**LETTER TO THE EDITOR**

# Should we try the antiinflammatory natural product, celastrol, for COVID-19?

Dear Editor,

Readers are aware of the global emergency caused by the novel coronavirus SARS-CoV-2 (2019-nCoV) infection that results in COVID-19. With high rate of transmission and proven lethality, especially to the elderly, there is currently no vaccine or drug therapy to COVID-19. The century-old strategy currently practised around the world including sanitary advice and social distancing is testimony to our poor preparedness for new respiratory viral diseases. In order to stimulate research in the field, particularly new therapeutics, the present perspective is presenting arguments for assessing the potential efficacy of the pentacyclic natural triterpenoid, celastrol, with multiple pharmacological effects including in the lungs as a potent antiinflammatory agent.

As always and where vaccines are not available, antiviral agents take the centre stage of trials and both old and new potential viral inhibitors (from attachment to host cells to replication and release) should be considered. On this basis, speculative arguments for potential application of pharmacological agents based on the emerging role of angiotensin converting enzyme 2 and related enzymes/proteins have been postulated (Fan et al., 2020). Such an approach or by any other direct antiviral agent would have profound effect on the first phase of the disease where viral clearance is critical. The main phase and that is more pathologically relevant to COVID-19 is, however, the delayed pneumonia which itself could vary depending on the disease severity level (Li et al., 2020). While it could be argued that immunosuppressants should not be used especially at the earlier stage of the disease, critically ill patients under exaggerated immune response leading to extensive lung injury (pneumonia) may benefit from targeted antiinflammatory approach.

The antiinflammatory properties of celastrol has been demonstrated in experimental animal models and proven to be mostly through suppression of NF- $\kappa$ B signalling (Zhang, Zhao, et al., 2019; Zhang, Zhou, et al., 2019). Specifically to the lungs, its potential in alleviating chronic obstructive pulmonary disease in mice was shown to be via antiinflammatory mechanism (Shi et al., 2018). In this case, it could reduce the levels of inflammatory cytokines such as interleukin-8 (IL-8), tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), and monocyte chemoattractant protein-1 while enhancing antioxidant defences (superoxide dismutase and catalase). In rats subjected to lipopolysaccharide (LPS)-induced acute respiratory distress syndrome, celastrol could also ameliorate the inflammation-mediated injury as well as the expression levels of pro-inflammatory cytokines (TNF- $\alpha$ , IL-1, IL-6, and IL-8) and NF- $\kappa$ B (Wei & Wang, 2017). Under asthmatic condition

or increased airway hyperresponsiveness, a positive outcome for orally administered celastrol both in the disease level and Th17 inhibition was observed in mice (Zeng, Lin, Zheng, Zhang, & Zhang, 2018). Furthermore, the organoprotective effects of celastrol were reported including in renal injury under diabetes (Zhang, Chen, et al., 2019), or drug-induced nephrotoxicity; all of which are related to downregulating NF- $\kappa$ B (Yu et al., 2018). Even though there are some studies showing a negative outcome such as in the LPS-induced liver and kidney damage (Wu et al., 2018), protection against inflammatory damage including those induced by TLR4-mediated immune response in steatotic liver cells have been shown (Han, Sun, Li, Xie, & Chen, 2018).

Of interest is also the in vitro immunomodulatory effect of celastrol against influenza A virus (Khalili, Karimi, Moradi, & Shirzad, 2018) where the expression of TNF- $\alpha$  and IL-6 were shown to be suppressed without direct effect on virus titration (Khalili et al., 2018). Through induction of interferon (IFN)- $\alpha$  expression and activation of downstream antiviral response, the compound also showed its potential in the mouse model of dengue virus infection (Yu et al., 2017). More importantly, celastrol was shown to ameliorate a ventilator-induced lung injury in mice (Ren et al., 2017).


In MERS-CoV and SARS-CoV infection, the inflammatory response mediated by the rapid acting NF- $\kappa$ B pathway was regulated by TMPRSS2 levels within the airway in a TMPRSS2 knockout murine model, suggesting that NF- $\kappa$ B pathway and Epitheliasin (TMPRSS2) are interrelated (Iwata-Yoshikawa et al., 2019). The epithelial and membrane localisation of TMPRSS2 in human heart, brain and apical surface of lung epithelial cells was emphasized by Jacquinet, Rao, Rao, and Hoidal (2000) and in upper airways by Bugge, Antalis, and Wu (2009). Airway proteases such as Epitheliasin seem to be involved in the pathology of viral infections with Influenza and also coronaviruses (Laporte & Naesens, 2017). Inhibiting TMPRSS2 could exert a dual effect on COVID-19, that of limiting viral entry by reducing the cleavage of the spike protein in ACE2 receptor mediated viral entry as shown by Hoffmann et al. (2020) and that of inhibiting NF- $\kappa$ B pathway leading to a weaker pro-inflammatory response with less severe lung pathology as shown by Iwata-Yoshikawa et al. (2019) on SARS and MERS-CoV, with celastrol likely mediating both mechanisms.

Even though application of antiinflammatory agents in COVID-19 may be debatable or one should say highly dependent on the disease stage, a trial of compounds like celastrol with promising effect in a variety of related lung diseases is highly encouraged. Although the toxicity of celastrol in numerous cellular and animal models of

inflammation and other diseases (e.g. cancer) has been well-established, its toxicity profile in human subjects also need to be established. Finally, there is the possibility that the studies discussed in this letter have not been performed in accordance to the perspective outlined as the best pharmacological research practice on bioactive plant preparations (Heinrich et al., 2020). Also, there is the possibility that the concentrations used in vitro are high and hardly reached in vivo following therapeutic administration.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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