

# Potential Role of Nrf2 Activators with Dual Antiviral and Anti-Inflammatory Properties in the Management of Viral Pneumonia

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**Abstract:** The outbreak of coronavirus disease 2019 (COVID-19) pandemic has already caused a huge burden to the global healthcare system, with the death toll reached tens of thousands. Although some antiviral agents were identified and used to inhibit viral replication, the management of cytokine storm is also a critical issue. In this article, we reviewed the literature on drug candidates for severe acute respiratory syndrome (SARS-CoV-1) and provided a brief overview of a class of drugs that exert antiviral and anti-inflammatory effects. These molecules mitigated inflammatory cytokine cascades induced by viral infections via Nrf2 activating capacity and might have additional anti-fibrotic and anti-remodeling properties. Besides, their effects on the regulation of scavenger receptors expression by macrophages may offer some benefits to the pulmonary antibacterial defense system after viral infection. The potential roles of these agents assessed on the basis of the pathophysiology of viral pneumonia and acute respiratory distress syndrome were also discussed. Further research is needed to ascertain whether Nrf2 activators are useful in the management of viral pneumonia.

**Keywords:** COVID-19, viral pneumonia, Nrf2 activators, curcumin, sulforaphane, macrolide

The coronavirus disease 2019 (COVID-19) pandemic has already caused a tremendous burden on the healthcare system globally and poses a threat to all human beings. Scientists and doctors have been desperately trying to find possible treatments since the outbreak of the disease. Some potential treatment options, including nucleoside analogs, protease inhibitors, and interferon, were proposed and tested.<sup>1</sup> Besides the existing antiviral drug options, naturally occurring phytochemicals might also have a role in combating viral pneumonia. In an in vitro study of severe acute respiratory syndrome coronavirus (SARS-CoV-1), several compounds with antiviral activity, including diterpenes, sesquiterpenes, lupane-type triterpenes, lignoids, and curcumin were identified.<sup>2</sup> Interestingly, curcumin and some triterpenoids were proven to be nuclear factor erythroid 2-related factor 2 (Nrf2) activators, and the potential role of Nrf2 activators in the management of respiratory viral infection has drawn some scientists' attention.<sup>3,4</sup> The Nrf2-antioxidant response element (ARE) pathway is known to maintain the redox balance in cells and reduces inflammation. These groups of plant-derived chemicals and their analogs might provide a class of drugs that possesses both antiviral and anti-inflammatory properties and might help tackle the pathophysiological changes in viral pneumonia and acute respiratory distress syndrome (ARDS).<sup>3</sup>

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Among the Nrf2 activators, curcumin is the most extensively studied and widely used product with established safety profile and biological effects.<sup>5–7</sup> Curcumin has been proven to have broad-spectrum antiviral properties against many RNA viruses, including influenza A virus, respiratory syncytial virus (RSV), and norovirus.<sup>5</sup> Animal experiments, mostly using influenza A virus, showed decreased pulmonary viral titers, decreased production of cytokines (such as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6) and matrix metalloproteinase-2 and 9 (MMP-2,9), decreased infiltration of inflammatory cells, decreased pulmonary histopathological injury score, and increased animal survival.<sup>8–11</sup> Interestingly, although curcumin did not affect the clearance of reovirus in a mouse model, it reduced collagen deposition in lung tissue and decreased the expression of myofibroblast phenotype.<sup>8</sup> The observed anti-fibrotic and anti-remodeling effects might offer additional benefits if they translate into clinical practice because CT images of COVID-19 pneumonia patients showed ground glass opacities with partial consolidation and were absorbed with formation of fibrotic stripes after improvement.<sup>12</sup> Whether the observed pulmonary fibrosis is a temporary phenomenon or may affect the functional recovery of patients remain to be studied. In another study, it was demonstrated that curcumin reduced the lipopolysaccharide (LPS)-induced mucin 5AC secretion in a mouse model.<sup>13</sup> Moreover, it is also known that Nrf2, a key mediator that combats oxidative stress, can be upregulated by curcumin.<sup>4</sup> Nrf2/ARE pathway targets more than 500 genes, including genes which regulate oxidative stress (HO-1, GCLM, and GCLC), and reduces inflammation by decreasing NF- $\kappa$ B and TGF- $\beta$ . Many studies have demonstrated the protective effect of Nrf2 activators in hyperoxia- or LPS-induced ARDS models.<sup>3</sup> Besides their function in the lung tissue, Nrf2 activators also have a renoprotective effect.<sup>14</sup> Whether Nrf2 activating drugs are useful in acute kidney injury induced by ARDS remains to be further studied.

