



Proceeding Paper

The Impacts of Anti-Inflammatory Agents on COVID-19 Cytokine Storm †

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Abstract: The re-emergence of severe acute respiratory syndrome coronavirus 2 A(SARS-CoV-2) in Wuhan, China, has placed an unprecedented economic and health burden globally. The SARS-CoV-2 high mortality rate has brought great challenges to researchers, clinicians, and health workers in their bid to discover appropriate therapeutic interventions. The search for the ultimate remedy was initially centered on the use of antiviral agents targeting receptors and proteins involved in the pathophysiology of SARS-CoV-2. However, the upsurge of interest in repurposing anti-inflammatory agents was born out of the reported risks posed by a cytokine storm on COVID-19-induced fatality. A cytokine storm, as a result of the unregulated production of pro-inflammatory cytokines and other chemical mediators, triggers coagulopathy, viral sepsis, pneumonitis shock, and acute respiratory syndrome, which may lead directly to respiratory and organ failure and ultimately the death of the patient. The overwhelming evidence has shown that the early prediction of cytokine storm using serum chemistry and hematological markers and the use of appropriate anti-inflammatory agents will avert COVID-19 complications. These include the use of repurposed interferon (IFN) therapy and inhibitors of interleukin-1 (IL-1 β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and Janus kinase (JAKs) to nip the cytokine storm in the bud. This review critically used information retrieved from PubMed, China National Knowledge Infrastructure, Embase, Medline, and Google Scholar to elaborate on the mechanism and complications of COVID-19 cytokine storm, therapeutic interventions, and the way forward to discovering effective biocompatible drug targets.

Keywords: COVID-19; SARS-CoV-2; antiviral activity; cytokine storm; anti-inflammatory activity; drug targets



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1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a single-stranded RNA virus, has held the world hostage as the major cause of morbidity and mortality lately [1], with about 116 million cases reported by March 2021 [2]. The virus was named severe acute respiratory syndrome coronavirus 2 by the International Viral Classification Commission due to its 80% genomic similarity to severe acute respiratory coronavirus [3]. Clinical features of COVID-19 vary greatly depending on severity. In mild cases, patients present signs such as dry cough, fever, and cold, which could progress to acute lung injury that may lead to acute respiratory distress syndrome (ARS), shock, multiple organ failure, and ultimately death in severe cases [3].

The intensified search for a vaccine and antiviral options for this ravaging virus has not yielded the desired results due to the complex mechanisms of pathogenesis of SARS-CoV-2. Moreover, reports from clinical studies have shown that antibodies to SARS-CoV-2 have a short life span [4], which adds a lot of clauses to the use of vaccines as a prophylactic option, while antiviral agents alone may not prove beneficial, as clinical and autopsy results from dead COVID-19 patients have revealed the presence of cytokine storm, coagulopathy, and thrombosis, which are indices of hyperinflammation and the major causes of disease severity and death [3,5]. This drew the attention of clinicians to the need to combine antiviral agents with anti-inflammatory agents to avert the cytokine-storm-mediated death of COVID-19 patients.

Mechanisms of COVID-19 Cytokine Storm

The entrance of SARS-CoV-2 occurs mainly into alveolar epithelial cells, vascular endothelial cells, airway epithelial cells, and macrophages that express a high level of angiotensin converting enzyme 2 (ACE2) receptor [6]. The virus's adhesion, fusion, and entry are mediated by proteases such as transmembrane serine protease, AP2-associated protein kinase, and cathepsin [7]. Once inside the infected cell, the viral genomic single-stranded RNA or other RNA compositions (double-stranded RNA) are recognized by a network of receptors called pathogen-recognition receptors (PRRs) such as Toll-like receptors (TLRs) and cytoplasmic retinoic acid-inducible gene 1 (RIG-1)-like receptors (RLRs) [6]. As part of innate immunity against SARS-CoV-2, recognition of the virus by PRRs leads to the activation of adaptor proteins (activator protein-1 (AP-1), interferon regulatory factor 3 (IRF3), and nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB)), which induces intracellular signaling responsible for both transcriptional and post-transcriptional production of interferons (IFNs), the key agent for antiviral immunity. IFNs use dependent and independent mechanisms of class 1 major histocompatibility complex (MIC) proteins to stimulate natural killer (NK) cells involved in immunomodulatory and anti-inflammatory activities [8]. Regrettably, the protective role of IFNs in viral clearance is abrogated by SARS-CoV-2 via different immune evasion mechanisms that not only impair viral clearance but also promote paradoxical hyperinflammatory cytokines [6].

