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# Attenuating the Effects of Novel COVID-19 (SARS-CoV-2) Infection-Induced Cytokine Storm and the Implications

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**Abstract:** The COVID-19 pandemic constitutes an arduous global health challenge, and the increasing number of fatalities calls for the speedy pursuit of a remedy. This review emphasizes the changing aspects of the COVID-19 disease, featuring the cytokine storm's pathological processes. Furthermore, we briefly reviewed potential therapeutic agents that may modulate and alleviate cytokine storms. The literature exploration was made using PubMed, Embase, MEDLINE, Google scholar, and China National Knowledge Infrastructure databases to retrieve the most recent literature on the etiology, diagnostic markers, and the possible prophylactic and therapeutic options for the management of cytokine storm in patients hospitalized with COVID-19 disease. The causative agent, severe acute respiratory coronavirus-2 (SARS-CoV-2), continually threatens the efficiency of the immune system of the infected individuals. As the first responder, the innate immune system provides primary protection against COVID-19, affecting the disease's progression, clinical outcome, and prognosis. Evidence suggests that the fatalities associated with COVID-19 are primarily due to hyper-inflammation and an aberrant immune function. Accordingly, the magnitude of the release of pro-inflammatory cytokines such as interleukin (IL)-1, (IL)-6, and tumor necrosis alpha (TNF- $\alpha$ ) significantly differentiate between mild and severe cases of COVID-19. The early prediction of a cytokine storm is made possible by several serum chemistry and hematological markers. The prompt use of these markers for diagnosis and the aggressive prevention and management of a cytokine release syndrome is critical in determining the level of morbidity and fatality associated with COVID-19. The prophylaxis and the rapid treatment of cytokine storm by clinicians will significantly enhance the fight against the dreaded COVID-19 disease.

**Keywords:** COVID-19, SARS-CoV-2, cytokine storm, hyper-inflammation, fatality

## Introduction

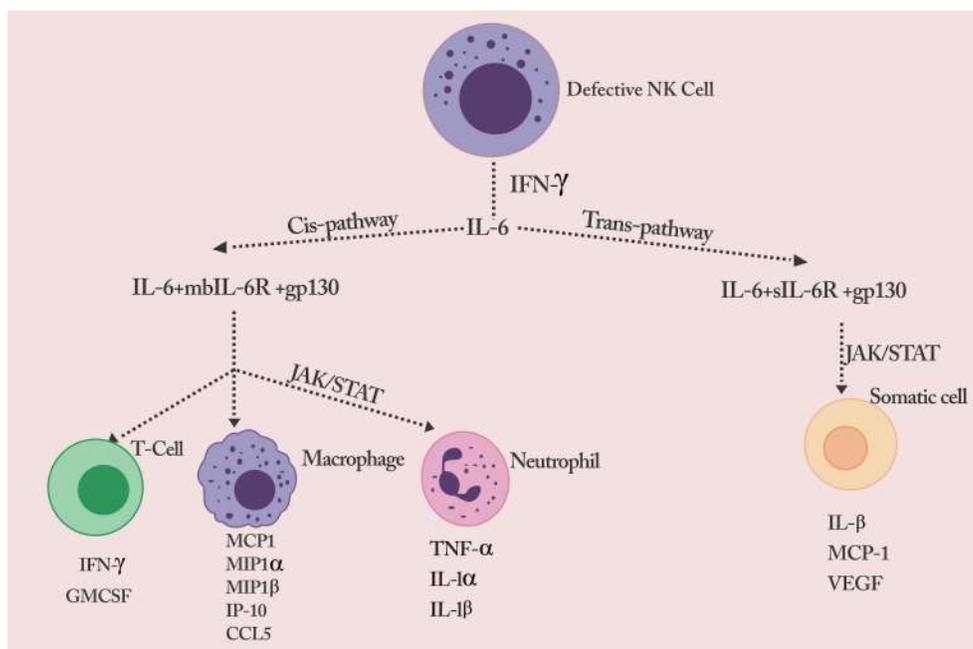
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the coronavirus disease 2019 (COVID-19), which broke out in Wuhan, China, in December 2019 and spread around the entire globe.<sup>1</sup> On the 11th March 2020, the World Health Organization (WHO) declared the disease a pandemic. Currently, 132 046 206 cases and 2 867 242 fatalities have been documented across 233 nations and regions by April 7–2021, 09: 34 pm GMT+8.<sup>2</sup> COVID-19 infection is characterized by complications of the lower respiratory system, including pneumonia, and clinical presentations of the disease range from asymptomatic, mild, moderate, to severe forms. Immunodeficiency, senility, and other disease conditions such as diabetes, coronary

heart disease, hypertension, cerebral infarction, pneumonia, severe asthma, and chronic bronchitis complicate the COVID-19 illness.<sup>3,4</sup>

SARS-CoV-2 is a single-stranded RNA virus that is classified into the beta-coronavirus genus and the Coronaviridae family. The genome of the coronavirus encodes four predominant proteins, which are the Envelope (E), Membrane (M), Nucleocapsid (N), and Spike (S) proteins. The S protein is responsible for viral access into respiratory tissue through the Angiotensin-Converting Enzyme 2 (ACE-2) expressing epithelial cells.<sup>5,6</sup> Being the first central point of contact with the host cell, the S protein is known to have strong immunogenic properties.<sup>5</sup> There are three main clinical stages of COVID-19. Stage one is the viral response phase, which is the period of early infection. It lasts for about four days, and it is typically characterized by non-specific symptoms such as fever, cough, and diarrhea.<sup>6</sup> Stage two is the pulmonary phase which usually lasts between days 5 to 13. At this phase, the pulmonary symptoms are first without hypoxia, and later hypoxia develops.<sup>6</sup> Stage three is the systemic hyperinflammation phase, which is usually from day 14.<sup>6</sup> Most times, patients report to the hospital at the end of stage 1 or the beginning of stage 2. At this time, the

innate immune system's potential to combat the infection has been threatened.<sup>7</sup>

Evidence proposes that deaths associated with COVID-19 are principally owing to hyperinflammation and uncontrolled immune response. The COVID-19 infection triggers a cytokine storm characterized by potentially life-threatening pathologies such as hyper-inflammation, septic shock complications, coagulation dysfunction, and impairment of several vital organs.<sup>8-11</sup> Hypercytokinemia in COVID-19 patients is characterized by the speedy propagation and hyperactivation of T-cells, macrophages, natural killer (NK) cells, and the excessive production of a host of pro-inflammatory cytokines (Figure 1) and chemical mediators discharged by immune or non-immune cells.<sup>8,12,13</sup> The early prediction, rigorous prevention, and therapeutic intervention of a cytokine release syndrome are crucial in reducing the level of morbidity and fatality related to COVID-19. The development of hypercytokinemia is a strong indication of disease progression, and immune suppression is a key therapeutic strategy in combating this complication.<sup>14</sup> Therefore, during the investigation and therapy of pneumonia caused by COVID-19 infection, it has become necessary to monitor cytokine levels and other markers to improve the rate of cure and, in turn, reduce the rate of human mortality from the



**Figure 1** Defective NK cell signals the production of a flurry of cytokines.

**Notes:** Reproduced from Rowaiye, A.; Okpalefe, O.; Onuh, O.; Ogidigo, J.; Oladipo, O.; Ogu, A.; Oli, A.; Olofinase, S.; Onyekwere, O. Preparing for the Storm: Mitigating the Effect of SARS-CoV-2 Induced Hypercytokinemia. Preprints 2020, 2020110604. Creative Commons license and disclaimer available from: <http://creativecommons.org/licenses/by/4.0/legalcode>.

burden of disease.<sup>15</sup> Concerning the COVID-19 infection and the host cell, this research paper focuses on the changing pathophysiological aspects of the COVID-19 infection, accentuating the cytokine storm's pathogenesis and markers. It also critically explores the current and potential therapeutic options that can be exploited to alleviate and control cytokine storms.

## Search Strategy

This study is a narrative review. Relevant literature was retrieved from the databases (PubMed, Embase, MEDLINE, and China National Knowledge Infrastructure) and search engine (Google scholar). The search keywords included but were not limited to COVID-19 pathogenesis, SARS-CoV-2, Cytokine Storm, Hyperinflammation markers, and hypercytokinemia. Over 600 articles written only in the English language were retrieved. These articles were assessed for quality and eligibility based on key features such as straightforward protocol/study design, flawless methodology, complete data, and lack of selection or reporting bias. A total of 236 articles, vital information on the etiology, pathogenesis, diagnostic markers, prophylaxis, and possible cure of cytokine release syndrome in patients hospitalized for COVID-19 pneumonia, was obtained.

