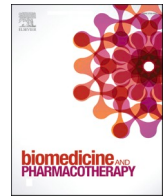




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Review

The potential role of resveratrol as supportive antiviral in treating conditions such as COVID-19 – A formulator's perspective

Roy van Brummelen^{*}, Anna C. van Brummelen

vBC Consultants, Pretoria, South Africa

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ABSTRACT

With an increased transmissibility but milder form of disease of the omicron variant of COVID-19 and the newer antivirals often still out of reach of many populations, a refocus of the current treatment regimens is required. Safe, affordable, and available adjuvant treatments should also be considered and known drugs and substances need to be repurposed and tested. Resveratrol, a well-known antioxidant of natural origin, shown to act as an antiviral as well as playing a role in immune stimulation, down regulation of the pro-inflammatory cytokine release and reducing lung injury by reducing oxidative stress, is such an option. New initiatives and collaborations will however need to be found to unleash resveratrol's full potential in the pharmaceutical market.

1. The problem

The past two years the world is reeling under the onslaught of the Coronavirus disease (COVID-19) pandemic caused by severe respiratory syndrome coronavirus 2 (SARS-CoV-2). For the first time in recent history the whole planet has been brought to a standstill and have been united in the fight against a common enemy. Even the biggest and best of countries' medical systems were buckling and struggling to handle the load of severely ill patients with the death toll rising to unprecedented levels [1,2]. Worldwide the race was on to find effective treatments for this virus. The World Health Organization (WHO) attempted to combine efforts between countries and clinical trials were being fast-tracked to save time. Several drugs from the antiviral and anti-parasitic arsenal were considered and attempted on patients, but often with limited success, side effects and/or cost constraints [3,4]. Cost and availability often place these advanced drug treatments out of reach of many populations especially in third world countries where it is so urgently needed [5].

Fortunately, vaccines were developed in record time, approved for emergency use, and rolled out – hoping to achieve herd immunity [6]. Despite 69.4% of Europe [7] and 63% of the United States [8] being vaccinated by 20 January 2022, this immunity was not achieved and health care systems in both regions were still under enormous pressure during the recent fourth waves due to the omicron variant. Although, the omicron variant is more contagious than the delta variant, patients appear to require less hospitalization or shorter periods thereof [9],

partly due to the inherent immunity resulting from previous infection or induced by vaccination [10]. However, hospitals in many countries were still under pressure due to the extremely high number of (less severe) cases, also among staff members, leading to a shortage of care givers with patient numbers far over capacity [11]. In many countries the critically ill patients due to the omicron variant were those that were not vaccinated – either by choice (vaccine hesitancy) or due to a lack of vaccine availability in some third world countries [12]. Currently, booster doses of the main vaccines are being distributed, while many population groups have not had COVID vaccination at all, and concerns for future more resistant variants especially among populations with high ratios of unvaccinated individuals remain.

2. A possible solution

This increased transmissibility of the omicron variant, leading to numbers of more than 800,000 million new cases per day (7-day average) in the US alone in January 2022 [13], demands a refocus of the current treatment regimens to treat these millions of patients. Hospitalization may be less indicated compared to previous strains, but these patients with a milder form of the disease still need to be treated effectively to speed up full recovery, also to free up space for those still requiring hospitalization. Another consideration is the question of “long COVID” [14] and the prevention thereof. Adjuvant treatments known to strengthen the immune system during viral infection should also be considered and safe, available, and affordable alternatives need to be

^{*} Correspondence to: vBC Consultants, Oulandsloop 425, Pretoria 0184, South Africa.
E-mail address: royvbc@gmail.com (R. van Brummelen).

found. Known drugs and substances need to be repurposed and tested. Resveratrol is such a substance – up to now known more as a potent antioxidant and used in many nutritional products for, amongst others, anti-aging properties, it has been tested and shows potential as an anti-viral agent [15]. In fact, several reviews concluded that resveratrol should be considered as one of the “*therapeutic options for the 2019 novel coronavirus (2019-nCoV)*” [16], or applied as part of a potential intervention strategy against the 2019-nCoV [17,18].

