

# Beneficial Effects of Anti-Oxidative Herbal Medicines in Diabetic Patients Infected with COVID-19: A Hypothesis

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**Abstract:** During the pandemic of Coronavirus Disease 2019 (COVID-19), it is critical to introduce potential medical treatments. Anti-oxidative herbal medicines with evidence-based beneficial impacts in the treatment of diabetes mellitus can be suggested as an adjuvant therapy to its conventional treatments in patients infected with COVID-19.

**Keywords:** herbal medicine, COVID-19, anti-oxidative, diabetes mellitus

## Introduction

The World Health Organization (WHO), declared a pandemic of the Coronavirus Disease 2019 (COVID-19) following its rapid spread after March 11, 2020.<sup>1</sup> As a viral disease, COVID-19 is characterized by some or all of the following symptoms: fever, dry cough, fatigue, dyspnea, pneumonia, and dysfunction of specific organs such as the respiratory tract, heart, liver, and kidney. Patients with underlying diseases such as diabetes mellitus, hypertension, severe obesity, and cardiovascular disease (CVD) have been proven to be at higher risk of complications and death than others.<sup>2,3</sup> According to recently published studies, patients suffering from type 2 diabetes mellitus (T2DM) have been hospitalized more than patients with non-T2DM, with severe forms and poor prognosis of COVID-19.<sup>4-6</sup> Based on the WHO situation report on July 21, 2020, the confirmed COVID-19 cases and deaths associated with COVID-19 were 14,348,858 and 603,691 worldwide, respectively.<sup>7</sup> Based on the 2019 International Diabetes Federation (IDF) report, the world prevalence of diabetes was 463 million, and is expected to reach 578 million in 2030, and 700 million in 2045.<sup>8</sup> It was estimated that nearly 20–50% of patients infected with COVID-19 have diabetes, much higher than the worldwide incidence rate of diabetes.<sup>9</sup>

Hyperglycemia and inflammation are the possible causes of severity and high mortality rates of COVID-19 in diabetic patients.<sup>10</sup> Hyperglycemia might worsen the prognosis and survival rate of COVID-19 and can be attended with a high proportion of inflammatory biomarkers and cytokines.<sup>11,12</sup> Abnormalities in the secretion and transportation of insulin within the tissues are associated with the changes in structure and function of endothelial cells and  $\beta$  cells as the result of cytokine secretions which lead to the apoptosis of the  $\beta$  cells, hyperglycemia, and insulin resistance. Furthermore, the cytokine storm might cause progressive failure of the liver and kidney functions.<sup>13</sup> Extensive damage of liver tissue in patients with

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COVID-19 reduces the production of glycogen and accelerates insulin resistance and hyperglycemia. Therefore, managing the hyperglycemia would result in the reduction of the cytokines serum level and improvement of the prognosis in COVID-19 patients.

Although some off-label drugs showed beneficial results in the treatment of COVID-19, no vaccine or specifically-approved drug is available to eradicate this disease, this necessitates the introduction of potential medical treatments or use of off-label drugs in this situation.<sup>14,15</sup> Therefore, considering alternative interventions such as traditional medicine as an adjuvant to the conventional treatments of diabetes in COVID-19 patients is required.

Oxidative stress, defined as an imbalance between reactive oxygen species (ROS) and anti-oxidative stress capacity, has been established as the primary pathologic mechanism of diabetes.<sup>16</sup> Changes in the activity and serum level of glucose-6-phosphate dehydrogenase (G6PD) as a marker of inflammation could generate nicotinamide adenine dinucleotide phosphate (NADPH) that induces oxidative stress and G6PD deficiency promotes folding, trafficking, and viral spread. In a study, a 12-fold higher viral production of coronavirus 229E was demonstrated. It shares sequence similarities with COVID-19 and clinically resembles it in human lung epithelial cells that have G6PD deficiency compared to control cells.<sup>17,18</sup> Acute lung injury in COVID-19 can result from the local generation of ROS. In patients infected with SARS-coronavirus (SARS-CoV), a significant increase in the production of oxidized lipids (oxLDL) was observed.<sup>19</sup> Caspase recruitment domain-containing protein 9 (CARD9)-dependent as a mediator of oxLDL in macrophages triggers the inflammatory signaling pathway in response to viral infection. The CARD9 could activate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) that increase the expression of cytokines.<sup>20</sup> Therefore, respiratory viral infections have generally been associated with cytokine production, inflammation, apoptosis, and other pathophysiological processes known as oxidative stress.<sup>21</sup> Although in clinical studies a clear correlation was found between oxidative stress biomarkers and the severity of many viral diseases, this correlation for SARS-CoV has been seen in limited experimental studies.<sup>22,23</sup>