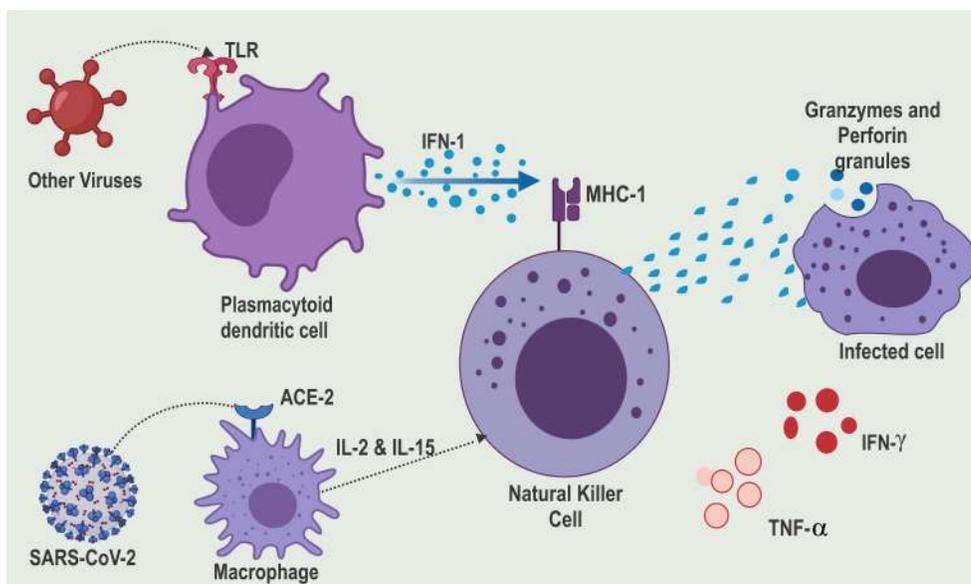
## Pathogenesis of COVID-19-Triggered Cytokine Storm

The term cytokine release syndrome (CRS), also known as a cytokine storm, has been used to describe an abnormal discharge of soluble mediators and the associated immunopathological event that occurs after severe bacterial and viral infections.<sup>16</sup> CRS is also referred to as hemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndrome (MAS), depending on the underlining medical condition. CRS is associated with exaggerating pro-inflammatory-mediated response and an ineffective control mechanism by the anti-inflammatory system, leading to tissue damage.<sup>16,17</sup> The human immune system plays an essential role in eradicating infectious agents such as influenza and coronaviruses through leucocyte recruitment and cytokines' release. An unconstrained and well-harmonized stimulation of immune responses is usually the first mechanism of action the body presents to build a defense against any viral infection.<sup>18</sup> Nevertheless, unregulated and aggravated immune responses may alter immunological function, leading to tissue damage and multiple organ failures.<sup>15,16</sup> The production of various

cytokines that cause cytokine storms in SARS-CoV-2 patients results in immunopathogenic injuries. Therefore, the effective lowering of pro-inflammatory cytokine levels in severe COVID-19 patients is crucial in preventing health deterioration in infected persons.<sup>19–21</sup>

The SARS-CoV-2 has been shown to infect the human respiratory epithelial cells, macrophages, and dendritic cells.<sup>22–24</sup> It also induces the stimulation of pro-inflammatory cytokines and chemokines.<sup>25</sup> The SARS-CoV-2 contains a receptor-binding domain (RBD) located in the S1 region that identifies a binding pocket in the Angiotensin-Converting Enzyme 2 (ACE2) and plays a role in the pathogenesis of COVID-19 infection.<sup>26</sup> ACE2 is expressed by epithelial cells of the human respiratory tract, digestive tract, kidney, veins, terminal ileum, and colon.<sup>27</sup> Due to genetic similarity, the ACE2 gene's polymorphisms may affect the susceptibility to the SARS CoV infection and COVID-19 disease.<sup>26,28,29</sup> As shown in a murine model, mutations might also alter the expression level of ACE2.<sup>30</sup>

In the infected cells, the nucleic acids of the invading virus are recognized by Pattern Recognition Receptors (PPR) like the Toll-Like Receptors (TLR3, TLR7, TLR8, and TLR9).<sup>31–33</sup> The single nucleotide polymorphisms in the gene coding for these TLR may lead to poor viral recognition and, subsequently, a susceptibility to cytokine storms.<sup>34</sup> The activated TLR release cytokines such as type 1 Interferon (IFN-1) are key for antiviral immunity and are made up of IFN- $\alpha$  and IFN- $\beta$ .<sup>35–38</sup> IFN-1 is produced in large quantities by activated plasmacytoid dendritic cells. On binding with the IFN-1 receptor, IFN-1 triggers the phosphorylation of transcription factors such as signal transducer and activator of transcription 1 (STAT1) in a downstream signaling pathway that triggers hundreds of IFN-stimulated genes in the nucleus.<sup>16,39</sup> IFN-1 stimulates the NK cells through dependent or independent mechanisms on class I major histocompatibility complex (MHC) protein.<sup>40</sup> Polymorphisms of class I MHC may also lead to increased susceptibility to COVID-19 infection.<sup>7</sup> Unfortunately, the SARS-CoV-2 evades the TLR8 and TLR9 receptors (Figure 2). This is achieved through an intricate capping mechanism of the mRNA by the methyltransferase.<sup>41</sup> This suppresses IFN-I production and the downregulation of interferon-stimulated genes in COVID-19 patients.<sup>42</sup> However, independent of IFN-1, the NK cells can be triggered through other cytokines such as IL-2 and IL-15. These



**Figure 2** SARS-CoV-2 evades TLR recognition and thereby suppressing IFN-I production.

**Notes:** Reproduced from Rowaiye, A.; Okpalefe, O.; Onuh, O.; Ogidigo, J.; Oladipo, O.; Ogu, A.; Oli, A.; Olofinase, S.; Onyekwere, O. Preparing for the Storm: Mitigating the Effect of SARS-CoV-2 Induced Hypercytokinemia. Preprints 2020, 2020110604. Creative Commons license and disclaimer available from: <http://creativecommons.org/licenses/by/4.0/legalcode>.

compensatory signaling mechanisms are essential in the innate antiviral defense of most COVID-19 survivors.<sup>43</sup>

The NK cells are responsible for the immune surveillance of tumor cells and cells infected by viruses.<sup>44</sup> To effectively carry out this role, the NK cells are furnished with a set of pro-inflammatory cytokines (IFN- $\gamma$  and TNF- $\alpha$ ) and cytotoxic molecules (perforin and granzymes).<sup>45</sup> Primarily due to the presence of inhibitory receptors and regulatory cytokines like IL-10, IL-3, and Granulocyte-macrophage colony-stimulating factor (GM-CSF), NK cells also play an immunomodulatory role. They can control exaggerated immune responses, as seen in auto-inflammatory conditions and cytokine storms.<sup>46</sup> However, reduced activity, decreased number, and genetic deficiency of NK cells have been associated with cytokine storm progression.<sup>46,47</sup> Mutations in the genes of specific proteins expressed by NK cells affect cytotoxic activities. For example, mutations in the *PRF1* and *GZMB* genes lead to defective perforin and granzyme B expression, respectively.<sup>47–50</sup> Perforinopathy and other cytotoxic protein expression deficiencies could induce intense inflammatory response signals seen in cytokine storm syndrome.<sup>51,52</sup> Empirical evidence suggests that the failure of Granzyme/Perforin-induced apoptosis of target cells causes severe immune dysregulation. The prolonged survival of target cells causes IFN- $\gamma$  secreted by the NK cells

to trigger naive macrophages, consequently overproducing proinflammatory cytokines.<sup>47</sup> Therefore, though there is an absence of the death of virally-infected cells due to a decrease in NK cell cytotoxic activity, a flurry of cytokines is released by macrophages resulting in the IL-6 cascade.<sup>52</sup>

Upstream of the IL-6 signaling pathway, IL-1 $\beta$ , and TNF alpha are two important pro-inflammatory cytokines involved in the pathogenesis of virus-induced cytokine storms.<sup>53</sup> The TNF- $\alpha$  and IL-1 $\beta$  trigger the Nuclear Factor kappa light chain enhancer of activated B cells (NF- $\kappa$ B) signaling pathway. On activation, the NF- $\kappa$ B, a DNA binding protein, activates the transcription of various genes and thereby regulates inflammation.<sup>53</sup>

The induction of NF- $\kappa$ B further triggers IL-6, other pro-inflammatory cytokines, chemokines, enzymes, and adhesion molecules. Additionally, the NF- $\kappa$ B regulates the proliferation, morphogenesis, and apoptosis of inflammatory cells.<sup>53–55</sup> IL-6 is a pleiotropic cytokine produced from multiple cell types, including macrophages, dendritic cells, fibroblasts, keratinocytes, mesangial cells, vascular endothelial cells, B and T cells.<sup>56</sup> It does not only have significant pro-inflammatory properties but can also trigger dual signaling pathways (cis or trans) based on their cellular distribution.<sup>57</sup> In the trans-signaling pathway, IL-6 binds to the soluble form of the

IL-6 receptor (SIL-6R) found on all somatic cells.<sup>57</sup> The IL-6/sIL-6R composite binds to gp130 and triggers the JAK-STAT3 signaling gateway. The CRS is aggravated through the release of monocyte chemo-attractant protein-1 (MCP-1), IL-8, vascular endothelial growth factor (VEGF), and monocyte chemo-attractant protein-1 (MCP-1), which are associated with tissue damage and inflammation. The vascular permeability and leakage associated with the hypotension and pulmonary dysfunction in ARDS are due to reduced E-cadherin and increased VEGF expression.<sup>58–61</sup>

In the cis signaling pathway, IL-6 binds with the membrane-bound IL-6 receptor (mbIL-6R), expressed on neutrophils, naive T cells, and monocytes/macrophages, which cover both the innate and acquired immune systems.<sup>57</sup> The IL-6/mbIL-6R complex binds with gp130 and triggers the Janus kinases (JAKs) and signal transmitter and inducer of transcription 3 (STAT3) proteins.<sup>57</sup> This signal cascade causes multiple effects on the cells involved and culminate in a cytokine storm. Cytokines are usually elevated according to the level of inflammation. Activated T cells secrete cytokines such as IFN- $\gamma$  and GM-CSF. The activated monocytes/macrophages secrete cytokines and chemokines such as Monocyte Chemoattractant Protein-1 (MCP1), Macrophage Inflammatory Protein 1-alpha (MIP1 $\alpha$ ), Macrophage Inflammatory Protein 1-beta (MIP1  $\beta$ ), monokine induced by gamma interferon (MIG), IFN- $\gamma$ -induced protein 10 (IP-10), and CCL-5. The triggered neutrophils also secrete pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1- $\alpha$ , and IL-1- $\beta$ .<sup>58–63</sup>