3. Resveratrol (as antiviral)

Resveratrol is a naturally appearing polyphenol (trans-3,4',5-trihydroxystilbene), mainly sourced from grape skin and red wine as well as medicinal plants e.g., Japanese knotweed, that has been used over many years in different chronic diseases for its antioxidant, anti-inflammatory and anti-tumorigenic properties [19]. There is growing evidence that the redox status of cells plays an important role in viral infections. RNA and DNA viruses can decrease glutathione levels and glutathione supplementation can inhibit viral replication [20,21]. Resveratrol inhibits the influenza virus replication - it was thought that this was due to resveratrol's influence on cellular redox status via glutathione. However, this inhibition was demonstrated not to be directly associated to glutathione mediated antioxidant activity, but by inhibiting nuclear-cytoplasmic translocation of viral ribonucleoproteins and reducing the expression of late viral proteins associated with the inhibition of protein kinase C [20]. Resveratrol derivatives have been tested in vitro with some success on viral particle infectivity for the possible development of new influenza treatments [22]. Combinations such as resveratrol with N-acetylcysteine or glutathione, which have both antioxidant and antiviral effects, inhibits the proliferation of influenza virus and are of specific interest for serious influenza-associated complications [23].

Resveratrol has also been found to be a moderate inhibitor of the N1L protein which is a virulence factor in viral infections such as smallpox [24]. Furthermore, resveratrol has been found to act synergistically with decitabine to inhibit human immunodeficiency virus type 1 (HIV-1) infectivity without a corresponding increase in cellular toxicity [25]. It also inhibited drug-resistant HIV-1 strains with reverse transcriptase containing the M184V mutation [26]. Resveratrol had an even greater antiviral activity against the “more difficult to treat” human immunodeficiency virus type 2 (HIV-2) than HIV-1 and its antiviral activity appeared to be selective for the reverse transcription phase of virus replication [27]. A novel synthetic resveratrol derivative namely 3,3',4,4',5,5'-hexahydroxy-trans-stilbene has also been developed and demonstrated to have potent anti-HIV 1 activity – the authors suggested that this derivative may have a potentially different mechanism of action to current anti-HIV-1 drugs including entry inhibitors [28].

It appears that resveratrol has inhibitory activity against various viral enzymes, for example it acts as an inhibitor of ribonucleotide reductase and antiretroviral synergy was described between resveratrol and 5-azacytidine, a ribonucleoside analog, which is of significance in HIV-1 treatment [29]. Resveratrol's antiviral activity against the herpes simplex virus appears to be via the same mechanism, namely inhibition of ribonucleotide reductase, impairing the expression of viral proteins [30]. Additionally, a resveratrol tetramer also showed high potency as inhibitor of the hepatitis C virus helicase [31]. Resveratrol also demonstrated a potent inhibitory effect on pseudorabies virus - a major devastating disease in the swine industry, due to its inhibition of nuclear factor kappa B (NF- κ B) activation and NF- κ B-dependent gene expression via its inhibitory effect on ikappaB (κ B) kinase degradation [32].

In vitro testing showed that resveratrol also partially inhibited the replication of respiratory syncytial virus - one of the most common pathogens of lower respiratory diseases in children, as well as decreased interleukin-6 production [33]. Resveratrol was also tested in combination with beta-glucan for the treatment of pediatric recurrent respiratory infections. In a global real-life randomized study with 82 children, an aerosolized solution of resveratrol plus carboxymethyl-beta-glucan

significantly reduced nasal symptoms, cough, and fever, as well as reducing the need for medication and medical visits [34]. This combination was furthermore tested in vitro for its effect on human rhinovirus replication (HRV) and was found effective to inhibit the production of several HRV-induced inflammatory mediators in the nasal epithelia, possibly due to resveratrol's ability to suppress viral replication [35].

