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## Opinion Paper

# Glucose-6-phosphate dehydrogenase inhibitor for treatment of severe COVID-19: Polydatin



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## SUMMARY

The COVID-19 pandemic as the largest global public health crisis is now considered as an emergency at the World Health Organization (WHO). As there is no specific therapy for SARS-CoV-2 infection at present and also because of the long time it takes to discover a new drug and the urgent need to respond urgently to a pandemic infection. Perhaps the best way right now is to find an FDA-approved drug to treat this infection. Oxidative stress and inflammation play a vital role in the progression of tissue injury in COVID-19 patients; furthermore, the G6PD activation is related to increased oxidative inflammation in acute pulmonary injury. In this regard, we propose a new insight that may be a good strategy for this urgency. Exploiting G6PD through inhibiting G6PD activity by modifying redox balance, metabolic switching and protein–protein interactions can be proposed as a new approach to improving patients in severe stage of COVID 19 through various mechanisms. Polydatin is isolated from many plants such as *Polygonum*, peanuts, grapes, red wines and many daily diets that can be used in severe stage of COVID-19 as a G6PD inhibitor. Furthermore, polydatin possesses various biological activities such as anti-inflammatory, antioxidant, immunoregulatory, nephroprotective, hepatoprotective, anti-arrhythmic and anti-tumor. Our hypothesis is that the consumption of antioxidants such as Polydatin (a glucoside of resveratrol) as a complementary therapeutic approach may be effective in reducing oxidative stress and inflammation in patients with COVID-19.

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## 1. Introduction

The COVID-19 pandemic as the largest global public health crisis is now considered as an emergency by the World Health Organization (WHO). Since there is currently no specific therapy for SARS-CoV-2 infection and also given the long time it takes to discover a new drug and the urgent need for an urgent response to pandemic infection. Perhaps the best way right now is to find an FDA-approved drug to treat this infection.

It has been confirmed that oxidative stress and inflammation related with SARS-Cov-2 (COVID-19) increase the severity of the tissue injury [1,2], also, the activation of G6PD is associated with increased oxidative inflammation in acute pulmonary injury [3,4]. The consumption of antioxidants such as Polydatin (a glucoside of resveratrol) [5] as a complementary therapeutic approach may be

effective in reducing oxidative stress and inflammation in patients with COVID-19. In this regard, we propose a new insight that may be a good strategy for this urgency.

## 2. Oxidative stress and SARS-CoV-2

Oxidative stress has been determined as a disruption in the prooxidant-antioxidant balance in favor of the prooxidants. Over-production of prooxidants such as reactive oxygen species (ROS) and antioxidants depletion such as glutathione (GSH) are crucial for viral replication and the subsequent virus-associated disease [6]. It seems that oxidative stress and antioxidant power depletion play a vital role in the progression and severity of COVID-19-associated sepsis [1]. Previous animal studies have shown improved ROS levels and disruption of antioxidant system during SARS-CoV infection [7]. It also showed that oxidative stress played a crucial role in severe acute respiratory syndrome coronavirus (SARS-CoV) infection [8]. Viral pathogens such as SARS-CoV trigger oxidative stress-nuclear factor κB- toll-like receptor (mainly TL4) signaling

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pathways, leading to acute lung injury. TLR4-TRIF (Toll/IL-1 receptor domain-containing adaptor inducing IFN- $\beta$ )-TRAF6 (tumor necrosis factor receptor associated factor 6) signaling was acknowledged as a pathogenic axis that can manage the severity of acute lung injury [9]. The theory that oxidative stress and associated inflammation play a major role in the pathogenesis of various chronic diseases [10] such as cardiovascular disease, diabetes and respiratory diseases, identified to increase the risk of severe stages and death in patients with COVID-19, is supported by increasing data [11].

### 3. Oxidative stress and G6PD

Glucose 6-phosphate dehydrogenase (G6PD) as a critical mediator of redox balance is one of the enzymes of the pentose phosphate pathway that metabolize glucose in aerobic conditions. One of the products of the pentose phosphate pathway is NADPH which is due to the activity of G6PD. NADPH in turn is involved in the synthesis of fatty acids and steroids, as well as maintaining the level of reduced GSH for antioxidant activity. Although G6PD deficiency studies have traditionally focused on erythrocyte disorders but recent researches depicted that G6PD participates in a variety of cellular processes through redox signaling [12].

Nitric oxide (NO) production, as an important factor in cell survival, immune response, insulin signaling and vascular and neural protection, depends on the status of G6PD. Moreover, altered G6PD activity is related to a myriad of pathological events and diseases including autophagy, insulin resistance, infection, inflammation, as well as diabetes and hypertension [13].

Increased G6PD activity is associated with increased lung cell capacity for proliferation and replacement of damaged cells. This enzyme causes excessive hypoxia-inducible factor1 (HIF1), Cyclin A, phospho-histone H3 expression which are promote undifferentiated CD133<sup>+</sup> cells and self-replication and changes in cellular settings. The enzyme inhibitor decreases the accumulation of CD133<sup>+</sup> and decreases cell damage [14].