The invasion of SARS-CoV-2 induces an alteration in T-cell responses leading to the elevated serum level of cytokines and chemokines in severe cases compared with mild or moderate cases. For example, IL-6 was reported to be 76% higher than normal in severe cases compared with 30% in mild conditions.<sup>3, 64–69</sup> As the cytokines and chemokines level increase, they tend to recruit many other inflammatory cells, including neutrophils and monocytes, which results in the permeation of the lung tissue, causing acute respiratory distress syndrome (ARDS). The ARDS is characterized by apoptosis of the pulmonary epithelial and endothelial cells, damages of the lung micro-vascular and alveolar epithelial cell barrier, vascular leakage, alveolar edema, hypoxia, and pulmonary fibrosis.<sup>8,70</sup>

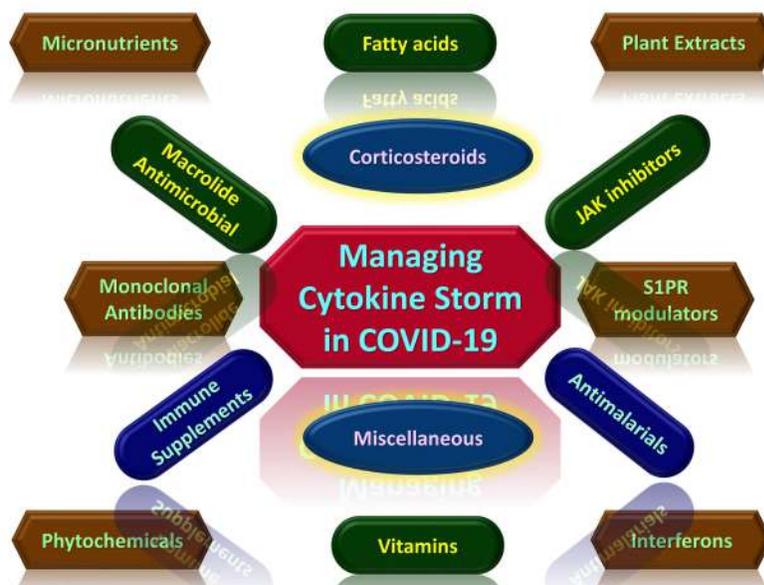
In addition to the direct attack of SARS-CoV-2 on CD4 lymphocytes, IL-6 has also been shown to inhibit lymphopoiesis through lymphocyte trafficking and the direct

suppression of progenitor cells.<sup>71,72</sup> The uncommitted hematopoietic stem cells, which contain precursors for both lymphoid and myeloid fates, express the IL-6 receptor- $\alpha$  chain. These cells respond to IL-6 activation through the JAK/STAT3 pathway, which causes the expression of the Id1 transcription factor. Consequently, lymphopoiesis is inhibited, and myelopoiesis is elevated in a mitogen-activated protein kinase (MAPK)-dependent manner.<sup>73,74</sup>

The overall immunopathology of COVID-19 infection suggests remarkable lymphocytopenia, thrombocytopenia, basopenia, eosinopenia, monocytopenia, hyper-gamma-immunoglobulinemia, neutrophilia, T-cell activation, lymphocyte dysfunction, and increased pro-inflammatory cytokine production.<sup>75</sup> Regarding specific clinical symptoms, IFN- $\gamma$  causes fever, headaches, chills, fatigue, malaise, cardiomyopathy, vascular leakage, lung injury, and acute-phase protein production. Also, TNF- $\alpha$  causes flu-like symptoms.<sup>75</sup> IL-6 induces cardiomyopathy, vascular leakage, activation of complement and the coagulation cascade, and diffuse intravascular coagulation.<sup>76–78</sup> The excessive production of cytokines also leads to the generation of tissue factors that culminate in the blood's overcoagulation. Tissue hypoxia and ischemia result from thrombosis and viscera embolization.<sup>66</sup>

## Markers of COVID-19-Induced Cytokine Storm

Generally, cytokine storms are diagnosed in the form of the underlying medical condition. Therefore, a viral infection-induced cytokine storm is different from a macrophage activation syndrome induced by autoimmune defects such as systemic juvenile idiopathic arthritis (JIA) and in lupus or familial hemophagocytic lymphohistiocytosis (HLH), which is induced by certain genetic syndromes.<sup>79,80</sup> The symptoms of cytokine storms include fatigue, fever, chills, nausea, emesis, headache, cough, seizures, tremor, dyspnea, lethargy, and rash.<sup>81</sup> Other symptoms include increased blood clotting, low blood pressure, multiple organ failure, and death.<sup>75,82</sup> The quick and early prediction of hypercytokinemia through specific biological markers would prevent many deaths. This use of these markers would allow for closer clinical monitoring and aggressive supportive treatment to avoid a poor prognosis (Figure 3).<sup>83</sup> The clinical markers (Table 1) that can diagnose tissue damage in COVID-19 infection include serum chemistry and hematological parameters.<sup>84</sup>



**Figure 3** Markers of cytokine storm associated with COVID-19.<sup>75,79–86,90–132</sup>

### Ferritin

The function of serum ferritin as a marker of inflammation and immune dysregulation is well established. While Ferritin is considered an early phase reactant, its synthesis does not occur within the serum but intracellular iron

storage protein.<sup>85</sup> Iron and inflammations are inescapably linked. An increase in cellular ferritin production allows for greater binding of intracellular iron. This is a host defense mechanism to inhibit free radical production.<sup>95</sup> Serum ferritin originates from the leakage from damaged

**Table 1** Markers of Cytokine Storm

| Marker                         | Source          | Association with Cytokine Storm              | Normal Range     | COVID-19 Marker Cut-Off | References |
|--------------------------------|-----------------|--|------------------|-------------------------|------------|
| Ferritin                       | Serum Chemistry | Cellular ferritin leaks from damaged cells   | 18–350 ng/mL     | ≥ 400 µg/L*             | [85]       |
| D-dimer                        | Serum Chemistry | Defective plasma coagulation                 | 250–500 ng/mL    | ≥ 1000 ng/mL*           | [86]       |
| Lactate dehydrogenase          | Serum Chemistry | Lactic acidosis                              | 140–280 U/L      | ≥ 450U/L *              | [83]       |
| C-Reactive Protein             | Serum Chemistry | Associated to IL-6 stimulation               | 0.3 to 1.0 mg/dL | ≥ 20 mg/dL*             | [87]       |
| ALT                            | Serum Chemistry | Damage of hepatocytes                        | 19 to 33 IU/L    | 67 (47–100) IU/L*       | [88]       |
| Cytokines                      | Serum Chemistry |  |                  |                         |            |
|                                | IL-1beta        | Pro-inflammatory activity                    | 0.10 pg/mL       | 0.67 pg/mL              | [89]       |
|                                | IL-6            | Pro-inflammatory activity                    | 0.5 to 5 pg/mL   | <25 pg/mL*              | [90,91]    |
|                                | TNF-α           | Pro-inflammatory activity                    | 0 to 8.1pg/mL    | < 35pg/mL*              | [92]       |
| Neutrophil/Lymphocyte Ratio    | Hematological   | Increased neutrophil counts and lymphopenia. | 1.0–3.0          | 6.6 (2.1–11.1)*         | [7,93]     |
| Erythrocyte Sedimentation Rate | Hematological   | Platelet destruction                         | 0 to 29 mm/hr    | >100 mm/hr*             | [94]       |

**Notes:** \*Marker levels suggest a remarkable increase from the normal range. They are not to be taken as fixed as they do vary as the disease progresses due to several other factors.

cells and therefore serves as an important disease marker. As ferritin exits the cells into the serum, it leaves an unbound Iron and lacks most of the Iron it contains intracellularly. Though serum ferritin is benign, the unbound Iron further causes cellular damage through lipid oxidation.<sup>85,95</sup> Unliganded Iron catalyzes hydroxyl radical formation and increases the production of markers such as malondialdehyde, 27-hydroxycholesterol, 8-hydroxydeoxyguanosine, 4-hydroxynonenal, and isoprostanes.<sup>85,95</sup> Since the red blood cells contain the highest ferritin volume, and unbound Iron distorts their structure and function. Unbound Iron also causes pathological changes in fibrin morphology, consequently making it trap deformed erythrocytes.<sup>85,95</sup> Clinical data suggest that increased ferritin level is linked to the severity of COVID19 disease, the normal serum ferritin range being 18–350 ng/mL.<sup>96</sup> In severe cases, ferritin levels are >400 µg/mL and could be between 1.5 and 5.3 times higher than moderate cases.<sup>97</sup> Notably, in the absence of liver disease or the need for blood transfusion for anemia, a disproportionately high and continuously increasing serum ferritin level suggests the presence of a cytokine storm.<sup>98</sup>

### D-Dimer (DD)

Soluble fibrin is generated during plasma coagulation. D-dimer is released as a product of degeneration of cross-linked fibrin. Hence, it is a sensitive biomarker to rule out venous thromboembolism. However, increased DD level is an indicator of the activation of coagulation.<sup>86</sup> There is a correlation between D-dimer and the progression of severe COVID-19 infection. D-dimer is directly connected with the activation of the proinflammatory cytokine cascade. On the contrary, it is not associated with anti-inflammatory cytokines (IL-10).<sup>99</sup>