Another postulated mechanism of action of resveratrol is to change cellular metabolism and signal transduction pathways by affecting enzymes, such as adenosine monophosphate kinase and the serine/threonine protein kinase that is the mechanistic target of rapamycin (mTOR), since these pathways influence immune function and cellular inflammation status [36]. Overall, the antiviral mechanisms of resveratrol in human and animal viral infections appear to include inhibition of viral replication, protein synthesis, inhibition of transcription and signaling pathways, as well as viral related gene expressions [37,38]. Resveratrol could also, by its effect of restoring glutathione levels, inhibit monocyte to macrophage differentiation and inflammation [39].

4. Treatment for COVID

One of the noteworthy resveratrol studies of 2017 found that it is a potent anti-Middle East Respiratory Syndrome (MERS) agent in vitro. At the time, this showed promise for resveratrol as a possible antiviral against MERS coronaviruses (MERS-CoV) of the future [18].

Bioinformatic studies showed that expression of nucleocapsid protein of MERS-CoV, necessary for replication, could be significantly decreased by resveratrol [40] further corroborating anti-viral potential against MERS-CoV. Resveratrol derivatives tested by molecular modeling techniques also presented as targets for drug development for COVID-19 [41]. This molecular docking analysis showed substances such as resveratrol to have better results than chloroquine, which is used in COVID-19, and predicted it to be less toxic than the antimalarial [42]. A network pharmacological approach with gene analysis showed resveratrol as a noteworthy candidate for COVID-19 with both antiviral as well as anti-inflammatory potential [43].

In vitro studies indicated that resveratrol inhibits SARS-CoV-2 replication with reduced cytotoxicity [44,45]. A study using specifically SARS-CoV-2 infected human primary bronchial epithelial cell cultures had similar results [46]. Xu et al. [47] demonstrated that resveratrol and polydatin, derived from the Chinese medicine, *Polygonum cuspidatum*, were specific and selective inhibitors of the 3-chymotrypsin-like protease and papain-like protease of SARS-CoV-2 in vitro. Moreover, Marinella suggested resveratrol (together with indomethacin) as adjuncts for the treatment or slowing progression of SARS-CoV-2 infection based on their results in a canine coronavirus model [48].

Recently a randomized double-blind placebo-controlled proof-of-concept trial of resveratrol demonstrated that the resveratrol group had a lower incidence of hospitalization, COVID-related emergency room visits, and pneumonia compared to the placebo group of outpatients with mild COVID-19 [49].

This therapeutic potential of resveratrol and its anti-viral activity against respiratory tract infections was further underlined in a review article by Filardo et al. [50]. The role that resveratrol can play in inhibiting hypoxia-inducible factor, makes its usage to help prevent severe COVID-19 symptoms, especially in obese patients, particularly attractive [51]. Resveratrol also has potential anti-thrombotic and anti-inflammatory properties which could help reduce the severity and mortality in COVID-19 [52,53] and should be further investigated for the possible relief of blood clotting side-effects associated with the DNA Adenovirus vector vaccines [54,55]. Further research should also investigate the role of resveratrol specifically in the pediatric population [56] and in aging COVID patients with excessive oxidative stress [57].

Resveratrol was demonstrated to suppress the harmful effects of the angiotensin II (Ang II)/angiotensin II type 1 receptor (AT1R) axis, while enhancing the AT2R/Angiotensin 1–7 (Ang 1–7)/Mas receptor axis,

protecting the aging kidney [58]. This effect of resveratrol on the two contrary pathways in the renin-angiotensin system (RAS) may also be beneficial in patients with SARS-CoV-2 infection [59]. Angiotensin-converting enzyme 2 (ACE-2) drives the classical RAS controlling blood pressure and fluid homeostasis, but this enzyme is hijacked by SARS-CoV-2 to enter cells [60]. In this respect, resveratrol effects the major pathways involved in SARS-CoV-2 pathogenesis namely regulation of RAS, expression of ACE-2, stimulating the immune system and suppressing pro-inflammatory cytokine release [61]. In adipose tissue where ACE-2 is highly expressed, resveratrol supplementation however showed a decrease in ACE-2 as well as a decrease in leptin, a pro-inflammatory adipokine, which may have a beneficial effect in the outcome of COVID-19 [62]. More studies regarding the exact mechanism on how resveratrol lowers SARS-CoV-2 entry or protects against COVID severity is needed to fully elucidate and understand this effect.

