducible gene I helicases (Vandini et al., 2013; Makris & Johnston, 2018). The engagement of these receptors induces a type I IFN response as well as the secretion of pro-inflammatory cytokines, like IL-6 and IFNγ, and chemokines like RANTES and IL-8, which drive the recruitment of immune cells to the site of infection, contributing to tissue damage (Doyle et al., 2010; Makris & Johnston, 2018).

hMPV infections are often responsible of mild, self-limiting, acute upper respiratory tract diseases, whereas the infection of vulnerable populations, like infants, children, the elderly and immunocompromised patients, may elicit severe lower respiratory tract diseases characterized by wheezing and pneumonia (Soto et al., 2018; Russel et al., 2020). The pathogenesis of hMPV-associated lower respiratory tract disease is likely dependent on the induction of a typical Th17-like immune response, with increased production of IL-6 and TNF-α, alongside a Th2 response characterized by early secretion of pro-inflammatory cytokines, like IL-4, IL-5 and IL-8 (Hastings et al., 2015; Li et al., 2018; Soto et al., 2018).

3. Potential therapeutic applications of resveratrol

3.1. Bioavailability

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) was described, for the first time, in 1939 by Takaota as bioactive component in the *Veratrum gandiflorum* roots (Takaoka, 1940). Later on, the resveratrol was found in several plants (grapes, blueberries, peanuts, *etc.*) in response to stressful conditions including ultraviolet radiation, ozone and fungal infections (Pannu & Bhatnagar, 2019). Resveratrol is poorly soluble in water and stable at body temperature only under acidic conditions, with its solubility and stability exponentially decreasing with increasing pH (Zupančič, Lavrič, & Kristl, 2015).

Resveratrol possesses peculiar pharmacokinetic characteristics, marked by a rapid and extensive metabolism accompanied by a very low plasma bioavailability of unmetabolized resveratrol, that depends also on its poor solubility above pH 7.4 (Walle, Hsieh, DeLegge, Oatis Jr, & Walle, 2004; Zupančič et al., 2015). As reported in literature, after resveratrol oral administration, 77–80% of this compound is absorbed in the gastro-intestinal tract and 49–60% of the latter is excreted in the urine (Chimento et al., 2019; Pannu & Bhatnagar, 2019); at the intestinal level and in the liver, resveratrol is rapidly metabolized, producing a variety of metabolites (sulfate and glucuronide conjugates) with very little bioactivity, that contribute to its low bioavailability (Gambini et al., 2015). Recently, several studies have also found that the intestinal microbiota seemed to play an important role in resveratrol metabolism, influencing either positively or negatively its bioavailability (Berretta et al., 2020; Bode et al., 2013). Gut bacteria were, indeed, demonstrated, to either promote the synthesis of resveratrol from its precursors (piceid) or its conjugates, or to metabolize resveratrol into its reduced form (dihydro-resveratrol), which in turn might be absorbed, conjugated and excreted (Berretta et al., 2020; Bode et al., 2013). Once in the bloodstream, resveratrol can be found essentially in three different forms: glucuronide, sulfate or unmetabolized (Chimento et al., 2019; Pannu & Bhatnagar, 2019). The latter, by binding with albumin and lipoproteins, such as LDL, forms complexes that are considered as polyphenolic reservoir, limiting, thus, its bioavailability (Chimento et al., 2019; Pannu & Bhatnagar, 2019). Several studies demonstrated that, in humans, an initial dose of 25 mg resulted in plasma concentrations ranging from 1 to 5 ng/ml, and increasing doses (up to 5 g) led to resveratrol plasma concentrations of up to 530 ng/ml (Boocock et al., 2007; Walle et al., 2004).

As a result, the rapid metabolism and poor bioavailability limit the use of resveratrol as a pharmaceutical drug, leading to the administration of very high oral doses in order to improve its therapeutic effects (Walle et al., 2004). Many studies suggested that resveratrol is a very well tolerated compound in humans, although there is evidence that concentrations higher than 1 g/Kg might lead to undesirable side effects, including diarrhea, nausea and abdominal pain(Shaito et al., 2020). Furthermore, a long-term intake of very high doses of resveratrol might

result in more severe side-effects related to its ability to act as a thyroid disruptor or to its high-dose associated pro-oxidant effects (Shaito et al., 2020).