In addition, the reduced number, decreased activity, and genetic deficiency of NK cells in COVID-19 patients enhance the release of pro-inflammatory cytokines, such as interleukin-6 (IL-6), by activated macrophages and dendritic cells. IL-6 has two main receptors: the membrane one (mIL-6R) present in leukocytes and the soluble one (sIL-6R). Activation of IL-6 receptors induces a pleiotropic response via the JAK-STAT (Janus kinases and signal transducer and activator of transcription) complex, such as activation of innate and cellular immunity, together with Th17 differentiation, decreased Treg formation, and neutrophil migration, culminating in the further formation of interleukin 6, thereby promoting inflammation [9]. The binding of high levels of IL-6 to sIL-6R subsequently leads to the production of more IL-6, IL-8, vascular endothelial growth factor, and CCL-2 [7]. Moreover, secretion of IL-1β and tumor necrosis factor-alpha (TNF-α) by neutrophils upregulates the NFκB signaling pathway, leading to the release of several cytokines, ranging from chemokines (CCL2, CCL3, CCL5, CXCL10), granulocyte-macrophage colony-stimulating factor (GM-CSF), and granulocyte colony-stimulating factor (G-CSF) [3,10]. TLRs also activate other signaling pathways, including Janus kinase (JAK)/signal transducer and activator of transcription (STAT), involved in antiviral response and the generation of several cytokines [11]. These cytokines exacerbate the inflammatory response by attracting T-cells involved in the production of TNF-α and IFNs, which then activate dendritic and endothelial cells, inducing more cytokine production and resulting in cytokine release syndrome (CRS) or cytokine storm (CS) [10].

2. Complications of Cytokine Storm

The abrupt release of numerous cytokines exerts complications of various degrees on the body. For instance, excessive IFN-γ secretion causes fever, dizziness, headaches,

fatigue, and chills. IL-6 causes vascular leakage and induces cardiomyopathy by stimulating complement, the coagulation cascade that results in coronary artery disease and myocardial dysfunction. More so, IL-6 and IL-1 β cause the recruitment of CD8+ T cells and neutrophils to the site of infection. These cells produce cytotoxic substances such as matrix-metalloproteinase (MMP), reactive oxygen species (ROS), and leukotriene that provoke tissue injury in the lung parenchyma of the host, thereby predisposing the host to acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) [10]. TNF- α could also cause flu-like symptoms such as fever, malaise, and fatigue, as well as vascular leaking, heart failure, acute-phase protein synthesis, and lung damage [11]. Collectively, CS not only induces myelopoiesis and emergency granulopoiesis that further aggravate lung and epithelial damage but also sustains the overproduction of systemic cytokines, particularly IL-2, TNF- α , IFN- γ , and GM-CSF, responsible for triggering macrophage activation (i.e., MAS) and erythro-phagocytosis (i.e., HLH), which helps to sustain the inflammation [11]. Consequently, there will be perturbation of coagulation, anemia, and vascular hemostasis, resulting in capillary leak syndrome, thrombosis, and disseminated intravascular coagulation (DIC) [2]. The hallmark of which is fibrin deposition, induction of cell apoptosis and necrosis, diffuse alveolar lesions, and the SARS syndrome, which causes multiple organ failures and the death of patients.

The clinical features of CS could be assessed from deregulated levels of acute-phase proteins, biochemical indices, renal function indices, liver function indices, cardiac biomarkers, coagulation profile, cytokines, and chemokines, as well as hematological indices as shown in Table 1. The cytokine profile of COVID-19 patients has similarities with that of cytokine release syndrome patients having abnormal levels of inflammatory cytokines and chemokines (tumor necrosis factor-alpha (TNF- α), lymphopenia as well as chemokine ligand-2, CCL-3, and CXCL10, interleukin (IL-1 and IL-6) [10].

Table 1. Changes in laboratory characteristics during a cytokine storm.