Different combinations and formulations with resveratrol are being investigated for COVID-19 e.g., a resveratrol-zinc nanoparticle drug-delivery system [63], liposome technology, nano emulsions, micelle solid dispersions [64–66] as well as a different route of administration i. e., inhalation [67], all with the aim of increasing effectiveness by improving its bioavailability. Chemically modified resveratrol analogs and precursors are also investigated. Pterostilbene is one such example, very similar in structure to resveratrol except that it contains two methoxy groups instead of two hydroxyl groups resulting in its increased oral absorption and bioavailability compared to resveratrol [63,68]. Yet, when compared with four other stilbenoids including pterostilbene, the unmodified resveratrol had the highest affinity for the spike protein S1: ACE-2 complex when analyzed using molecular docking studies [69]. This is often a challenge when trying to modify a molecule to improve bioavailability, the modification may lead to decreased efficacy.

5. Safety of resveratrol

Regarding its safety, resveratrol is generally accepted and used in countries all over the world for many years as a nutritional supplement. As a potent antioxidant resveratrol also has the potential to act as a pro-oxidant. It is therefore essential not to use too excessive dosages. Long-term clinical trials however noted very little side effects and resveratrol appeared to be safe and well-tolerated up to 5 g per day with some side effects such as nausea and diarrhea etc. at dosages of 2.5 g per day and higher [19,70]. There are also still questions regarding resveratrol's effect in conditions of demyelination i.e., multiple sclerosis [71] and should be used with care in these patients.

6. The potential

Due to its safety record, established role as an antioxidant supplement and the evidence of antiviral activity, as presented here, we propose that resveratrol should be used, not only to treat COVID-19 positive symptomatic patients, but also for patients that has recently been exposed to the virus for prophylactic use or those that had just been diagnosed and are still asymptomatic. This may be of value for the great number of patients currently infected with the omicron variant that do not require hospitalization. In many countries patients do not have access to current or new antiviral treatments and are often only treated symptomatically or sometimes with additional nutritional support in the form of vitamins and minerals i.e., vitamin D and zinc. In these cases, resveratrol can prove a valuable addition to the supportive treatment regime, whether alone or as an adjuvant supportive antiviral treatment. As discussed before, not only does resveratrol act as an antiviral but can also play a role in stimulation of the immune system and down regulation of the pro-inflammatory cytokine release, as well as reducing lung injury by reducing oxidative stress [61].

7. The challenge

Clearly, further clinical trials are required to further elucidate the possible role of this compound in the supportive treatment of COVID-19 and future similar diseases. However, as medicinal product developers and formulation consultants for the pharmaceutical industry for the last 20 plus years, we have found that there is a general lack of support for funding of substances from natural origin such as resveratrol in the pharmaceutical industry. This is independent of the potential and effectiveness of the substance, but rather due to patent challenges. If intellectual property cannot be protected effectively, the risk to spend billions on development and clinical trials become too high for the pharmaceutical industry. To overcome this, alternative strategies sometimes investigated are trademarking, using synergistic combinations, or chemically modifying the molecule – trying to increase its specificity, activity, or bioavailability, as discussed earlier, but at the same time to enable patenting. This, however, eventually leads to increased costs of the eventual treatment, often without necessarily improved efficacy.

New initiatives need to be sought involving the public and private sectors. Government, private sector, and non-profit organizations need to find new ways to collaborate, for the health of the broader population. Otherwise, the benefit of resveratrol and similar substances of potential could be lost at a time when it is most needed.

CRediT authorship contribution statement

Roy van Brummelen conceptualized and wrote the review manuscript. **Anna C. van Brummelen** assisted in writing the review manuscript.

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