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Ursodeoxycholic acid as a candidate therapeutic to alleviate and/or prevent COVID-19-associated cytokine storm

Dear editor

Coronavirus disease 2019 (COVID- 19), caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused an unprecedented global public health crisis. Worldwide, around 4 million infected cases and around 278,000 related-deaths have been reported by May 10, 2020. Mounting evidence has suggested that critical cases are due to development of acute respiratory distress syndrome (ARDS) and subsequent respiratory failure, owing to what is called a cytokine storm syndrome (CSS). As the name implies, the CSS is characterised by a sudden, abnormal release of inflammatory cytokines including many interlukins (IL) like IL-1β, IL-12, IL-6, IL-18, and IL-33, interferon α and γ (IFN- α and γ), tumor necrosis factor α (TNF-α), and tumor growth factor β (TGFβ), due to over-reaction of the innate immunity [1]. Additionally CSS has been shown to induce many reactive oxygen species [2]. As mentioned earlier, CSS is strongly associated with severe tissue damage, contributing to the fatal outcomes of COVID-19 [1].

Ursodeoxycholic acid (UDCA) is a hydrophilic bile acid. It is the therapeutically active component of bear bile, and has been used in traditional Chinese medicine for more than 3000 years. Normally, UDCA is present in human bile but in a low concentration: 3% of bile acid pool. It has been shown to possess anti-inflammatory, antioxidant, immunomodulatory and anti-apoptotic properties [3,4]. In many studies, UDCA inhibited the pro-inflammatory cytokines like TNF-α, IL-1β, IL-2, IL-4 and IL-6 at the mRNA and protein levels [5,6]. Additionally, one study showed that UDCA has strong antioxidant properties and remarkable scavenging efficiency [7]. Given that UDCA is a well known liver-protective agent, and plays a rescuing role from serious health problems like drug-induced liver injury, it is highly expected to play an auxiliary protective role in COVID-19 treatment, as both share almostly the same mechanism of pathogenesis: hyperinflammation. UDCA, at a dose of 13–15 mg/kg/day, is a safe and recommended.

UDCA has been approved by the US Food and Drug Administration (FDA) for dissolving gall stone, and for treatment of several cholestatic liver diseases such as primary biliary cholangitis [8]. The beneficial action of UDCA in respiratory diseases has been previously demonstrated; it showed a significant improvement in all histopathological changes that occurred in context of airway remodeling. These beneficial effects might be ascribed to the efficient modulation of Th-2 derived cytokines and the inhibition of apoptosis of airway epithelial cells [9]. Recently, UDCA has been shown to stimulate alveolar fluid clearance in lipopolysaccharide-induced pulmonary edema via ALX/cAMP/PI3K pathway resulting in an improvement of acute respiratory distress syndrome [10]. The latter study clearly indicates that UDCA may have promising therapeutic effects in COVID-19- induced pneumonia and related lung oedema.

Given its anti-inflammatory and immune modulating actions, we suggest adding UDCA to the current treatment protocols of COVID-19 as it might be effective in tackling CSS due to its ability to suppress the immune mediators. This hypothesis merits clinical trials.

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Declaration of Competing Interest

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Saleem Abdulrab[a,b,*], Sadeq Al-Maweri[c], Esam Halboub[d,e]
[a] *Madinat Khalifa Health Center, Primary Health Care Corporation, Doha, Qatar*
[b] *Ministry of Public Health and Population, Sana'a, Yemen*
[c] *Department of Oral Medicine and Diagnostic Science, Al Farabi Colleges, Riyadh, Saudi Arabia*
[d] *Department of Maxillofacial Surgery and Diagnostic Sciences, College of Dentistry, Jazan University, Jazan, Saudi Arabia*
[e] *Department of Oral Medicine, Oral Pathology and Oral Radiology, Faculty of Dentistry, Sana'a University, Sana'a, Yemen*
E-mail addresses: dentistsalim@gmail.com, sabdulrab@phcc.gov.qa (S. Abdulrab), sadali05@hotmail.com (S. Al-Maweri), mhelboub@gmail.com (E. Halboub).

[*] Corresponding author at: Madinat Khalifa Health Center, Primary Health Care Corporation, Doha, Qatar.