Given these critical limitations, extensive research is ongoing on different methodological approaches aiming to improve resveratrol bioavailability and its potency. Currently, the most promising tools are the synthesis of novel resveratrol analogues and the development of nano-carrier based drug-delivery systems (Chimento et al., 2019).

Amongst its analogues, methoxylated, hydroxylated and halogenated resveratrol derivatives showed a stronger pharmacological potency and a better pharmacokinetic profile than resveratrol itself in *in vitro* and animal-based models (Chimento et al., 2019; Nawaz et al., 2017). In particular, methoxylated resveratrol analogues have been demonstrated to enhance resveratrol lipophilicity, absorption, cellular uptake and oral bioavailability (Chimento et al., 2019). Hydroxylated resveratrol derivatives were also reported to be rapidly absorbed (Biasutto et al., 2017; Chimento et al., 2019), whereas halogenated resveratrol derivatives were characterized by a high lipophilicity (Chimento et al., 2019; Li et al., 2012; Nawaz et al., 2017).

Lastly, considering innovative drug-delivery systems, resveratrol encapsulation in lipid nanocarriers or liposomes, emulsions, micelles, as well as its insertion into polymeric nanoparticles, solid dispersions and nanocrystals (Chimento et al., 2019; Francioso et al., 2014; Santos et al., 2019) were demonstrated to enhance resveratrol aqueous solubility and chemical stability in *in vitro* or *in vivo* studies, improving, thus, its bioavailability as well as reducing its side-effects (Chimento et al., 2019; Santos et al., 2019).

3.2. Biological properties

Over the course of the last decades, numerous biological effects of resveratrol have been observed, including cardioprotective, anticancer and anti-microbial activities (Pannu & Bhatnagar, 2019; Vestergaard & Ingmer, 2019).

The cardioprotective effects of resveratrol were attributed to its antioxidant and anti-inflammatory properties by several studies. (Baur & Sinclair, 2006; Cottart, Nivet-Antoine, Laguillier-Morizot, & Beaudeux, 2010; Di Pietro, De Santis, Schiavoni, Filardo, & Sessa, 2013; Di Pietro, Filardo, Falasca, Turriziani, & Sessa, 2017; Pannu & Bhatnagar, 2019; Xia, Daiber, Förstermann, & Li, 2017). Some human clinical trials indicated, indeed, that the administration of resveratrol (20 mg/day for 2 months to 350 mg/day for 6 months) led to a significant improvement of the lipid profile (Bhatt, Thomas, & Nanjan, 2012; Tome-Carneiro et al., 2012) or the inflammatory state (Militaru et al., 2013) in patients with high cardiovascular risk (*i.e.* diabetes, hyperlipidemia) or cardiovascular diseases (Militaru et al., 2013; Tome-Carneiro et al., 2012; Tome-Carneiro et al., 2013). However, other studies failed to demonstrate any effect of resveratrol on lipid profile and inflammatory state (Bo et al., 2016; Kjaer et al., 2017). These contradictory results are also evident from the several meta-analyses performed over the last years, and it might be explained by major differences in research protocols, including experimental settings, sample size, health status, dose and treatment duration (Breuss, Atanasov, & Uhrin, 2019).

Despite the contrasting evidence from human clinical trials, *in vitro* studies generally supported the cardioprotective properties of resveratrol, pointing out its ability to interact with multiple molecular targets of the intracellular pathways underlying the atherosclerotic process (Cheng et al., 2020; Cottart et al., 2010; Pannu & Bhatnagar, 2019; Xia et al., 2017). For its antioxidant activity, resveratrol was described to restore reactive oxygen species (ROS)/antioxidant balance and, hence, to counteract the oxidative stress-mediated tissue damage (Cottart et al., 2010; Xia et al., 2017). In this context, resveratrol was found to affect the activity of several redox–enzymes, including nicotinamide-adenine dinucleotide phosphate (NADPH) oxidases and superoxide dismutase, in the endothelium, vascular smooth muscle cells, cardiomyocytes and adventitia, preventing the development and progression of atherosclerosis (Cheng et al., 2020; Pannu & Bhatnagar, 2019). However, other studies have shown that resveratrol can also behave as a pro-oxidant in relation to several factors, including the dose (Chan & Chang, 2006) and the microenvironment (*i.e.* pH) (de la Lastra & Villegas, 2007; Yang, Lee, & Song, 2010). In this regard, high doses of resveratrol (≥10 μM) or a high pH were demonstrated to increase the oxidation state, leading to vascular endothelial cell damage (Posadino et al., 2015; Yang et al., 2010).