A defective coagulation system in severe COVID-19 patients and DD can identify patients at increased risk of the cytokine storm.<sup>86</sup> Beyond inflammation and coagulopathy is strongly involved in the pathogenesis of severe COVID-19 illness. Thrombosis, especially venous thrombosis, is a serious complication in COVID-19 patients, and it leads to multiple infarcts and ischemia of the extremities.<sup>99</sup> D-dimer is an important marker of coagulopathy, and elevated level is a predictor of COVID-19 progression.<sup>99</sup> The normal plasma level of D-dimer is below 250ng/mL for D-dimer units or below 500 ng/mL for fibrin equivalent units.<sup>100</sup> D-dimer levels higher than

1000 ng/mL indicate poor clinical prognosis and the need for anticoagulant therapy.<sup>101,102</sup>

### Lactate Dehydrogenase (LDH)

This is an enzyme found in nearly all living cells. It is an essential indicator of cytokine storm in COVID-19 infection because it is associated with metabolic acidosis.<sup>103</sup> In viral infections, tissue hypoxia conditions prevail when pyruvate is converted to lactic acid and accumulates. Lactic acidosis induces the monocytes and macrophages to produce IL-1β and triggers the inflammasome to activate inflammatory responses.<sup>104,105</sup> In homeostatic response to the acidosis, the LDH level is increased. Therefore, LDH is a marker of tissue damage caused by viremia and dysregulated immune response because as tissue deterioration progresses, the LDH increases. It reflects the degree of various pathophysiological processes, and therefore it can predict the progression or regression of disease. There is a significant difference in LDH levels between mild and severe groups of COVID-19 pneumonia patients.<sup>106</sup> Normal LDH levels range from 140 –280 units per liter (U/L), and the upper limit of 450U/L is used as a threshold for severe COVID 19 infection.<sup>81</sup>

### C-Reactive Protein (CRP)

In response to IL-6 stimulation, CRP is released from the liver cells. CRP is an acute-phase reactant, which is markedly elevated in COVID-19 patients. CRP is a useful indicator to determine the severity of disease and a reliable predictor of cytokine release syndrome. Extremely high CRP levels are directly linked to poor disease prognosis. Based on the relationship between CRP levels and IL-6, it can be used as a surrogate marker. Daily monitoring is important to distinguish between those whose fever would resolve and those whose symptoms would gravitate to a cytokine storm. The normal CRP range is 0.3 to 1.0 mg/dL but values greater than 20 mg/dL suggests hyper-inflammation.<sup>87</sup> A patient whose CRP exceeds this threshold is at particularly high risk of the cytokine storm.<sup>107</sup> The LDH and CRP may also be associated with respiratory function; may also be used to predict respiratory failure in COVID-19 patients.<sup>87</sup>

### Alanine Aminotransferase (ALT)

Alanine aminotransferase is an enzyme found inside the hepatocytes and is released excessively into the bloodstream during liver damage. Liver damage is a clinical sign characteristic of COVID-19 infection, and it has

been reported in at least one-half of patients suffering from the disease.<sup>108,109</sup> Impaired liver function is characterized by ALT elevations in multiples factors of the upper reference limit.<sup>88</sup> During SARS-CoV-2, the ACE-2 receptor acts as a target for entrance into the cells. This receptor plays a crucial role in propagating the virus as it is expressed on the bile duct and liver's endothelial cells, therefore exposing the organ to possible infection.<sup>110</sup> A direct viral attack on the hepatocytes and the cholangiocytes elevates ALT levels. Other causes of liver damage in COVID-19 patients include drug-induced toxicity.<sup>109</sup>

### Blood Urea Nitrogen (BUN) to Creatinine Ratio

The glomerulus filters blood Urea, Nitrogen, and Creatinine (Cr). While the creatinine's tubular reabsorption is minimal, that of BUN can either be increased or decreased. The normal BUN range is 7–20 mg/dL, and that of creatinine is 0.7–1.2 mg/dL.<sup>111</sup> When the BUN to Cr ratio exceeds 20, this is predictive of acute kidney injury, making BUN reabsorption increased due to the kidneys' hypoperfusion. BUN is generally increased during COVID-19 infection due to acute kidney damage and other factors.<sup>112</sup> Gastrointestinal bleeding has been observed in patients with severe COVID-19 disease. The gastrointestinal tract's epithelial cells, which positively express the ACE2 protein, are attacked by SARS-CoV-2.<sup>113</sup> Consequently, histological degeneration, necrosis, and varying degrees of mucosal spillage are detected in a deceased COVID-19 patient's gastrointestinal mucosa.<sup>113</sup> Gastrointestinal bleeding may also be due to an existing coagulopathy developed from multiple organ failure or the use of corticosteroids with heparin or salicylic acid in intravascular thrombosis treatment.<sup>114</sup> Gastrointestinal bleeding can cause an elevation in the BUN to Cr ratio due to amino acid digestion. Hemoglobin is metabolized into amino acids by the enzymes in the upper intestinal tract. The reabsorbed amino acids are broken down into urea, and this increases BUN level.<sup>115,116</sup> High BUN level is associated with mortality in COVID-19 patients.<sup>117</sup>

### Creatinine Kinase-Muscle/Brain Activity (CK-MB)

Cardiac damage possibly occurs during SARS-CoV-2 infection, and this is due to the activity of proinflammatory cytokines such as TNF- $\alpha$ , IL-1, and IL-6. These cytokines may play an important role in the development and progression of heart failure.<sup>118</sup> CK-MB is a marker for myocarditis. Meta-analysis reveals that elevated CK-MB levels

suggest cardiac damage and are significantly associated with disease severity and an increased risk of mortality in COVID-19 patients.<sup>119,120</sup>

### Cytokines

Though expensive to test, cytokines can be used to predict the cytokine storm. The rise in the levels of pro-inflammatory cytokines such as IL-1beta, IL-6, and TNF alpha are predictors of disease progression and an impending cytokine storm.<sup>121,122</sup> These cytokines can also be used as prognostic markers to determine the clinical outcome of therapeutic agents administered to combat the SARS-CoV-2 disease. The normal range of IL-6 for healthy individuals is 0.5–5 pg/mL, and it could exceed 25pg/mL during infection.<sup>90,91</sup> The normal range for IL-1beta is 0.10pg/mL, and it could exceed 0.67pg/mL during infection.<sup>89</sup> The normal range for TNF-alpha is 0.0–8.1 pg/mL, and it could exceed 35pg/mL during infection.<sup>92,121</sup> Cytokine cut-offs are difficult to establish and may vary depending on population genetics, pleiotropic nature, and patient's health status. Therefore, it is ideal for comparing cytokine signatures with their baseline values to establish a diagnostic or prognostic decision.<sup>123</sup>

### The Neutrophil/Lymphocyte Ratio (NLR)

The Neutrophil/Lymphocyte Ratio is potentially a predictive prognostic biomarker in patients infected with the SARS-CoV-2.<sup>93</sup> Severe COVID-19 is characterized by high levels of circulating pro-inflammatory cytokines, increased neutrophil counts, and lymphopenia.<sup>124</sup> Lymphopenia as a reliable and effective predictor for the COVID-19 disease state.<sup>125</sup> While the neutrophilia is due to prolonged neutrophil activation, and the lymphocytopenia could result from a straight attack of SARS-CoV-2 on lymphocytes, sequestration of the lymphocyte in the lung, suppression of hematopoietic stem cells, or the cytokine-mediated disruption of lymphocyte trafficking.<sup>126</sup>

### Erythrocyte Sedimentation Rate (ESR)

The Erythrocyte Sedimentation Rate measures the rate at which red blood cells (RBC) settle in anti-coagulated whole blood. During inflammation, the ESR is faster than usual because a high proportion of fibrinogen in the blood causes the RBC to stick together and increases its density.<sup>94</sup> In SARS-CoV-2 infection, thrombocytopenia is due to a direct attack of the virus on the platelets and megakaryocyte progenitor cells in the bone marrow.<sup>127,128</sup> Platelets express specialized PRR and can activate thrombo-inflammatory responses against viruses. Functional

interaction between the platelets and the innate immune system promotes thrombo-inflammation and tissue damage.<sup>129</sup> Platelet activation potentiates the recruitment, activation, and transmigration of innate immune cells. The progression and resolution of the inflammation of platelets are promoted in a disease-specific manner. Also, thrombo-inflammation is differentially regulated by platelet-leukocyte interactions.<sup>130</sup> As the severe COVID-19 disease progresses, the platelet counts decrease, and consequently, the erythrocyte sedimentation rate is lowered. The normal ESR ranges for men and women are usually is very high during severe inflammation due to infection.<sup>131,132</sup>

## Mitigation and Therapeutic Intervention of COVID-19-Induced Cytokine Storm

To effectively prevent or mitigate a cytokine storm, several pathological factors must be considered. The earliest possible time pharmacological interventions (Figure 4) have a higher possibility of success in managing severe COVID-19 infected cases.<sup>133,134</sup> These include viremia, cellular oxidation, immuno-senescence, and comorbidities.<sup>7</sup> The administration of immunomodulators would further strengthen the therapeutic strategy (Table 2). While WHO is yet to approve any cure for COVID-19, many antiviral agents have been proposed. Some of these are natural compounds that can also serve as antioxidants to combat oxidative stress caused by SARS-CoV-2 infection.<sup>7</sup> Immuno-senescence is an age-related decline in immune function. This is one of the most important reasons for the increased morbidity and mortality in elderly patients hospitalized with COVID-19.



