

NSAIDs Immunomodulation in COVID-19 Might Inhibit SARS CoV-2 ORF Proteins  
Induced Caspase Activation, Necroptosis and Endoplasmic Reticulum Stress.

Mina T. Kelleni, MD, PhD

Pharmacology Department, College of Medicine, Minia University, Egypt

[mina.kelleni@mu.edu.eg](mailto:mina.kelleni@mu.edu.eg); [drthabetpharm@yahoo.com](mailto:drthabetpharm@yahoo.com)

Mobile: +201200382422

<https://orcid.org/0000-0001-6290-6025>

## Abstract

We have previously suggested numerous immunomodulatory and anti-inflammatory benefits when NSAIDs are administered to manage COVID-19 and in this commentary, we add other potential benefits related to SARS CoV-2 ORF proteins dependent activation of caspases with subsequent mitochondrial dysfunction, endoplasmic reticulum stress and necroptosis that were described with complicated COVID-19 as NSAIDs are known to be caspase inhibitors. Moreover, NSAIDs might independently inhibit other COVID-19 associated downstream pathological signaling mechanisms. We also postulate that CARD-14, a caspase recruitment domain-containing protein, polymorphisms might play a role in development of severe and critical COVID-19. We believe that it is very unfortunate that for more than one year of relentless struggle, our recommendation to adopt NSAIDs as first choice COVID-19 therapy has not adopted while lives are lost are succumbed every day.

## Keywords

COVID-19, NSAIDs, Caspases, Endoplasmic reticulum stress, CARD-14 polymorphisms.

To date, May 13, 2021, COVID-19 has globally succumbed more than three million and three hundred thousand lives and the search for the underlying pathophysiological mechanisms induced by SARS CoV-2 infection, especially in severe and critical cases, is still evolving including genetic polymorphisms which have been postulated to influence the course and complications of COVID-19<sup>1,2</sup>.

Interestingly, SARS-CoV-2 infection was reported to activate caspase-8 triggering pro-inflammatory cytokines, including IL-1 $\beta$ , TNF- $\alpha$ , IL-7, IL-8 as well as apoptosis, necroptosis, activation of the NF $\kappa$ B pathway in lung epithelial cells and caspase-8-dependent inflammatory responses were suggested to share in COVID-19 induced downstream immune pathogenesis causing lung damage<sup>3</sup>. Interestingly, open reading frames (ORF) 3a protein of SARS-CoV-2 was shown to significantly induce cellular apoptosis which was shown experimentally to be significantly inhibited by either a caspase 8 or caspase 9 inhibitor<sup>4</sup> to be noted that several ORF SARS CoV proteins were previously shown to induce apoptosis and ORF-6 protein overexpression was shown to induce caspase-3 mediated c-Jun N-terminal kinase (JNK)-dependent apoptosis that was blocked by a specific caspase 3 inhibitor or JNK inhibitor<sup>5</sup>.

Importantly, several caspases were reported to modulate B and T cell proliferation and altered transcriptome levels of caspase genes were reported in natural killer cells and neutrophils. Moreover, uncontrolled caspase response in COVID-19 was suggested to share the immune pathological processes as well as in the inflammatory microvascular thrombi found in multiple organs leading to severe outcomes. Interestingly, caspase-1 in CD4+ T cells was shown to be upregulated in hospitalized COVID-19 patients and caspase-3 levels were reported to be significantly upregulated, compared to controls, in circulating red blood cells from COVID-19 patients as well as in tissue macrophages in postmortem analysis and were also demonstrated to be suppressed ex vivo by a pan caspase inhibitor<sup>6</sup>. Thus, unsurprisingly, suppression of apoptosis was suggested to prevent viral pathogenesis in some diseases including SARS and targeting virus-induced apoptosis was implied as a promising strategy in COVID-19 management<sup>7</sup>. Similarly, inhibition of the necroptosis signaling pathway, a subsequent outcome of caspase-8 activation, was suggested to possess a potential to protect against COVID-19 complications<sup>8</sup>.

We would like to pharmacologically declare that NSAIDs are well known, at physiologic in vivo concentrations, caspase inhibitors <sup>9</sup> and notably, NSAIDs were relentlessly suggested, and used, by the author to safely and effectively manage COVID-19 through their potent anti-inflammatory and immunomodulatory effects<sup>10-14</sup> that might prevent or restore the immune dysregulation that is well described in COVID-19 and other diseases <sup>15</sup>.

Furthermore, endoplasmic reticulum stress (ERS) was suggested to play an important role in the development of COVID-19<sup>16</sup> and ERS markers were shown to be significantly increased in SARS CoV-2 infection and COVID-19 pneumonia <sup>17</sup> and interestingly, several NSAIDs including diclofenac, indomethacin, ibuprofen, aspirin, and ketoprofen were shown to suppress the ERS induced human neuroblastoma SH-SY5Y cell death<sup>18</sup>. Similarly, oxicam-derived NSAIDs have been demonstrated to possess neuroprotective effects potentially through suppressed activation of caspase-3 and cell death as well as amelioration of ERS and/or mitochondrial dysfunction signaling pathways<sup>19</sup> and thus, NSAIDs potential direct and indirect positive immunomodulatory effects in COVID-19 are further amplified through their potential anti-ERS effects.

Finally, we postulate that CARD 14, a caspase recruitment domain-containing protein of the membrane-associated guanylate kinases family <https://www.ncbi.nlm.nih.gov/gene/79092>, mutations might play a crucial role in COVID-19 pathogenesis and complications especially in severe and critical patients and we further suggest that the quest to design and develop novel caspase inhibitors and/or modulators might evolve to be corner stone in management of several immune-inflammatory diseases, yet until this goal is fulfilled, NSAIDs are being acknowledged as safe tools to manage COVID-19 and we suggest that inexpensive, safe and readily available immunomodulators are available to help us to win our current COVID-19 battle <sup>13</sup>.

## **Conflict of interest**

The author has no conflict of interest to declare.

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