Resveratrol was also able to attenuate inflammatory response related to ROS-mediated oxidative stress as a result of its antioxidant activity, contributing to its cardioprotective effects (Meng, Zhou, Zhao, Gan, & Li, 2020). Additionally, resveratrol (6.25–50 μM) modulated the cytokine and chemokine profile both in immune and endothelial cells (Misawa et al., 2015; Schwager, Richard, Widmer, & Raederstorff, 2017) to protect against inflammation, through different mechanisms. For example, resveratrol upregulated sirtuin-1, suppressed NF-κB and inhibited the activation of Nod-like receptor family pyrin domain containing-3 inflammasome (Meng et al., 2020; Misawa et al., 2015).

Similarly, several *in vivo* studies demonstrated that resveratrol was able to modify different aspects underlying the atherosclerotic process, such as lipid metabolism (Zang et al., 2006), endothelial function (Chen et al., 2013), oxidative stress and inflammation (Guo et al., 2014), plaque formation (Do et al., 2008) and platelet aggregation (Schmatz et al., 2013).

In addition to its cardioprotective effects, resveratrol also showed potential protective effects against tumor initiation and progression (Meng et al., 2020). In particular, its anticancer activity was mostly attributed to the induction of apoptosis in several human tumor-established cell lines, through the direct activation of caspase cascade or the inhibition of antiapoptotic pathways (Berretta et al., 2020). By contrast, animal-based studies provided inconsistent results (Carter, D'Orazio, & Pearson, 2014; Meng et al., 2020) that could be attributed to variability between studies with respect to cancer models, methods of tumor initiation, animal species as well as administration route and dose of resveratrol. Similarly, inconclusive results came from the few clinical trials performed to date, suggesting that the efficacy of resveratrol was dependent on the type and stage of cancer, dose and treatment periods (Berman, Motechin, Wiesenfeld, & Holz, 2017; Ko et al., 2017; Meng et al., 2020).

Resveratrol was also described as an antibacterial and antifungal agent. In this regard, several studies demonstrated a better antifungal [minimal inhibitory concentration (MIC) 10–50 μg/ml] than antibacterial activity (MIC 25 - >100 μg/ml). Amongst bacteria, resveratrol was shown to be bactericidal against Gram-negative pathogens (MIC >200 μg/ml), whereas it displayed only a bacteriostatic effect against Gram-positive pathogens (MIC 100–200 μg/ml) (Vestergaard & Ingmer, 2019). Furthermore, resveratrol was also observed to inhibit biofilm production, an important virulence factor known to contribute to the development of chronic and recurrent infections (Lee et al., 2019; Vestergaard & Ingmer, 2019). Despite all the *in vitro* promising findings, there are still few *in vivo* studies about the therapeutic potential of resveratrol towards bacterial infections. Euba et al. (2017), *for example,* highlighted that the oral administration of resveratrol (150 mg/kg), *in* a mouse model of respiratory infection *with Haemophilus influenzae,* significatively reduced the bacterial burden in lung tissue, whereas a lower dose had no effect (100 mg/kg).

4. Potential anti-viral activity of resveratrol against respiratory viruses

Interestingly, resveratrol has showed inhibitory activity against viral replication and virus-induced inflammation in diseases caused by several pathogenic human viruses including respiratory viruses like influenza virus, RSV, HCoV and HRV, that will be extensively described below (Abba, Hassim, Hamzah, & Noordin, 2015).

4.1. Influenza virus

An anti-viral activity of resveratrol was demonstrated in several *in vitro* studies, evidencing multiple cellular and molecular mechanisms (Table 1, Fig. 1). Resveratrol treatment efficiently inhibited influenza virus replication in a dose-dependent manner (10–20 μg/ml), decreasing the translation of late viral proteins and blocking the nuclear-cytoplasmic translocation of viral RNPs, key step of viral replication preceding virion assembly and release. These effects were mediated by the inhibition of intracellular signaling pathways, like protein kinase C (PKC) and MAPK (Palamara et al., 2005). Later on, it was also demonstrated that a resveratrol analogue restored the host-cell redox imbalance in a dose dependent manner (5–20 μg/ml), caused by the virus-induced depletion of GSH levels, hindering the maturation of hemagglutinin (Fioravanti et al., 2012).

