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Cucurbitacin: As a candidate against Cytokine Storm in Severe COVID-19 Infection

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ABSTRACT

The severity of SARS-CoV-2 infection is marked by elevated cytokines and chemokines levels like interleukin 6 (IL-6), interferon-gamma (IFN-γ), tumour necrosis factor (TNF), IL-2 and monocyte chemotactic protein 1. This hyperactive pro-inflammatory response identified as the Cytokine Storm (CS) complicates the disease leading to extensive damage of the host tissue, Acute Respiratory Distress Syndrome (ARDS), which further result in multiple organ failures. CS is very critical for the disease progression and is responsible for high death rate in an infected patient. Accordingly, various therapeutic modalities are currently investigated for their effectiveness in subsiding the hyper-inflammatory syndrome either using immunomodulatory agents or anti-inflammatory therapies. Phytochemical (herbal) compounds are demonstrated to possess anti-inflammatory, antimicrobial or antioxidants properties. Various signalling pathways and molecules exacerbating the inflammation state complicate the pathophysiology of COVID-19. Cucurbitacins are tetracyclic bioactive phytochemical compounds found in cucurbitaceous plants. More than 100 species of cucurbitacins possess various pharmacological properties, including anti-inflammatory. Cucurbitacin E and R have shown to be down-regulated the expression of TNF alpha and IL-1beta. Cucurbitacin II B also alleviates the expression of TNF-α as well as IFN-γ and IL-6. Cucurbitacin1 has the potential to reduce the oxidative stress-induced with the reactive oxygen species, and thus prevents cardiovascular damage. Thus cucurbitacins may be pharmacologically manipulated to establish its clinical efficacy in minimizing the disease state and improvising the prognosis of the patients.

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INTRODUCTION

The COVID-19 pandemic commenced across the globe due to the spread of positive-sense ssRNA novel coronavirus 2019 (also known as SARS-CoV-2). The disease severity is marked by elevated cytokines and chemokines levels like interleukin 6 (IL-6), interferon-gamma (IFN-γ), tumour necrosis factor (TNF), IL-2 and monocyte chemotactic protein 1 etc. Such hyperactive pro-inflammatory response is identified as the Cytokine Storm (CS) that complicates the disease leading to extensive damage of the host tissue, Acute Respiratory Dis-

tress Syndrome (ARDS) and may result in multiple organ failures. CS is very critical for the disease progression and is responsible for high death rate in an infected patient (Zhou *et al.*, 2020). Accordingly, various therapeutic modalities are currently investigated for their effectiveness in subsiding the hyper-inflammatory syndrome either using immunomodulatory agents or anti-inflammatory therapies. Phytochemical (herbal) compounds are demonstrated to possess anti-inflammatory, antimicrobial or antioxidants properties. Cucurbitacins are tetracyclic bioactive phytochemical compounds found in cucurbitaceous plants. More than 100 species of cucurbitacins possess various pharmacological properties, including anti-inflammatory (Aeri *et al.*, 2015).

SARS-CoV-2 binding to toll likes receptors up-regulates IL-1 beta by formation and activation of pro-IL-1 and inflammasome respectively. Hyper-secretion of IL-1beta aggravates the inflammation in the lung inducing fibrosis in the pulmonary tissue (Conti *et al.*, 2020). In an in-vitro study cucurbitacin E down-regulated the expression of TNF alpha and IL-1beta by repressing the nuclear factor-kappa B (NF-kB) translocation. This inhibition of pro-inflammatory cytokines may be due to disruption in the actin cytoskeleton of the cells inhibiting NF-kB translocation (Qiao *et al.*, 2013). In a rat model of adjunct arthritis, cucurbitacin R also suppressed TNF alpha and IL-1beta via suppression of the signal transducer and activator of transcription 3 **(**STAT3) signalling (Escandell *et al.*, 2007).

Further, Cucurbitacin II B not only suppressed NF-κB translocation but also prevented phosphorylation of extracellular-signal-regulated kinase 1/2 (ERK1/2) and c-Jun N-terminal kinase (JNK), alleviating the expression of inflammatory cytokines like TNF-α, IFN-γ and IL-6 (Wang *et al.*, 2014). Cucurbitacin 1 has the potential to reduce the oxidative stress-induced with the reactive oxygen species (ROS) in H9c2 cardiomyoblasts (Yang and Kim, 2018). Thus, cucurbitacins may prevent cardiovascular damage associated with COVID-19 disease.

Various signalling pathways and molecules exacerbating the inflammation state complicate the pathophysiology of COVID-19. Cucurbitacins may be pharmacologically manipulated to establish its clinical efficacy in minimizing the disease state and improvising the prognosis of the patients. However, the effect of these compounds on the human body and its metabolism needs further investigations. Besides, research experts in phytochemical compounds may explore the antiviral properties of cucurbitacins.

CONCLUSION

The interleukin 6 (IL-6), interferon-gamma (IFN-γ), tumour necrosis factor (TNF), IL-2 and monocyte chemotactic protein 1 are few of the cytokines and chemokines, known to be elevated in SARS-CoV-2 infection. Various therapeutic modalities using phytochemical compounds are currently investigated for their effectiveness in subsiding the hyper-inflammatory syndrome. Cucurbitacin E and R have shown to be down-regulated the expression of TNF alpha and IL-1beta. Cucurbitacin II B also alleviates the expression of TNF-α as well as IFN-γ and IL-6. Cucurbitacin1 has the potential to reduce the oxidative stress-induced with the reactive oxygen species, and thus prevents cardiovascular damage. Thus cucurbitacins may be pharmacologically manipulated to establish its clinical efficacy in minimizing the disease state and improvising the prognosis of the patients.

Conflict of interest

The authors declare that they have no conflict of interest for this study.

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