S/N	Biomarkers	Normal Range	The Expected Outcome in COVID-19 CS	References
Acute-phase reactants				
1	C-reactive protein	0.3 to 1.0 mg/dL	≥ 20 mg/dL	[8]
	Ferritin	8–350 ng/mL	>400 ng/mL	[8]
	Albumin	35–50 g/L	<30 g/L	[12,13]
	Erythrocyte sedimentation rate	0 to 29 mm/h	>100 mm/h	[8]
	Procalcitonin	<0.1 ng/mL	> 0.1 μ g/L	[14,15]
Biochemical indices				
2	Lactate dehydrogenase	140–280 U/L	>320 U/L	[12]
	Alanine transaminase	19 to 33 IU/L	67 (47–100) IU/L	[8]
	Aspartate transaminase	15–37 U/L	37 U/liter	[14]
	Creatinine	45–100 μ g/L	47.66 μ g/L	[13]
	Urea	2.5–7.5 mmol/L	>7.5 mmol/L	[13]
	Glucose status; glycosylated hemoglobin; HbA1C	4.8–6.0%	$>6\%$	[14]
Cardiac markers				
3	Troponin	0–14 pg/mL	>60 ng/L	[13,14]
	N-terminal of the prohormone brain natriuretic peptide	<125 pg/mL	>88.64 pg/mL	[15]

Table 1. Cont.

S/N	Biomarkers	Normal Range	The Expected Outcome in COVID-19 CS	References
	Coagulation profile			
4	D-dimer	50–500 ng/mL	>1000 ng/mL	[5,8]
	Fibrinogen	225–434 mg/dL	740 mg/dL	[1]
	Prothrombin time	11.9–14.2 s	>14.8 s	[1]
	International normalized ratio	<1.1	>1.1	[14]
	Platelet count	150–450 × 10 ³ /μL	250 × 10 ³ /μL	[1,13]
	Cytokines and chemokines			
5	IL-1	0.10 pg/mL	0.67 pg/mL	[8]
	IL-6	0.5 to 5 pg/mL	<25 pg/mL	[8]
	TNF-α	0 to 8.1 pg/mL	<35 pg/mL	[8]
	Hematological parameters			
6	White blood cells	4–11 × 10 ⁹ /L	>11 × 10 ⁹ /L	[13]
	Hemoglobin	11.5–16.5 g/dL	>16.5 g/dL	[13]
	Lymphocytes	1.5–4.5 per cmm	>4.5 per cmm	[13]
	Neutrophils	2–7.5 per cmm	>2–7.5 per cmm	[13]

Early identification of the biochemical markers of a cytokine storm from serum chemistry and hematological indices will facilitate the use of an optimal drug for the management and treatment of COVID-19 severity, thereby avoiding CS-induced mortality. A cytokine storm could be predicted from abnormal levels of serum chemistry and hematological indices including D-dimer (≥ 1000 ng/mL), ferritin (≥ 400 μg/L), C-reactive protein (≥ 20 mg/dL), lactate dehydrogenase (≥ 450 U/L), TNF-α (< 35 pg/mL), IL-6 (< 25 pg/mL), and alanine transaminase (> 1 IU/L) as well erythrocyte sedimentation sediment (> 100 mm/h). and neutrophil/lymphocyte ratio (2.1–11.1) [8]. Hence, abnormal levels of these biomarkers are a major predictive index of disease severity and chances of mortality, which guides clinicians in the management and use of effective treatment options under advanced stages of COVID-19 CS.

Several studies have realized that elevation of D-dimer, liver enzymes, LDH, and troponin 1 predicts massive cell death leading to damage to the liver, kidney, and cardiovascular system as a result of COVID-19 CS [9]. A D-dimer concentration > 1 μg/mL indicates thromboembolic disorders, which result in multiple infarcts as well as ischemia of the extremities, a major pointer to poor prognosis and lower chances of survival [5]. Furthermore, a higher level of procalcitonin (> 0.1 ng/mL) indicates sepsis as a result of cytokine storm [14]. Elevated levels of liver enzymes (ALT and AST) above the upper limit occur when the liver is damaged after COVID-19 infection. More so, an increase in LDH is a measure of tissue damage produced by viremia and a dysregulated immune response as a result of metabolic acidosis under CS in COVID-19 infection [8]. More strikingly, the elevation of cardiac troponins in COVID-19 infection is a result of hypoxia, viral myocarditis, renin–angiotensin system (RAS) impairment, inflammatory-storm-driven myocardial damage, and microangiopathy [15]. Hence, a significant increase in troponin during hospitalization was associated with a higher risk of death [12]. Multiple studies have also realized that increased levels of IL-6 and hyperferritinemia are warning signs of disastrous clinical effects, including death [9]. Thus, monitoring the level of IL-6 is an accurate biomarker of disease progression, and a higher IL-6 to interferon-gamma (IFN-γ) ratio is used to define the severity of COVID-19 [12]. Remarkably, the level of C-reactive protein (CRP) released by hepatocytes stimulated by TNF-α and IL-6 is also used to predict COVID-19 mortality [15].