Further *in vitro* studies confirmed the anti-viral activity of resveratrol, as well as of other compounds belonging to the stilbene class, against different subtypes of influenza viruses through the inhibition of neuraminidases (Kim, Narayanan, & Chang, 2010; Liu et al., 2010). Indeed, natural stilbenoids, extracted from plants, like *Gnetum pendulum*, possessed efficacy against H1N1 and H3N2 influenza A viruses (inhibitory concentration: 45 μM; toxic dose for 50% cell death: 90 μM; therapeutic index: 2) (Liu et al., 2010). Interestingly, resveratrol was also able to inhibit the infection of human influenza B virus as well as of swine influenza A virus (Kim et al., 2010).

In addition to the direct inhibition of virus replication (IC_{50}: 24.7 μM; average growth inhibition of 50%: >100 μM; therapeutic index: 4), recently, resveratrol was also demonstrated to modulate the host-cell immune response against several clinical strains of H1N1 and H3N2 Influenza A virus (Lin et al., 2015). The increased IFNβ gene expression through the TLR9/IRF7 pathway, observed following resveratrol treatment, suggested that IFNβ likely acted synergistically with resveratrol to inhibit virus replication (Lin et al., 2015).

Lastly, *in vivo* studies revealed that resveratrol improved disease-free survival and decreased pulmonary viral titers in influenza A virus-infected mice (Palamara et al., 2005).

Notably, a significant variability of the effective dosage of resveratrol was observed in either *in vitro or in vivo* studies. For example, the EC_{50} of resveratrol towards several subtypes of influenza A and B viruses *in vitro* ranged from 5 to 26.3 μg/ml, whereas the concentrations of resveratrol used for treating influenza A infected mice ranged from 1 to 30 mg/Kg/day (Liu et al., 2010; Palamara et al., 2005).

4.2. Respiratory syncytial virus

Since the last ten years, the therapeutic potential of resveratrol against RSV has been explored in view of the fact that current treatments showed questionable beneficial effects on clinical outcomes, such as airway inflammation and AHR (Mazur et al., 2015).

In vitro studies suggested resveratrol as a promising anti-viral agent since it inhibited RSV replication and ameliorated the virus-associated airway inflammation and AHR, by modulating the host-cell signaling pathways involved in chronic inflammation and lung injury (Table 1, Fig. 1) (Liu et al., 2014; Xie et al., 2012). In this regard, it was observed

Table 1
Effects of resveratrol on respiratory virus infections.

Virus	Cell line/animal	Resveratrol concentration	Mechanisms/Target	Effects	References
A/Puerto Rico/8/34 H1N1 (PR8)	MDCK cells BALB/c mice	10, 20 μg/ml 1 mg/Kg/day, 7 days	Nuclear-cytoplasmatic translocation of viral RNPs PKC/MAPK pathways	Reduced viral replication Reduced expression of late viral proteins Decreased pulmonary viral titers Increased survival	Palamara et al., 2005
H1N1, H3N2 B/Jiangsu/10/2003	MDCK cells	5.0 to 26.3 μg/ml (IC50)	Neuraminidase	Reduced viral replication	Liu et al., 2010
A/Puerto Rico/8/34 H1N1 (PR8)	MDCK cells NCI-H292	10, 20 μg/ml	Nuclear-cytoplasmatic translocation of viral RNPs Redox-sensitive pathways (depletion of intracellular GSH) / maturation hemagglutinin protein	Reduced viral replication Restored intracellular redox balance	Fioravanti et al., 2012
A/WSN/33(H1N1) H3N2 clinical strain H1N1 clinical strain	A549 cells	24.7 μM (IC50)	Neuraminidase Hemagglutinin TLR9/myD88/IRF5/IRF7/IFN-β	Reduced viral replication	Lin et al., 2015
RSV	BALB/c mice	30 mg/Kg/day 5 days	TLR3/TRIF pathway M2R	Reduced lung viral titer Decreased inflammation Reduced levels of IFN-γ	Zang et al., 2011
RSV	HEp-2 cells 9HTEo cells	50 μM 100 μM	TRIF/TBK1	Reduced viral replication Decreased production of IL-6	Xie et al., 2012
RSV	BALB/c mice	30 mg/Kg/day 5 days	TRIF/SARM	Reduced production of IFN-γ	Liu et al., 2014
RSV	BALB/c mice	30 mg/kg/day 21 days	Neurotrophins (NGF, BDNF)	Reduced production of IFN-γ Decreased inflammation	Zang et al., 2015
RSV	BALB/c mice	30 mg/kg/day 6 days	NK cells	Reduced persistent airway inflammation Reduced airway hyperresponsiveness	Long et al., 2016
SARS-Cov	Vero E6 cells	0.5 mg/ml (2.05 mM)	Not investigated	Reduced viral replication Reduced cytopathic effect	Li et al., 2006
MERS-Cov	Vero E6 cells	31.5–250 μM	Caspase 3 Nucleocapsid protein	Antiapoptotic activity Reduced viral RNA levels and infectious titers	Lin et al., 2017
HRV-16	HeLa cells *Ex-vivo* human nasal epithelial cells	50 μM	IL-6 IL-8 RANTES ICAM-1	Reduced viral replication Decreased inflammation	Mastromarino et al., 2015
HMPV	A549 cells	50 μM	NF-κB/IRF3	Reduced viral replication Decreased inflammation Reduced cellular oxidative damage	Komaravelli et al., 2015