According to the literature, herbal medicines, especially those containing polyphenols, have shown strong antioxidant potential helpful for the treatment of diabetes.<sup>24–26</sup> However, rather than having hypoglycemic

and antioxidant effects, some of these compounds have exhibited many other useful effects. Fruits and vegetables rich in flavonoids showed significant reductions in biomarkers of inflammation and improved microvascular reactivity through inhibition of NF- $\kappa$ B.<sup>27,28</sup> Beneficial effects of flavonoids were reported in the prevention and treatment of influenza viruses through suppression of neuraminidase, inhibition hemagglutinin activity, modifying cellular signaling pathways, and transcription factors that resulted in the reduction of viral replication.<sup>29</sup> These anti-influenza effects were observed after the administration of *Geranium sanguineum L.* extract in *in vitro* study of embryo fibroblast cells.<sup>30</sup> Another example is theaflavin derivatives (polyphenols from black tea) that their anti-influenza activities have been shown via down-regulation of IL-6 expression.<sup>31</sup>

Evidence suggest that the extract of *Scrophularia striata* has anti-oxidative, anti-cancer, anti-inflammatory, anti-asthmatic, and neuroprotective effects, secondary to its two flavonoid components, quercetin, and isorhamnetin 3-O-rutinoside.<sup>32</sup> The antiviral and antidiabetic effects of quercetin have been discussed in several studies.<sup>25,33</sup> Antiviral activity of quercetin against influenza virus and SARS-CoV was confirmed by inhibition of SARS-CoV 3-chymotrypsin-like protease (3CLpro) expression in *Pichia pastoris*.<sup>33,34</sup> It has been identified that 3CLpro has a vital role in viral replication. Therefore, 3CLpro can be considered as the targeted therapy. Due to the high similarity between the 3CLpro sequence of COVID-19 and that of SARS-CoV,<sup>35</sup> it could be hypothesized that quercetin may also exhibit antiviral effects on SARS-CoV-2.

Another example is curcumin – that is, the active ingredient of the dietary spice turmeric, from the plant *Curcuma longa* – has anti-inflammatory, anti-cancer, renal, cardioprotective, and antiviral effects, as well as cytokine suppression in both human and animal studies.<sup>36</sup> Inhibition of virus replication, 3CLpro activity, blocking the NF- $\kappa$ B signaling, and inhibition of bio-inflammatory markers production can mediate the antiviral impacts of curcumin.<sup>37,38</sup> In a clinical trial, daily dose of 1 gram curcuminoid for 8 weeks significantly increased serum level of superoxide dismutase (SOD) as an anti-oxidative biomarker, reduced serum level of malondialdehyde (MDA) as an oxidative biomarker, and decreased circulating C-reactive protein (CRP) concentration compared with placebo.<sup>39</sup>

In the recent viral outbreaks of COVID-19 and SARS-CoV, clinical pieces of evidence on the beneficial effects of Traditional Chinese Medicine (TCM) and certain

polyphenolic compounds have been suggested.<sup>40,41</sup> Positive improvement responses in clinical symptoms such as fever, quicker clearance of lung infection, better control of fungal infection, and decrease of mortality rate in SARS-CoV infected patients were observed in the intervention group (TCM with/without combination with conventional medicine) compared to control group.<sup>41</sup> The antiviral activity of TCM herbal extracts might be related to their active compounds such as baicalein and quercetin that are capable of COVID-19 inhibition by blocking 3CLpro activity and NF- $\kappa$ B signaling.<sup>41</sup> Besides, the TCM applied for the treatment of COVID-19 infected patients have shown anti-inflammatory effects through reduction of cytokine production.<sup>41</sup> All of these studies suggest that herbal medicines be used as adjuvant to currently prescribed drugs to treat COVID-19 in patients with diabetes and also can be considered as a suitable source to identify novel therapeutic agents for COVID-19. However, better designed experimental and clinical studies are urgently required to confirm their beneficial effects.

## Disclosure

The authors certify that there is no conflict of interest.

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