**Figure 4** Potential therapeutic agents for managing cytokine storm associated with COVID-19.<sup>7,30,44,76,121,133–137,139–249</sup>

Immunosenescence is characterized by the diminished activity of hematopoietic stem cells due to continuous oxidative damage to DNA and the decreased number or activity of circulating phagocytes, dendritic cells, NK cells, and B-cells.<sup>135</sup> Patients from 65 years and above stand a high risk of COVID-19 fatality.<sup>135</sup> Immunosenescence can be combated through bone marrow transplantation and genetic reprogramming, which is not logistically or economically feasible in treating COVID-19.<sup>135</sup> Comorbidities constitute a significant risk factor for cytokine storm syndrome in COVID-19. Immunity in patients with SARS-CoV-2 infection is further weakened by other diseases like hypertension, diabetes, cardiovascular diseases, and lung diseases.<sup>136</sup> These conditions reduce the resistance to the invading virus and, therefore, enhance the disease's progression. The clinician should take care of these comorbidities to prevent a cytokine storm.<sup>136</sup>

Immunomodulators are therapeutic agents that can be used in regulating immune responses. In the case of COVID-19, the suppression of hypercytokinemia may be able to resolve ARDS fully. Immunomodulators are of different categories, and some are currently being developed or repurposed for use based on compassionate recommendations for the management of COVID-19 [Figure 5].<sup>137</sup> They are usually administered in combination with other drugs. They can be used as prophylaxis to prevent cytokine storms by promoting an effective innate immune response cascade through specific TLR to bring about viral clearance.<sup>30</sup> Therapeutically, immunomodulators can also be used to activate an adaptive immune response.<sup>137</sup> Immunomodulators range from synthetic drugs, natural compounds to recombinant antibodies, many of which are still undergoing clinical trials.

## Micronutrients

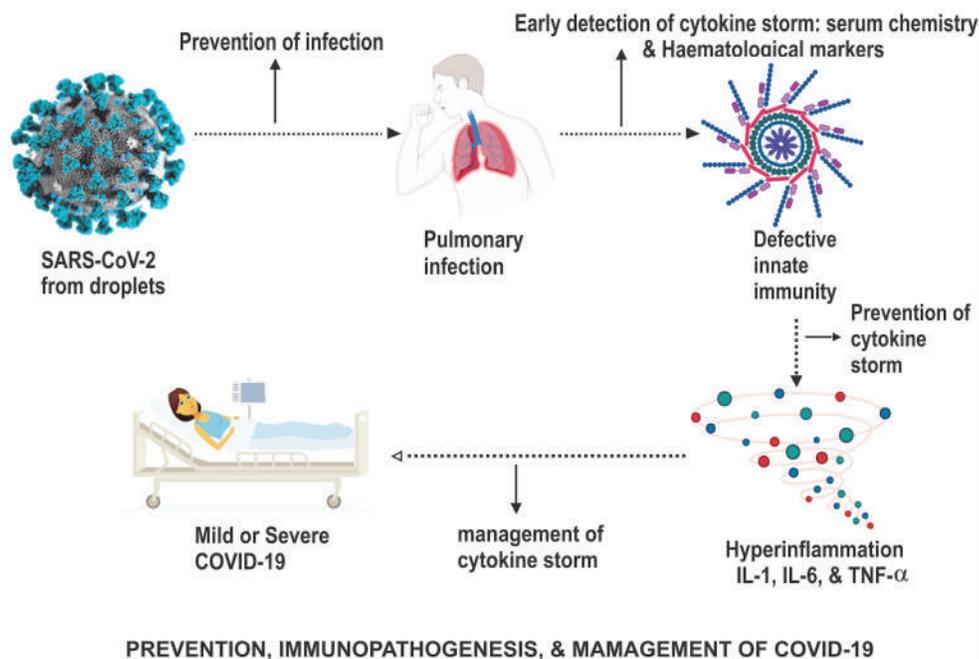
These include trace elements, polyunsaturated fatty acids (PUFA), and vitamins.

### Trace Elements

Zinc is an indispensable trace element involved in gene expression, protein folding, enzymatic reactions, and physiological processes.<sup>169–173</sup> Indeed, zinc's multifunctional effects are cell-specific, and many proteins bind to zinc through their zinc finger motifs.<sup>174</sup> In combating SARS-CoV-2 viremia and its associated cytokine storm, zinc is vital in decreasing oxidative stress and optimizing immune function.<sup>175</sup> Zinc modulates the activities of immune cells. As a signaling molecule, it triggers several cascades.<sup>175</sup> It

**Table 2** Potential Therapeutic Agents for Mitigating and Managing COVID-19 Cytokine Storms

| Class                    | Therapeutic Agent              | Mechanism of Action  | Stage of Development | References |
|--------------------------|--------------------------------|--|----------------------|------------|
| Micronutrients           | Zinc                           | Decreased gene expression of pro-inflammatory cytokines, Regulates several enzymes within the apoptotic cascade, Recruitment of Lck to the TCR complex | Nutraceutical        | [138,139]  |
| Fatty acids              | Omega-3 Fatty acid (PUFA)      | Induce apoptosis in leucocytes   | Nutraceutical        | [140]      |
|                          | Butyrate                       | Suppress IL-12 expression, Enhance IL-10 expression  | Nutraceutical        | [141]      |
| Vitamins                 | Vit. C                         | Inhibit mRNA expression of pro-inflammatory cytokines, increased production of type I interferons  | Nutraceutical        | [142]      |
|                          | Vit. D                         | Suppress IL-17 production  | Nutraceutical        | [143]      |
| Phytochemicals           | Resveratrol                    | Increased expression of IL-10  | Nutraceutical        | [144]      |
|                          | Kaempferol                     | Decreased expression of IL-6 and TNF-alpha   | Nutraceutical        | [144]      |
|                          | Apigenin                       | Decreased expression of IL-6 and TNF-alpha   | Nutraceutical        | [144]      |
|                          | Quercetin                      | Decreased expression of IL-6 and TNF-alpha   | Nutraceutical        | [144]      |
| Plant Extracts           | <i>Echinacea purpurea</i>      | Inhibit the release of TNF- $\alpha$   | Nutraceutical        | [145]      |
|                          | <i>Camellia sinensis</i>       | Promote $\gamma\delta$ T lymphocyte functions  | Nutraceutical        | [146]      |
|                          | <i>Echium amoenum</i>          | Decrease expression of IL-1 $\beta$ , IL-6, TNF- $\alpha$ , iNOS and COX2  | Herbal Tea           | [147]      |
|                          | <i>Abelmoschus esculentus</i>  | Activation of NK cells   | Nutraceutical        | [148]      |
|                          | <i>Andrographis paniculata</i> | Activation of NK cells   | Nutraceutical        | [44]       |
| Interferons              | IFN- $\lambda$                 | Suppression of neutrophil infiltration and IL-1 $\beta$ production.  | Clinical trial       | [149,150]  |
| Monoclonal Antibodies    | Tocilizumab                    | Blocks IL-6 receptors  | Approved             | [151,152]  |
|                          | Anakinra                       | Interleukin-1 receptor antagonist  | Approved             | [153,154]  |
| S1PR modulators          | Fingolimod                     | Agonist of S1P1R, S1P3R, S1P4R, and S1P5R receptors.   | Approved             | [155,156]  |
| JAK inhibitors           | Baricitinib                    | JAK1, JAK2, JAK 3, and Tyrosine Kinase 2 inhibition  | Approved             | [157,158]  |
|                          | Pacritinib                     | JAK2 and IRAK1 inhibition  | Under investigation  | [159]      |
| Antimalarials            | Hydroxychloroquine             | Inhibits antigen processing  | Approved             | [160,161]  |
| Macrolides (Antibiotics) | Azithromycin                   | Inhibits bacterial protein synthesis and neutrophil activity   | Approved             | [162]      |
|                          | Clarithromycin                 | Inhibits bacterial protein synthesis and neutrophil activity   | Approved             | [163]      |
| Immune Supplements       | Transfer Factor                | Activate NK cells, Reduce IL-6, and Increase IL-10   | Nutraceutical        | [164,165]  |
| Corticosteroids          | Dexamethasone                  | Promote anti-inflammatory activities   | Approved             | [166]      |
|                          | Methylprednisolone             | Promote anti-inflammatory activities   | Approved             | [167]      |
| Others                   | Ulinastatin                    | Increases IL-10 level, reduces the levels of TNF- $\alpha$ , IL-6, and IFN- $\gamma$   | Approved             | [168]      |
|                          | Eritoran                       | TLR4 antagonist  |                      | [167]      |



**Figure 5** The prevention, immunopathogenesis and management of COVID-19.

is involved in regulating lipopolysaccharide (LPS) signaling through the TLR-4 receptor in macrophages/monocytes and dendritic cells (DCs) of the innate immune system. In the adaptive immune system, zinc is involved in T Cell Receptor (TCR) signaling by recruiting lymphocyte-specific protein tyrosine kinase (Lck) to the TCR complex. Zinc is also a regulator of the activity of enzymes of apoptotic signal transduction of B cell function.<sup>138,175</sup> Studies have shown that zinc modulates the response B-cell response (antibody production), monocytes, NK cells, neutrophils, and lymphocyte development, including mediating the killing of viruses.<sup>139</sup> Zinc deficiency triggers the release of cytokines such as IL-1 $\beta$ , IL-2, IL-6, and TNF- $\alpha$ , which triggers the expression of cellular zinc transporters.<sup>175</sup> Conversely, zinc supplementation alters plasma cytokines in a dose-dependent manner.<sup>176</sup> It causes the downregulation of pro-inflammatory cytokines due to the decreased gene expression of TNF- $\alpha$ , IL-1 $\beta$ , and IL-8.<sup>177</sup>