that resveratrol inhibited virus-induced TIR-domain-containing adapter inducing interferon-β (TRIF) and TANK binding kinase 1 protein expression (TBK1), by either decreasing the production of IL-6, a key cytokine correlated to disease severity, or reducing INFγ levels *via* the expression of the Sterile α and HEAT/Armadillo motif–containing protein (SARM) (Liu et al., 2014; Xie et al., 2012).

In vivo studies demonstrated that the administration of resveratrol decreased virus titer, the levels of IFNγ as well as the number of inflammatory cells (*i.e.* NK cells, macrophages and CD3+ T) in the lungs, thereby attenuating airway inflammation and hyperresponsiveness (Long et al., 2016; Zang et al., 2011). Of clinical importance, the levels of neurotrophins (nerve growth factor and brain-derived neurotrophic factor), involved in the long-term inflammation associated with RSV infection, were also reduced following resveratrol treatment (Zang et al., 2015).

4.3. Other respiratory viruses

SARS-cov and MERS-cov were recently shown to be sensitive to resveratrol in *in vitro* studies, suggesting promising anti-viral and anti-inflammatory effects (Table 1, Fig. 1). Synthesized resveratrol-derivatives were demonstrated to suppress SARS-cov replication and decrease its cytopathic effect, whereas no effect was observed for the resveratrol itself (Li et al., 2006). As for MERS-cov, resveratrol was described to reduce viral RNA expression and viral yield in a dose-dependent manner (31.5–250 μM and 150–250 μM, respectively) (Lin et al., 2017). Interestingly, consecutive treatments with resveratrol at lower concentrations (62.5 μM) still inhibited MERS-cov replication (Lin et al., 2017). This anti-viral effect was responsible of the reduction of virus-induced apoptosis resulting in increased cell survival, as evidenced by the decreased levels of caspase-3 in infected cells after treatment with resveratrol (Lin et al., 2017).

Concerning HRV, resveratrol was found to exhibit a high dose-dependent antiviral activity against its replication in cell cultures and *ex vivo* nasal epithelia (therapeutic index: > 111) (Mastromarino et al., 2015) (Table 1, Fig. 1). Also, the activation of inflammatory response in infected nasal epithelia was reversed following the exposition to resveratrol (Mastromarino et al., 2015). Resveratrol, indeed, reduced virus-induced secretion of IL-6, IL-8 and RANTES to levels similar to those of uninfected nasal epithelia. Expression of ICAM-1, the cellular receptor for HRV that is also functionally involved in inflammation, was also reversed by resveratrol (Mastromarino et al., 2015). These results might be of particular interest since the production of HRV-induced pro-inflammatory cytokines and chemokines appears to be involved in the pathogenesis of rhinovirus infections (Gern et al., 2002).