Anti-Inflammatory Agents Repurposed for the Management and Treatment of COVID-19 Cytokine Storm

The treatment regimen mostly employed in COVID-19 CS is potential cytokine blockers that regulate signaling pathways involved in the synthesis, activation, and release of pro-inflammatory cytokines such as interleukins (IL-1 and IL-6), TNF- α , IFNs, GM-CSF, and JAK. The use of anti-inflammatory agents as therapeutic targets for COVID-19 CS is seriously gaining momentum with many synthetic and natural products displaying recommendable potential for averting CS-induced fatality.

Synthetic drugs: Several synthetic anti-inflammatory drugs are currently being repurposed for COVID-19 CS, ranging from those that inhibit specific proteins involved in the inflammatory response to those that target receptors and signaling pathways. Some of the commonly used drugs and their pharmaceutical actions are presented in Table 2 [8,12,16]. Administration of type 1 IFNs (IFN α , β , and κ) to COVID-19 patients at the early stage of infection is effective in preventing CS. Since recent findings revealed that the decrease in type I and III IFNs' response to SARS-CoV-2 is a major risk factor for the development of COVID-19 CS [16]. The safety and efficacy of pegylated IFN lambda-1A (NCT04388708) and pegylated IFN lambda (NCT04343976) as sources of IFNs have been registered in clinical trials [5]. From the results obtained, IFN administration significantly shortened the recovery time and the need for invasive mechanical ventilation and also reduced the mortality rate. The use of interleukin antagonists is geared mainly to inhibit IL-1 β and IL-6. Anakinra and canakinumab are two commonly used IL-1 β inhibitors that treat CS syndromes such as macrophage activation syndrome, Still's disease, and hemophagocytic lymphohistiocytosis [2]. IL- β inhibitors bind at the same binding receptor as IL-1 β , thereby preventing IL-1 β binding to induce signaling transduction involved in the release of pro-inflammatory cytokines. Several studies have investigated the clinical effects of anakinra on COVID-19, and a total of 35 clinical trials are currently registered in ClinicalTrials.gov to determine its efficacy in averting COVID-19 severity and fatality [2]. In a similar manner, inhibitors of IL-6 prevent transcriptional induction via JAK/STAT and increase pulmonary capillary permeability. The use of tocilizumab, clazakizumab, sarilumab, situximab, and levilimab as IL-6 antagonists has also shown encouraging outcomes in many published clinical trials [7,17].

Table 2. Synthetic therapeutic options for COVID-19-induced cytokine storm.

Targeted Inhibitors	Available Drugs	Mechanisms of Action
IL-1 β	Anakinra, canakinumab	They bind at the same binding receptor for IL-1 β , thereby preventing IL-1 β binding to induce signaling transduction involved in the release of pro-inflammatory cytokines.
IFNs	Emapalumab	They inhibit the immunomodulatory action of interferons.
TNF- α	Entanercept, golimumab, adalimumab, infliximab	They block TNFRI receptors, thereby controlling the TNF-dependent cytokine cascade.
IL-6	Tocilizumab, clazakizumab, sarilumab, situximab, and levilimab	They inhibit binding of IL-6, which prevents transcriptional induction via JAK/STAT and increases pulmonary capillary permeability.
GM-CSF	Mavrillimumab, lenzilumab, sargramostim, gimsilumab	They inhibit signaling pathways that produce macrophages and granulocytes.
JAK	Baricitinib, tofacitinib, ruxolitinib	They limits amplification of the immune response via JAK/STAT, entry of virus and also inhibit cytokine signaling.