Interestingly, significantly lower levels of Zinc have been found in COVID-19 patients than in uninfected persons. This low zinc level has also increased the risk of complications by 5-fold.<sup>178</sup> Also, in the treatment of COVID-19, zinc supplementation has proved to be essential due to the micronutrient's natural antiviral and immunomodulatory properties. It is useful for the majority of the

population, particularly those having suboptimal zinc levels.<sup>176</sup> A case report on four COVID-19 patients revealed that administering a high dose of oral zinc salts had a beneficial effect on COVID-19 progression.<sup>178</sup> On a larger scale, there are 12 different RCTs (as of August 2020) associated with Zinc Supplementation in the prophylaxis and therapy of COVID-19.<sup>179</sup> Other trace elements play an essential role in the management of cytokine storms include copper, iron, magnesium, and selenium.<sup>180–182</sup>

### Polyunsaturated Fatty Acids (PUFA) and Butyrate

Polyunsaturated fatty acids, including Omega-3 fatty acid, can be found in fish, seafood, and plant oils such as soybean and canola oils. Omega-3 fatty acids are responsible for modulating monocyte and lymphocyte functions and modify host immunity during inflammatory disease.<sup>183,184</sup> Omega-3 fatty acids are made up of eicosapentaenoic and docosahexaenoic acids, which extensively enhance an immune response to viral infections.<sup>140,180</sup> The conversion of Omega-3 by lipoxygenase to lipids mediators such as lipoxins, resolvins, and protectins facilitates a dual role of promoting pro-resolution of inflammation and anti-inflammation.<sup>183</sup> The programmed resolution of acute inflammation reduces neutrophils' infiltration, increases the recruitment of monocytes, and activates the macrophages to consume dead neutrophils.<sup>183,185</sup> Consequently,

a high dose of Omega-3 supplementation causes decreased plasma concentration of IL-1, IL-6, and TNF- $\alpha$ . This anti-inflammatory property makes PUFA useful in the prevention and treatment of COVID-19 cytokine storms.<sup>186</sup> There is an ongoing RCT on the efficacy of using Omega-3 Polyunsaturated Fatty Acids to combat cytokine storms in COVID-19 patients. It is a single-blinded, randomized, placebo-controlled study involving 40 participants.<sup>187</sup>

Butyrate is a short-chain fatty acid synthesized by intestinal microbiota as a lactic acid fermentation product, and it serves as a source of energy for the intestinal epithelial cells. It also enhances the protection of the epithelium barrier through its anti-inflammatory activities.<sup>188</sup> By the inhibition of NF $\kappa$ B activation and the degradation of I-kappa B alpha (I $\kappa$ B $\alpha$ ) protein, butyrate suppresses the production of IL-12. It also suppresses the discharge of other pro-inflammatory cytokines like IL-2 and IFN- $\gamma$  in anti-CD3-stimulated peripheral blood mononuclear cells.<sup>141,188,189</sup> Butyrate also enhances the production of anti-inflammatory cytokines, IL-10 and IL-4.<sup>189</sup> There are several ongoing RCTs on the efficacy of probiotics species such as *Bifidobacterium* and *Lactobacillus* in treating COVID-19 patients.<sup>190</sup>

## Vitamins

These are known to have immunomodulatory, anti-viral, and antioxidant properties.<sup>142</sup> Vitamin C is an essential micronutrient that modulates both innate and adaptive immune functions. By stimulating p38 mitogen-activated protein kinase, vitamin C inhibits TNF-mediated activation of NF $\kappa$ B by the phosphorylation of I $\kappa$ B $\alpha$ .<sup>191</sup> Dietary supplementation of vitamin C significantly decreases the mRNA expression of pro-inflammatory cytokines and the 70 kilodalton heat shock protein (HSP70).<sup>192</sup> Also, the intravenous administration of vitamin C in high doses can ameliorate the neutrophil-related cytokine storm in COVID-19 patients.<sup>191,192</sup> Vitamin C also causes increased production of IFN-1, which causes the suppression of SARS-CoV-2 replication.<sup>7,192</sup> IFN-1 modulates the NK cell via both direct and indirect pathways.<sup>193,194</sup> There is an ongoing study on the efficacy of Vitamin C in treating Acute Lung Injury in COVID-19 patients. The protocol is 50 mg/kg of Vitamin C administered intravenously every 6 hours for 96 hours.<sup>195</sup>

Vitamin D has also been shown to suppress cytokine production in COVID-19 patients.<sup>143</sup> Vitamin D binds with the vitamin D receptor (VDR) on Th17 cells and suppresses the production of the IL-17 by inducing C/EBP homologous protein (CHOP) expression. Consequently, the recruitment of

neutrophils is impaired.<sup>196</sup> Data from observational studies suggest that vitamin D supplementation can reduce the risk of developing respiratory infections, especially in vitamin D-deficient people.<sup>197</sup>

## Phytochemicals and Plant Extracts

The extracts of many plants such as fruits, herbs, and spices can produce anti-inflammatory activities. For instance, the extract of *Echinacea purpurea* has been proven to stimulate phagocytosis in macrophages and inhibit the release of TNF- $\alpha$ . It also acts as an agonist against cannabinoid B2 receptor, trigger NK cells, and increase leucocyte circulation.<sup>145</sup> *Camellia sinensis* (green tea) extract reportedly reduced flu infection's clinical symptoms in a double-blind study and promoted  $\gamma\delta$  T lymphocyte functions.<sup>146</sup> *Echium amoenum* (Boraginaceae) extract to act on the macrophages to reduce iNOS and COX2 enzymes and TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 cytokine levels.<sup>147</sup> The extracts of plants such as *Abelmoschus esculentus* and *Andrographis paniculata* have been predicted to be stimulators of the KIR2DS2 and KIR2DS4 receptors of NK cells, respectively.<sup>144,148</sup> The stimulation of these activating receptors, which engage the DAP12-ZAP 70/Syk ITAM-dependent signaling pathway, would prevent cytokine storm by reducing the viral load.<sup>44</sup> Thereby, multiple studies reported that assessment of cytokinin levels with differentiation was a potentially beneficial correlation with the prognosis of severe COVID-19 infected cases.<sup>121,198-200</sup>

Natural compounds such as resveratrol, kaempferol, diosmetin, naringenin, capsaicin, apigenin, chrysin, quercetin, and luteolin can reduce the expression of TNF- $\alpha$ , IL-6, inducible nitric oxide synthase (iNOS), or cyclooxygenase-2 (COX2). They can also increase the expression of anti-inflammatory cytokines such as IL-10.<sup>201</sup> Dietary polyphenolic compounds such as flavonoids have been shown to have beneficial effects on host defense reactions and inhibit the transcription factor, NF- $\kappa$ B, from producing pro-inflammatory cytokines.<sup>202,203</sup> 544

Clinical trials using only medicinal plants for the prevention and treatment of COVID-19 are scarce. However, numerous ongoing RCTs use these natural products as the adjuvant component. For example, in China, diazotized glycyrrhizinate, extracted from licorice root, has been tried to control COVID-19 alongside Vitamin C and a standard antiviral agent. In Iran, clinical studies have been carried out to investigate the anti-COVID-19 efficacy of the combination of several medicinal plants such as

licorice, mallow, turmeric, echinacea, ginger, sage, fennel, and St. John's wort.<sup>204</sup>

## Interferons

Interferon lambda (IFN- $\lambda$ ) is a Type III interferon with established antiviral activity in the respiratory tract's epithelial cells.<sup>149</sup> In nature, Type III interferons act as the first line of the weapon in fighting viruses. IFN- $\lambda$  is induced because of pathogen identification through pattern recognition receptors (PRR).<sup>150</sup> The receptors of Type III interferon are expressed on all epithelial cells. Hence, they are found prominently in the respiratory, gastrointestinal, and reproductive tracts.<sup>205,206</sup> IFN- $\lambda$  binds to IFN- $\lambda$  receptor 1 (IFNLR1) via strong affinity and recruits its subunit, IL10Rb.<sup>207</sup> The complex formed transduces signals through the JAK-STAT pathway, culminating in the expression of hundreds of IFN-stimulated genes (ISG) such as NF- $\kappa$ B.<sup>150</sup> Consequently, IFN- $\lambda$  relieves inflammation by the suppression of neutrophil infiltration into the epithelial cells. IFN- $\lambda$  also suppresses IL-1 $\beta$  production and reduces the activity of IFN- $\alpha\beta$ , thereby downplaying immune-response in inflammation.<sup>208</sup> With these anti-inflammatory properties, IFN- $\lambda$  has the therapeutic potential to combat neutrophil-related cytokine storms.<sup>209</sup>