Lastly, resveratrol was also demonstrated to reduce hMPV replication, in a dose-dependent manner (10–50 μM), in airway epithelial cells, with no effect on viral gene transcription and protein synthesis,

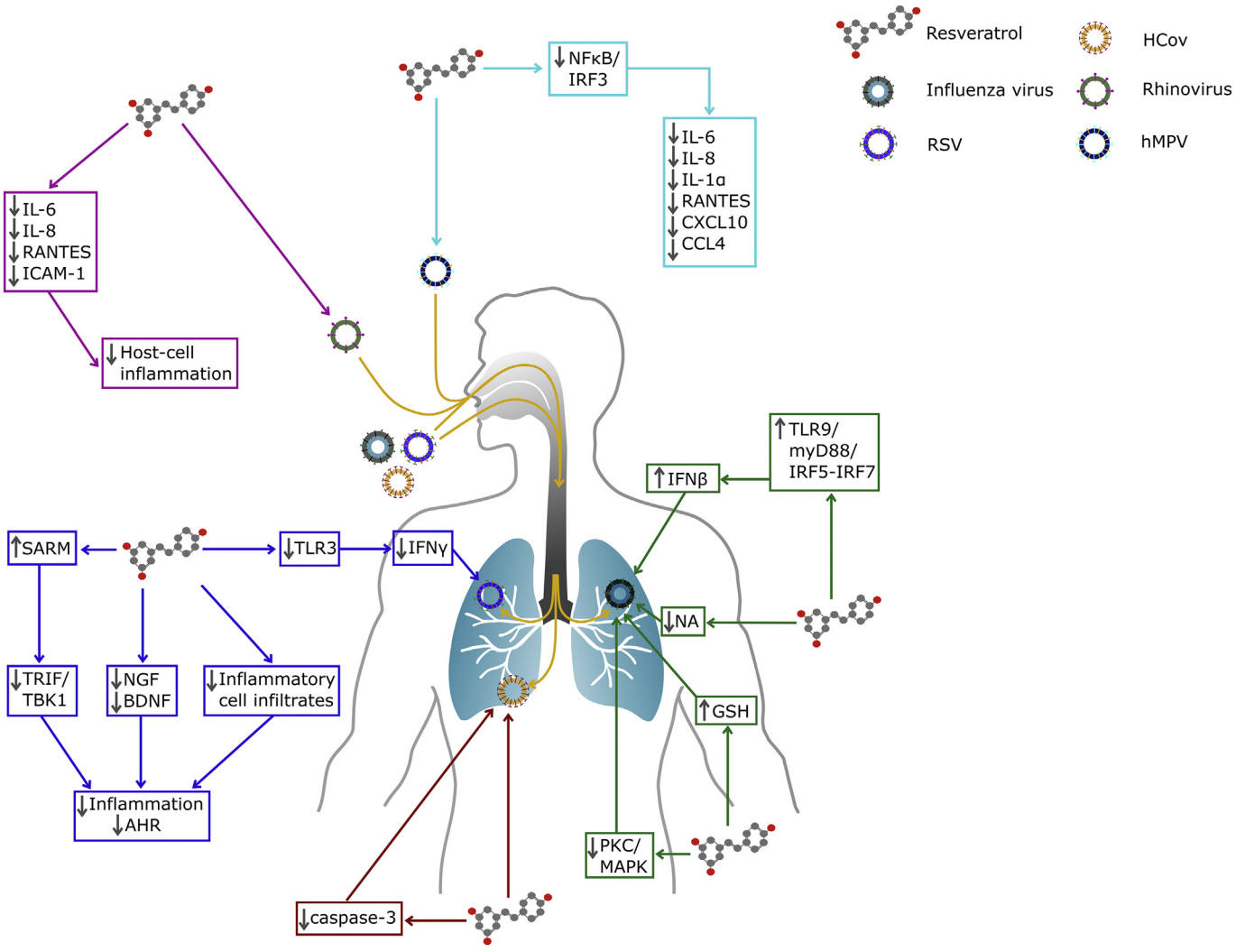

Fig. 1. Anti-viral and immuno-modulatory mechanisms underlying the efficacy of resveratrol against Influenza viruses, human coronaviruses (HCoV), respiratory syncytial virus (RSV), rhinovirus and human metapneumovirus (hMPV).

indicating that the inhibition of viral replication occurred at the level of viral assembly and/or release (Komaravelli et al., 2015). The secretion of inflammatory mediators were also significantly reduced through the inhibition of the transcription factor NF-κB and IRF-3 binding to their cognate site of endogenous gene promoters, modulating the expression of pro-inflammatory mediators (IL-8, RANTES, IL-1α, IL-6, TNF-α, CXCL10 and C—C Motif Chemokine Ligand-4) (Komaravelli et al., 2015) (Table 1, Fig. 1).