Although curcumin has been studied in various inflammatory and proliferative diseases, its effects on human respiratory tract infection have rarely been tested. In a clinical study, the effects of lactoferrin and curcumin in healthy children with recurrent respiratory infection were examined, and the results showed reduced infection and skewing of CD8+ T lymphocyte maturation.<sup>15</sup> Direct clinical evidence of curcumin in human viral pneumonia is still limited. Besides, one of the major drawbacks of curcumin is its poor absorption and rapid metabolism. Several formulation and conjugation strategies were used to increase the bioavailability of oral curcumin.<sup>16</sup> Different

routes of administration, such as inhalation and intravenous routes, were also evaluated.<sup>17,18</sup> However, turmeric infusion by a naturopathic practitioner even caused mortality and was considered to be related to the presence of PEG 40 castor oil.<sup>19</sup> Therefore, pharmaceutical-grade preparation of intravenous curcumin should be used in medical institutions by qualified personnel.

Another group of molecules, namely terpenes, was also studied for its Nrf2 activating effect.<sup>4</sup> Several semisynthetic and synthetic triterpenoids, including bardoxolone methyl and omaveloxolone, are currently undergoing clinical trials for kidney diseases. Some evidence indicates that bardoxolone methyl suppresses RNA viruses such as dengue virus and Zika virus.<sup>20</sup> Although some experiments showed its positive effects in LPS-induced acute lung injury mouse model,<sup>21</sup> its effect on respiratory tract infection is still largely unknown. Another Nrf2 activator named sulforaphane was also studied for its antiviral capacity, and could suppress respiratory viruses, such as RSV<sup>22</sup> and influenza virus.<sup>23</sup> In a human study using live attenuated influenza virus on human subjects, sulforaphane was found to increase granzyme B production in natural killer (NK) cells after inoculation.<sup>24</sup> Lower granzyme B levels were related to the risk for influenza in institutionalized older adults, and serum granzyme B levels correlated with protection against influenza in older adults following vaccination.<sup>25,26</sup> Besides, a study also showed that sulforaphane increased the expression of macrophage receptor with collagenous structure (MARCO) in alveolar macrophages, and thus, provided survival benefits in an animal model of postinfluenza bacterial pneumonia.<sup>27</sup> However, although *in vitro* studies showed improved phagocytosis of bacteria by alveolar macrophages from patients with COPD,<sup>28</sup> an *in vivo* study of sulforaphane failed to induce Nrf2 target gene expression in alveolar macrophages from the same disease population.<sup>29</sup> Therefore, the effects of sulforaphane observed in healthy subjects may not be accurately extrapolated to patients with COPD. Besides, another advantage of sulforaphane over curcumin is that it has good oral bioavailability.<sup>30</sup> The overall benefits of curcumin and sulforaphane were demonstrated by their ability to increase survival rates in influenza and sepsis animal models.<sup>10,11,27,31–33</sup> However, in many experiments animals were pretreated with drugs or drugs were used on the same day of virus inoculation; the results may be different in clinical settings because patients may be at a more advanced disease stage. Whether these agents are useful for chemoprevention or treatment remains to be elucidated.

**Table 1** Summary of the Effects of Nrf2 Activators and Macrolides on the Pathophysiology of Viral Pneumonia/ARDS Based on Current Evidence

|  | Curcumin  |   | Sulforaphane  |   | Macrolides  |   |
|--|---|---|---|---|---|---|
|  | Influenza virus                                       | Other disease models  | Influenza virus   | Other disease models  | Influenza virus   | Other disease models  |
| Positive effect on the pathophysiology of viral pneumonia/ARDS |   |   |   |   |   |   |
| Antiviral effect   | In vitro <sup>5,10,11</sup> and in vivo <sup>11</sup> | In vitro and in vivo studies showed broad spectrum antiviral effect. <sup>6,7</sup>   | In vitro: antiviral effect against influenza virus <sup>23</sup><br>In vivo: antiviral effect against RSV <sup>22</sup> |   | In vitro and in vivo: antiviral effect against rhinovirus, RSV, and influenza virus <sup>35</sup> |   |
| Decreased infiltration of inflammatory cells                   | In vivo <sup>9,10</sup>                               | In vivo: mouse model of reovirus infection <sup>8</sup>   | –   | In vivo: oleic acid induced ARDS rabbit model <sup>42</sup>                                     | In vivo <sup>43</sup>   | Various inflammatory disease models <sup>36</sup>                           |
| Decreased production of proinflammatory cytokines              | In vitro and in vivo <sup>9–11</sup>                  | In vivo: mouse model of reovirus infection <sup>8</sup>   | –   | In vivo: LPS-induced acute lung injury mouse model <sup>44</sup>                                | In vitro, in vivo, and human studies <sup>35</sup>  |   |
| Increased production of granzyme b by NK cells                 | –   | –   | Human study <sup>24</sup>   | –   | –   | –   |
| Decreased levels of MMPs                                       | In vitro and in vivo <sup>10</sup>                    | In vivo: LPS and ovalbumin challenged mouse model <sup>45</sup>   | –   | In vivo: LPS-induced acute lung injury mouse model <sup>44</sup>                                | In vivo <sup>43</sup>   | Various inflammatory disease models <sup>36</sup>                           |
| Inhibition of fibrosis   | –   | In vivo: mouse model of reovirus infection <sup>8</sup>   | –   | –   | –   | –   |
| Inhibition of mucin secretion                                  | –   | In vitro: LPS stimulated human bronchial epithelial cells (NCI-H292) <sup>13</sup><br>In vivo: LPS intratracheal instillation mouse model <sup>13</sup> | –   | In vitro: neutrophil elastase challenged human airway epithelial cells (NCI-H292) <sup>46</sup> | –   | In vitro: rhinovirus infected human tracheal epithelial cells <sup>47</sup> |