The early administration of IFN- $\lambda$  as an immunomodulator during the low viral titer stage of coronavirus infection recorded considerable clinical therapy success. Similarly, some research work has shown considerable success in IFN- $\lambda$  in combating the COVID 19 infection. The WHO has approved IFN- $\lambda$  to manage COVID-19 patients due to the promise it has shown.<sup>149</sup> A multicentre, double-blind, placebo-controlled RCT investigated the safety and efficacy of peginterferon lambda in treating mild-to-moderate cases of COVID-19. The study titled Interferon Lambda for Immediate Antiviral Therapy at Diagnosis in COVID-19 (ILIAD) involved 60 participants. The study revealed that Peginterferon lambda accelerated viral decline compared with the placebo indicating its usefulness in preventing clinical deterioration and reducing the time the virus is shed.<sup>210</sup> Similarly, the safety and efficacy of interferon (IFN)  $\beta$ -1 in treating severe COVID-19 cases have been evaluated by an open-label RCT. It was observed that IFN  $\beta$ -1b significantly reduced mortality, decreased the need for invasive mechanical ventilation, and shortened the recovery time of patients.<sup>211</sup>

## Interleukin 6 (IL-6) Inhibitors

IL-6 Inhibitors block the pro-inflammatory activity of IL-6, which is critical in developing cytokine storms in severe COVID-19 infection. Sarilumab and Tocilizumab are human monoclonal antibodies that inhibit IL-6 signaling by binding to the IL-6 receptor, responsible for processes such as activation of T-cells, stimulation of immunoglobulin secretion, the proliferation of the hematopoietic cell, and differentiation stimulation.<sup>76</sup> Tocilizumab interacts with transmembrane and soluble forms of IL-6 receptors, thereby blocking the transduction of signals that trigger an immune response.<sup>76</sup> Tocilizumab has been recommended for severe COVID-19 patients showing extensive bilateral pulmonary injury and high IL-6 levels.<sup>151,212</sup> A retrospective examination of 20 COVID-19 cases revealed that Tocilizumab decreased fever and lung lesion opacity and improved the number of lymphocytes in peripheral blood.<sup>152</sup> However, at 15 days, RCT shows that in severe cases of COVID-19, tocilizumab plus standard care did not perform better than standard care alone in improving clinical outcome.<sup>213</sup> Furthermore, there are documented reports of tocilizumab linked with increased chances of developing opportunistic infections such as fungal, tuberculosis, or other viral infections due to immune suppression.<sup>153</sup>

## Interleukin 1 (IL-1) Receptor Antagonists

The pro-inflammatory properties of IL-1 pre-dominate the innate immune system and are closely linked to damaging inflammation. A study revealed that the primary inflammatory cells found in the broncho-alveolar fluids and lung tissues of COVID-19 patients are the highly inflammatory pro-fibrosing monocyte-derived macrophages.<sup>154</sup> This shows that IL-1 $\alpha$  and IL-1 $\beta$ , two major juxtacrine and paracrine stimulatory cytokines of macrophagic-monocyte cells, are good targets for combating hypercytokinemia.

The management of cytokine storms resulting from infection has been meticulously studied by testing the agonists' activities of IL-1 cytokines produced during infection. Inhibition of IL-1 $\beta$ , a cytokine of the IL-1 family, produced alongside IL-33 and IL-18 during infection by a drug named Anakinra, has considerably reduced cytokine storm.<sup>154</sup> Anakinra is a human recombinant monoclonal antibody antagonist that connects to the IL-1R receptor and has shown efficacy in treating COVID-19 hypercytokinemia.<sup>154</sup> Investigation on some individuals suffering from either moderate or severe COVID-19 pneumonia treated with Anakinra showed good clinical and

biological outcomes.<sup>214</sup> However, on a full-scale multicentre, open-label, Bayesian RCT, Anakinra did not improve clinical outcome in mild-to-moderate cases of COVID-19 pneumonia.<sup>215</sup>

## Tumor Necrosis Factor (TNF) Blocker

Tumor necrosis factor blockers are agents that inhibit the TNF signaling pathway and consequently suppress hyperinflammation. Anti-TNF therapies have been proven to suppress inflammation in inflammatory ailments like rheumatoid arthritis and inflammatory bowel disease.<sup>216</sup> Empirical evidence reports that TNF-inhibitors could treat the cytokine storm in COVID-19 patients.<sup>216</sup> Several natural compounds have also been shown to inhibit TNF production. They include curcumin from turmeric and catechins from green tea.<sup>217</sup> One major advantage TNF inhibitors have over cytokine blockers is that they down-regulate the expression of several pro-inflammatory intermediaries such as IL-1, IL-6, and Granulocyte-macrophage colony-stimulating factor (GM-CSF) as well as down-regulate clotting markers such as DD and prothrombin fragments.<sup>218</sup>

Multiple sourced, observational data generated from the management of COVID-19 patients on anti-TNF therapy show improved clinical outcomes and reduced death rate. In the face of this body of compelling evidence, there is a compelling need for a full-scale evaluation of TNF inhibitors through an RCT.<sup>219</sup> However, there are safety concerns about secondary bacterial infection following the administration of TNF inhibitors.<sup>220</sup>

## Sphingosine-1-Phosphate Receptor (S1PR) Agonists

Sphingosine-1-phosphate receptors are a group of G-protein-coupled receptors (GPCRs) to which the biologically active lipid called sphingosine 1-phosphate (S1P) has a strong affinity. They are sub-divided into S1PR1, S1PR2, S1PR3, S1PR4, and S1PR5.<sup>155</sup> S1P acts as a lipid signaling molecule that targets and up-regulates these receptors as a potential strategy in combating hyperinflammation associated with SARS-CoV-2 infection.<sup>156,221</sup> Specifically, S1PR1 abundantly found on endothelial cells plays two critical roles: (a) modulation of immune responses by regulating the maturation, migration, and trafficking of lymphocytes.<sup>222,223</sup> (b) Protection of the vascular endothelium against infection by regulating the

vascular maturation, migration, cytoskeletal structure, and capillary-like network formation of endothelial cells.<sup>224,225</sup>

The use of S1PR1 signaling can significantly reduce the immunopathology associated with cytokine storms. This is because the treatment with S1PR1 ligands has a profound anti-inflammatory effect. Activated by phosphorylation, S1PR1 ligands bind to the S1P1 receptor inhibiting the release of specific lymphoid cells, suppress excessive cytokine production, and consequently reduce immune-mediated pulmonary injury.<sup>226,227</sup>

Fingolimod is an approved activator of S1PR1, S1PR3, S1PR4, and S1PR5 receptors. The oral administration of Fingolimod in COVID-19 patients stabilized the pulmonary endothelial barrier, decreased the inflammatory infiltrate, and reduced histopathology associated with ARDS.<sup>156,228</sup> Widely used in the treatment of multiple sclerosis, Fingolimod is yet to undergo RCT for its efficacy in the treatment of COVID-19.<sup>229</sup>

Also, CYM5442, S1PR1-specific agonist, significantly reduced hyper-inflammation in H1N1-induced mice and improved survival. It also alleviated H1N1-induced acute lung injury (ALI).<sup>230</sup> It has been suggested that it should be used as adjunctive therapy in battling COVID-19 disease.<sup>208</sup>

## Janus Kinase (JAK) Inhibitors

Interleukin (IL)-1 and IL-6 signaling are critical to cytokine syndrome in COVID-19 patients. Janus kinase inhibitors have dual therapeutic potential.<sup>157</sup> They exhibit their antiviral effect by blocking viral endocytosis and blocking multiple pro-inflammatory cytokines activation.<sup>157</sup> A known example is baricitinib, a typical numb-associated kinase (NAK) antagonist (a JAK1/2 antagonist). It also inhibits other enzymes such as tyrosine kinase 2 and JAK3.<sup>158</sup> Baricitinib has a high affinity for a clathrin-mediated viral endocytosis regulator, AP2-linked protein kinase - 1 (AAK1), found in pulmonary AT2 alveolar epithelial cells.<sup>231</sup> The binding of baricitinib to AAK1 prevent SARS-CoV-2 penetration into the AT2 alveolar epithelial cells.<sup>232</sup>

In an open-labeled investigation, patients administered baricitinib and existing therapies for two weeks significantly showed improvement in fever, oxygen saturation, the partial pressure of arterial oxygen/percentage of inspired oxygen ratio, C-reactive protein, and early warning scores.<sup>232</sup> 1033 COVID-19 patients were subjected to another randomized, double-blind, placebo-controlled trial and the results revealed that baricitinib administer with remdesivir showed better clinical outcomes than

remdesivir alone by accelerating improvement and reducing recovery time.<sup>233</sup>

Another example of JAK inhibitors is pacritinib, which is under investigation. Pacritinib is Interleukin-1 receptor-associated kinase 1 (IRAK1) and JAK2 inhibitor that could mitigate IL-1 and IL-6 expression and macrophage activation syndrome.<sup>159</sup> Due to its anti-inflammatory potential, pacritinib has recently undergone a multicenter Phase 3, randomized, double-blind placebo-controlled study. The study called PRE-VENT evaluates the ability of pacritinib to prevent the disease progression into ARDS in hospitalized patients with severe COVID-19 with or without cancer.<sup>234</sup>

## Hydroxychloroquine (HCQ)

Hydroxychloroquine is employed in the management of rheumatoid arthritis, malaria, and the autoimmune disease, Lupus.<sup>160</sup> Quinoline, a component of HCQ, is a potential immunomodulator that can reduce the production of pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1, IL-6, and IFN- $\alpha$  implicated in hypercytokinemia. This can be achieved by inhibiting MHC II expression, antigen processing, immune activation through TLR signaling, and the cyclic GMP-AMP synthase (cGAS) stimulation of interferon genes T-cells.<sup>160</sup> HCQ increases endosomal pH inhibiting intracellular viral activity and its presentation on the MHC 1 protein.<sup>7</sup> HCQ shows several potential antiviral and anti-inflammatory effects against COVID-19 infection during the early stages, and its prompt administration is key to the prevention of disease progression and severity.<sup>161,235</sup> Additionally, it has been reported that administration of HCQ had a positive association with serious psychiatric conditions including suicide, and, between these patients, some of them committed suicide among COVID-19 cases<sup>236</sup> and rheumatoid arthritis patient.<sup>237</sup>