5. Conclusions and future prospective

Respiratory viral infections are a critical public health problem for their high transmissibility and the lack of cross-reactive immune responses, causing substantial morbidity and mortality in pediatric and immunocompromised patients or the elderly, and, hence, resulting in a considerable economic burden worldwide (Dandachi & Rodriguez-Barradas, 2018).

Severe complications, including pneumonia, respiratory failure, ARDS and multi-organ failure, may result from lung inflammation and damage caused either by the direct viral infection of the respiratory epithelium or by the immune responses recruited to handle the spreading virus. In fact, as previously described, during influenza virus, RSV, HRV and hMPV infections, the overproduction of pro-inflammatory cytokines (*i.e.* IL-6, IL-8, IFNγ, *etc.*) and the overactivation of immune cells (neutrophils, macrophages, CD4+ and CD8+ T cells, *etc.*) can augment virus related lung tissue injury (Tan et al., 2019).

Currently, few drugs are at our disposal for the treatment of respiratory viral infections, targeting, especially, the most widespread etiologic agents, like influenza viruses and RSV. By contrast, no clinically validated anti-viral drugs are available, at the moment, for pandemics caused by emerging respiratory viruses, like SARS-cov, MERS-cov and SARS-cov-2 (Lu, 2020).

In view of the scarce anti-viral therapies available for the respiratory viruses and the complexity of the pathological picture underlying the severe virus-associated complications, alternative potential therapeutic approaches have been explored to improve the management of the disease.

Over the course of the last years, resveratrol, a natural compound, has acquired importance for its therapeutic potential in respiratory viral infections. As previously described, resveratrol and its analogues displayed anti-viral activity against influenza viruses, RSV, HCoV, HRV and hMPV, *via* either the direct inhibition of viral replication as well as the modulation of the host immune response. In addition, the anti-inflammatory and antioxidant activities, underlying the cardioprotective effects of resveratrol, might contribute to relieve the symptoms associated with respiratory virus-related pathological manifestations.

Despite its potential anti-viral effects, resveratrol cannot be used as such in clinical practice because of its low bioavailability following oral administration, since it is readily metabolized and has low water solubility, resulting in poor absorption. Indeed, human plasma concentrations (up to 530 ng/ml) following resveratrol intake (up to 5 g) (Shaito et al., 2020) are much lower than those effective against respiratory viruses *in vitro* (Fioravanti et al., 2012; Kim et al., 2010; Li et al., 2006; Lin et al., 2015; Lin et al., 2017; Liu et al., 2010; Liu et al., 2014; Mastromarino et al., 2015; Palamara et al., 2005; Xie et al., 2012). This implies that much even higher doses of resveratrol might be needed in humans, potentially leading to severe adverse effects due to lipid peroxidation, DNA damage and cell death (Shaito et al., 2020).

Therefore, several challenges remain to be addressed. For example, the dosage of resveratrol, able to maximize its health benefits without adverse effects, remains an area of extensive research. Indeed, as previously described, *in vivo* studies investigating the antiviral activity of resveratrol used different doses as well as treatment times, all observing a decreased viral load as the main outcome. In addition, the analysis of the pharmacokinetic profile of resveratrol should be performed alongside the study of its anti-viral properties, in order to provide a more comprehensive picture.

To overcome resveratrol limitations, several ways have been explored and, amongst them, aerosolized suspensions like a resveratrol-containing spray and co-spray dried microparticles showed beneficial effects on individual health, supporting their potential application in the complications associated with respiratory infections (Miraglia Del Giudice et al., 2014; Trotta et al., 2016). Further ongoing approaches are the usage of synthesized resveratrol analogues (*i.e.* pterostilbene) or innovative drug-delivery systems (*i.e.* nanoparticles, nanoliposomes, nanoemulsions, *etc.*), showing enhanced bioavailability and delivery as well as increased therapeutic potential towards cancer, cardiovascular (Chimento et al., 2019; Estrela, Ortega, Mena, Rodriguez, & Asensi, 2013; Fulda, 2010; Kapetanovic, Muzzio, Huang, Thompson, & McCormick, 2011; Lushchak et al., 2020).

In the future, the development of nanotechnology-based applications for the delivery of resveratrol or its analogues may be a promising strategy for the treatment of respiratory viral infections in view of the continuous emergence of novel pathogens responsible for epidemic or pandemic worldwide, like SARS-cov-2.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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