(Continued)

Table 1 (Continued).

|  | Curcumin                 | Sulforaphane  |  | Macrolides   |  |   |
|--|--------------------------|---|--|--|--|---|
| Positive effects against bacterial infection and modulation of scavenger receptor expression | –                        | In vitro and in vivo studies showed broad spectrum antibacterial effect. <sup>6,7</sup><br>In vitro: enhanced phagocytosis of inactivated <i>Staphylococcus aureus</i> bioparticles through up-regulation of CD36 surface expression on macrophages <sup>48</sup> | In vitro: improved bacterial phagocytosis in INFγ treated macrophages through MARCO upregulation <sup>27</sup><br>In vivo: improved bacterial clearance in a postinfluenza bacterial pneumonia mouse model <sup>27</sup> | In vitro: improved phagocytosis of bacteria by alveolar macrophages from patients with COPD <sup>28,49</sup><br>In vivo: increased MARCO expression and enhanced phagocytic ability of macrophages in a mouse model <sup>49</sup><br>Human study: increased MARCO expression in peripheral blood mononuclear cells <sup>49</sup> | Antibacterial effect by inhibiting bacterial ribosome 50S subunit.<br>In vivo: mitigated influenza-induced decline in MARCO expression in a mouse model of COPD with postinfluenza bacterial pneumonia <sup>50</sup> | – |
| Increased survival   | In vivo <sup>10,11</sup> | In vivo: CLP murine model of sepsis <sup>31,33</sup>  | In vivo: postinfluenza bacterial pneumonia mouse model <sup>27</sup>   | In vivo <sup>35</sup><br>In vivo: HMGB1-induced mouse sepsis model <sup>32</sup>   | Human study: decreased mortality in patients with ARDS <sup>51</sup>   |   |

**Abbreviations:** MMP, matrix metalloproteinase; CLP, cecal ligation and puncture; COPD, chronic obstructive pulmonary disease.

According to a recent publication, azithromycin and hydroxychloroquine combination treatment was associated with SARS-CoV-2 viral load reduction and decreased the duration of virus carriage in a small group of patients.<sup>34</sup> The efficacy of macrolides in respiratory viral infections and inflammatory diseases has been extensively researched,<sup>35,36</sup> and their anti-inflammatory profiles are similar to the aforementioned Nrf2 activators. An in vitro study using human small airway epithelial cells revealed that clarithromycin decreased H<sub>2</sub>O<sub>2</sub>-induced inflammation through upregulation of Nrf2 expression.<sup>37</sup> Another study also found that azithromycin alleviated cigarette smoke extract induced inflammation in human airway epithelial cells by activating Nrf2.<sup>38</sup> Whether the observed effects of macrolides in viral infections are related to Nrf2 activating property remains to be clarified. Another group of antibiotics, including tetracycline, minocycline, and doxycycline, is a well-known class of antibiotics with anti-inflammatory features and was proposed as a potential repurposing candidate for the management of COVID-19 diseases.<sup>39</sup> Although a study revealed that minocycline upregulated Nrf2 in retrovirus infected astrocytes,<sup>40</sup> another study showed that doxycycline inhibits malondialdehyde-acetaldehyde-induced activation of Nrf2 in HEK 293 Nrf2/ARE cells.<sup>41</sup> Therefore, the impact of different drugs of the tetracycline group on the Nrf2 pathway remains to be further clarified. The effects of Nrf2 activators on the pathophysiology of viral pneumonia/ARDS based on evidence are summarized in Table 1.

In conclusion, the activation of Nrf2 pathway by drugs has been researched for its antiviral and anti-oxidative mechanisms and can be the foundation for further clinical development. The Nrf2 activators and their analogs might be tested for their potential antiviral efficacy and might become drug candidates, either alone or in combination with other antiviral agents, for further clinical trials in viral pneumonia.

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