## Macrolides

Macrolides are antibiotics with immunomodulatory properties such as neutrophil activation and clearance through apoptosis, prevention of pro-inflammatory cytokine released by immune cells, modulation of macrophage differentiation, and inhibition of mucus, etc.<sup>238</sup> Macrolides have been suggested for use in controlling hypercytokinemia in influenza infections.<sup>239</sup> Chronic inflammation of the lung parenchyma is characterized by an elevation of alveolar macrophages, Th1 and Th17 T-cells, neutrophils, and innate lymphoid cells. There is also an elevation of the blood levels of pro-inflammatory cytokines such as IL-1 $\beta$ , IL-4, IL-8, and TNF- $\alpha$ .<sup>239</sup> Azithromycin, erythromycin, and Clarithromycin are

macrolides that have been used frequently in combination with other therapies for the treatment of COVID-19. Beyond treating bacterial infections, these macrolides have been shown to significantly decrease neutrophil count, inhibit neutrophil chemotaxis, and reduce the concentration of neutrophil elastase concentration, IL-4, IL-8, TNF- $\alpha$ , IFN- $\gamma$ , C-reactive protein, calprotectin, myeloperoxidase (MPO), and serum amyloid A in the blood, through various immunological mechanisms.<sup>162,240</sup>

In an intervention study involving 90 participants, the oral administration of 500 mg clarithromycin twice daily for seven days significantly increased anti-inflammatory activity and improved clinical outcome in early moderate COVID-19 infection.<sup>163</sup> The proposed mechanism of action of clarithromycin is the modulation of the Th1/Th2 mononuclear responses and the suppression of SARS-CoV-2 viral load.<sup>163</sup>

In a randomized clinical trial conducted among patients with chronic obstructive pulmonary disease (COPD), azithromycin showed decreased platelet and white blood cell counts; and decreased concentrations of IL-8, C-reactive protein, E-selectin, and lactoferrin in the plasma.<sup>163</sup> Interestingly, the University of Oxford reported that the Platform Randomised Trial of Interventions against COVID-19 in older people (PRINCIPLE) trial showed that azithromycin is not effective the treatment of COVID-19 in older people. 500mg of azithromycin was administered three times daily for 14 days to 526 subjects. These were compared with 862 subjects receiving usual care. No beneficial effect of azithromycin was observed in subjects aged over 50 years treated in the early stages of COVID-19.<sup>241</sup> Also, clinical outcomes were not improved when azithromycin was added to standard of care treatment (which included hydroxychloroquine) in severe COVID-19 patients. This was observed in an open-label RCT that took place in 37 locations across Brazil.<sup>242</sup>

## Transfer Factors (TF)

Transfer factors are low molecular weight polypeptides fractions obtained from natural sources such as colostrum, egg yolks, or porcine spleen.<sup>164</sup> Specifically, it is derived from T-lymphocytes, and the immunomodulatory properties of TF have been well documented. It has been used to combat viral infections successfully.<sup>164</sup> Transfer factors increase innate defense by the activation of NK cells against viruses. TF can decrease IL-6 production and trigger the release of IL-10. Thus, TF can potentially combat immune hyper-responsiveness and hyper-

inflammatory associated with COVID-19.<sup>165</sup> Though yet to undergo RCT, TF's use has been proposed as a therapeutic option against COVID-19.<sup>243</sup> However, a 7-week double-blinded study evaluates the effect of TF supplementation in healthy adults against Upper Respiratory Tract Infections caused by Influenza or Rhinovirus. There are no results posted for this study.<sup>244</sup>

## Corticosteroids and Other Agents

Corticosteroids such as methylprednisolone and dexamethasone have significantly decreased the death toll in COVID-19 patients with ARDS.<sup>245</sup> Methylprednisolone has been found to decrease death risk in ARDS patients in China's clinical study.<sup>245</sup> Another study revealed that a single-dose of 40–500 mg of methylprednisolone stopped the hyper-inflammation without a negative effect of virus removal and specific IgG production. However, continuous administration of methylprednisolone slowed down a viral clearance and suppressed the immune system.<sup>246</sup> Prolonged use of methylprednisolone can also cause infections and other adverse effects, which include musculoskeletal effects such as osteoporosis, myopathy, and osteonecrosis; endocrine effects such as Cushing syndrome and growth impairment; cardiovascular effects such as hypertension and arrhythmias; dermatologic effects such as ecchymosis, mild hirsutism, and facial erythema; ophthalmologic effects such as cataract and glaucoma; gastrointestinal effects such as gastritis, gastric ulcer, and fatty liver; and neuropsychiatric effects such as psychosis, sleep disturbances, and akathisia.<sup>247</sup>

According to the findings by the UK Recovery Group headed by Horby P, dexamethasone emerges as the most reliable remedy for lung inflammation due to COVID-19 infection to date. It significantly suppressed cytokine storm, reduced mortality, and the duration of hospital stay among 6425 patients with severe COVID-19 infection.<sup>166</sup> Also, dexamethasone has been reported to reduce the risk of death linked to hypercytokinemia in 33% of patients with severe COVID-19 disease who received mechanical ventilation.<sup>248</sup> Dexamethasone is beneficial in hospitalized women who are COVID-19 patients and require mechanical ventilation or supplemental oxygen support. Though the same is beneficial in pediatric COVID-19 patients who also require mechanical ventilation or any other form of supplemental oxygen support, this should be considered on a case-by-case basis.<sup>249</sup>

Glucocorticosteroids have been used to manage lung inflammation during SARS and MERS epidemics but

produced harmful effects such as prolonged viral presence (due to immunosuppression) and induced diabetes.<sup>248</sup> The WHO has recommended the administration of systemic corticosteroids in severe COVID-19 patients; however, it discouraged its use in treating COVID-19 patients with mild infection.<sup>167</sup> This is to prevent worsening of a problem with complications such as asthma and cardiogenic shock. The WHO advised that the risk and benefit analysis should be done for individual patients before administering corticosteroids.<sup>167</sup>

Unlike corticosteroids, ulinastatin, a non-immunosuppressant drug, is a widely used clinical drug to combat inflammation. It increases IL-10 level (anti-inflammatory factor) and reduces TNF- $\alpha$ , IL-6, and IFN- $\gamma$  (proinflammatory factors). Therefore, ulinastatin may have a good prospect in treating COVID-19 infection, although further RCT is needed to substantiate this claim.<sup>168</sup>

In infections with pathogenic human coronaviruses, there is an accumulation of oxidized phospholipids (OxPL) in the pulmonary tissues.<sup>250</sup> The OxPL stimulates the Toll-like receptor 4 (TLR4), which increases the production of cytokines/chemokines in the macrophages of the lungs. Eritoran is a TLR4 antagonist, and therefore, it decreases the secretion of OxPL, pro-inflammatory cytokines, and chemokines. Along with other OxPL inhibitors, Eritoran is a potential therapeutic candidate for COVID-19 disease.<sup>250</sup>

## Conclusion

The COVID-19-induced cytokine storm is characterized by immune dysregulation and hyperinflammation. It is also associated with tissue damage, multi-organ failure, and death. The early diagnosis and aggressive mitigation of cytokine storms are essential to reduce COVID-19 morbidities and mortalities effectively. Clinical data suggests that specific hyper-inflammation markers have proven to be accurate and reliable in distinguishing between mild and severe cases of COVID-19 infection. Laboratory tests using these markers on the first day of hospitalization and a few days after would be useful in the clinical evaluation of disease status and progression. For would-be severe cases, a quick and aggressive administration of the potential therapeutic agents discussed would prevent or attenuate the effect of the advancing cytokine storm.

## Recommendation

Several diagnostic markers for cytokine storms indicate that they could be easily identified and promptly arrested. Rapid prophylaxis and treatment of cytokine storm by

clinicians will significantly enhance success in the fight against the dreaded COVID-19 pandemic. Policymakers should consider the recommendation for the off-label use of medications with potential activity against cytokine storm. Original studies on the genetic and other remote causes of the defective innate immune system are needed.

## Key Messages

- The cytokine storm is a major cause of mortality and morbidity in COVID-19 infection.
- COVID-19-induced cytokine storm is caused by a defective innate immune response and an exaggerated adaptive immune response.
- The magnitude of the release of pro-inflammatory cytokines such as IL-1, IL-6, and TNF- $\alpha$  significantly differentiates between mild and severe cases of COVID-19.
- Through the effective use of serum chemistry and hematological markers, a cytokine storm may be promptly diagnosed and controlled.
- Several biologicals, synthetic drugs, and herbal products have shown good promise in combating COVID-19-induced cytokine storms, but there is a need to validate their efficacy and safety in randomized clinical trials.
- Reports from clinical trials by the UK RECOVERY Group reveal that dexamethasone is the most promising drug in combating cytokine storms and consequently preventing and reducing mortality caused by the COVID-19.

## Consent for Publication

Every author had reviewed and approved the final copy of the manuscript and has agreed to be responsible for all aspects of the work, including any issues related to accuracy or integrity.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or

in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors declare that they do not have any financial involvement or affiliations with any organization, association, or entity directly or indirectly with the subject matter or materials presented in this article. This also includes honoraria, expert testimony, employment, ownership of stocks or options, patents or grants received or pending, or royalties.

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