Studies have shown that increasing G6PD expression and activation plays an important role in the progression of hypoxic pulmonary vasoconstriction (HPV) and the development of pulmonary hypertension. The regression analysis of G6PD activity and the ratio of NADPH to NADP<sup>+</sup> to HPV response clearly showed a positive linear relationship between G6PD and HPV activity. The findings suggest that G6PD and NADPH redox have played an important role in the mechanism of HPV and, in turn, in increasing pulmonary arterial pressure, which plays a role in pulmonary hypertension. Acute pulmonary injury leads to increased G6PD activity, and data also show that activation of G6PD is associated with increased oxidative inflammation in acute pulmonary injury. Therefore, inhibition of G6PD may be a useful strategy in acute pulmonary injury to limit oxidative damage and improve airway inflammation [3,4].

Excessive G6PD expression also increases the activity of the inducible nitric oxide synthase (iNOS) to increase the bioavailability level of NO. G6PD modulation affects ROS mediated by NOX2 in airway epithelial cells (AEC) during acute lung injury [4,15]. In diabetes, increased G6PD activity and increased NADPH levels are associated with endothelial and vascular dysfunction. There is also a 10-fold increase in myocardial G6PD expression and a 2-fold increase in G6PD activity in pacing-induced heart failure compared to normal hearts. In addition, inhibition of G6PD improves chronic hypoxic pulmonary hypertension. Finally, G6PD plays a mediating role in smooth muscle hypertrophy caused by angiotensin II and in the progression of atherosclerosis [16,17].

### 4. G6PD and COVID-19

In severe stage of COVID19, patients suffer from acute disorders in vital organs such as acute lung damage, cardiovascular problems, high blood sugar due to an imbalance of glucose metabolism, kidney damage as well as inflammatory response known as cytokine storm [18,19].

On the other hand, many studies have shown the role of G6PD in acute cell damages and inflammatory response as well as diabetes, hypertension and smooth muscle hypertrophy [17].

A recent study found that GSH was effective in maintaining antioxidant balance and reducing oxidative damage caused by SARS-CoV-2. Another study found that vitamin B3 is very effective in reducing lung damage, which is a major problem in patients with severe COVID 19 to prevent lung tissue damage and it has been suggested as a wise way to improve lung problems in these patients. Glutathione and vitamin B3 are important factors and products in the pathway of pentose phosphate that are regulated by G6PD [20,21]. Both N-acetyl cysteine and alpha lipoic acid are able to help regenerate GSH levels, and clinical data suggest that N-acetyl cysteine and its antioxidant properties may play a role in the treatment or prevention of acute viral respiratory infections [22].

Therefore, it is recommended that G6PD activity may be evaluated as one of the diagnostic markers and its relationship with the severity of the disease should be statistically analyzed so that, if the hypothesis is confirmed, it is possible to use methods to modify this enzyme in the COVID-19 disease process.

Furthermore, exploiting G6PD through inhibiting G6PD activity by modifying redox balance, metabolic switching and protein–protein interactions can be proposed as a new approach to improving of patients with severe stage of COVID 19.

### 5. Polydatin

Polydatin is also referred to as piceid (3,4',5-trihydroxystilbene-3- $\beta$ -D-glucoside) (Fig. 1), is a glycoside form of resveratrol which is isolated from many plants such as Polygonum, peanuts, grapes, red

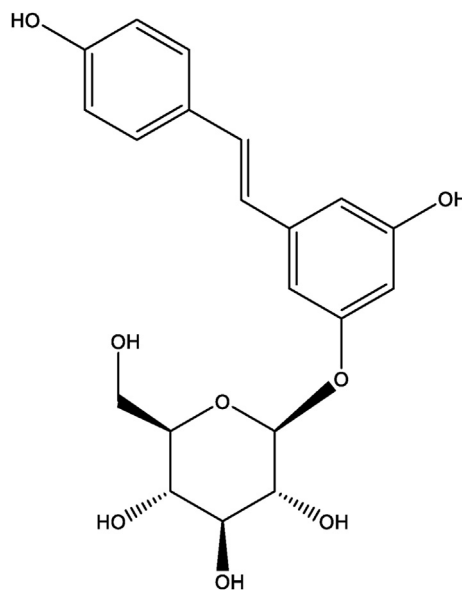


Fig. 1. 3,4',5-trihydroxystilbene-3- $\beta$ -D-glucoside.

wines, hops, cocoa products, chocolate products and many daily diets. Polydatin possesses various biological activities including anti-inflammatory, antioxidant, immunoregulatory, nephroprotective, hepatoprotective, anti-arrhythmic and anti-tumor [23]. Polydatin has been demonstrated to directly inhibit G6PD which result in redox imbalance and causing elevated endoplasmic reticulum stress [24]. Moreover, Polydatin reduced ROS and attenuated oxidative stress through the Keap1/Nrf2/ARE pathway in Graves' orbitopathy [5]. Polydatin suppressed the inflammatory cytokines secretion, and restrained the TLR6/MyD88/NF- $\kappa$ B pathway by *Mycoplasma gallisepticum* infection (a main cause of chronic respiratory disease) in vivo and in vitro [25]. Another study showed that Polydatin weakens cadmium-induced oxidative stress through inducing SOD activity and regulating mitochondrial function in *Musca domestica* larvae [26]. Moreover, Polydatin supplementation reduces hepatic pathological changes and reduces insulin resistance, as demonstrated by the improved evaluation of the homeostasis model of baseline insulin resistance values and glucose tolerance testing [27]. We conclude that Polydatin may lessen oxidative stress and inflammation via the mentioned pathways in COVID-19 patients. However, before implementing this type of treatment, more studies are needed.

#### Authors' contributions

All authors contributed equally to perceive the idea and write the manuscript.

#### Declaration of competing interest

The authors declare no competing interests for the content of this paper.

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