Apart from cytokine inhibitors, the blockade of signaling pathways such as TNF- α , JAK, or GM-CSF is also employed as a CS therapeutic regimen. TNF-inhibitors such as entanercept, golimumab, adalimumab, and infliximab are currently used to block TNFRI receptors, thereby controlling the TNF- α -dependent cytokine cascade in COVID-19 infec-

tion [16]. Inhibition of TNF- α results in a decline in adhesion molecules, IL-1 and IL-6, as well as vascular endothelial growth factors (VEGFs) [11]. Similarly, inhibition of the JAK pathway, which is central to the release of pro-inflammatory cytokines, has been proposed as an effective preventive and therapeutic option for COVID-19 CS. In addition to tofacitinib, targeting JAK1 and JAK2, the major synthetic agents registered in the clinical trial as JAK inhibitors are roxolitinib and baricitinib, which are inhibitors of JAK1 and JAK2. JAK inhibitors limit the amplification of immune responses via JAK/STAT and curtail the entry of viruses and also inhibit cytokine signaling [8]. GM-CSF plays a pathological function in the phase of CS, implying that blocking GM-CSF signaling may achieve clinical benefits in COVID CS. The use of mavrilimumab, lenzilumab, sargramostim, and gimsilumab in several studies led to decreased inflammatory markers, reduced progression to ARDS, and fewer inflammatory myeloid cells [2]. Their molecular mechanisms of action are through the inhibition of signaling pathways that produce macrophages and granulocytes [12]. More so, several clinical trials for lenzilumab (NCT04351152, NCT04583969, NCT04534725), and gimsilumab (NCT04351243) have been registered for the treatment of severe cases of COVID-19 [2].

Natural products: Herbal medicine has demonstrated therapeutic efficacy in the management and treatment of several inflammatory diseases. Recently, several traditional medicines from Traditional Chinese Medicine (TCM) and other plant-derived products are being employed as management and treatment options for COVID-19. These agents not only exert antiviral effects, thereby inhibiting replication of SARS-CoV-2, but also dampen excessive inflammation reaction through immune regulation. Remarkably, a plethora of studies have shown that phytoconstituents regulate levels of pro-inflammatory cytokines produced during the inflammatory condition [10]. The list of plant phytoconstituents that have demonstrated anti-inflammatory effects includes chlorogenic acid, quercetin, luteoloside, anthocyanins, gallic acid, myricetin, resveratrol, prodelfinidin, catechin, gallic acid, stilbenoid, naringenin, procyanidins, and geranilated flavonoids [18]. Interestingly, these secondary metabolites from plants could also be repurposed for the treatment of COVID-19 CS. Thus, herbal drugs with potent anti-inflammatory and antioxidant activities might help in alleviating the hyperinflammatory activities associated with COVID-19 due to their already-documented effects as shown in Table 3. Currently, a plethora of herbal remedies employed as phytopharmaceuticals for the management and treatment of COVID-19 are undergoing various stages of clinical trials, such as artemisinin, *Azadirachta indica* (neem), *Nigella sativa* (black seed), and traditional Chinese medicine, while other natural products are also being repositioned as therapeutic targets for a cytokine storm based on their already established anti-inflammatory potential [10].

Table 3. Natural products with potential target against cytokine storm.

Natural Product	Active Constituents	COVID-19 CS Targets
<i>Salvia rosmarinus</i>	Carnosic acid, carnosol	↓ IL-1 β , NF-kB, iNOS in alveolar macrophages
<i>Mentha balsamea</i>	Ursolic acid, phenolic acid, flavones, flavonones,	↓ IL-1 β , IL-6, and TNF- α
<i>Sambucus nigra</i>	Phenolic acids, flavonols, flavonoids, total phenol	↓ IL-1 β , IL-6, COX2, TNF- α
<i>Commiphora wightii</i>	Guggulsteron, lignans, ketosterol, flavonnes, guggulipid	↓ IL-1 β , IL-6, and TNF- α
<i>Panax ginseng</i>	Ginsenosides, panax notoginseng saponin (PNS)	↓ IL-1 β , IL-6, IL-8, TNF- α , and NF-kB
<i>Taraxacum officinale</i>	Polysachharides	↓ IL-1 β , IL-6, IL-8, NF-kB, and STAT3
<i>Tanacetum vulgare</i>	Flavonoids	↓ IL-1 β , IL-6, IL-8, iNOS, and TNF- α

3. Combination of Antiviral Treatment

The treatment of COVID-19 CS is more challenging because blocking inflammatory cytokine function without effective antiviral drug support may exacerbate the infection [2]. Therefore, antiviral drugs are used as combination therapy to eliminate the adverse effects of SARS-CoV-2 pathogenesis. Antiviral agents commonly used for treating COVID-19 include ribavirin, remdesivir, oseltamivir, galidesivir, favipiravir, arbidol, and darunavir [19]. Antiviral medications inhibit several phases of viral growth by targeting particular receptors and proteins required for viral entrance and replication, such as papain-like protease (PL^{pro}, part of nsp3), spike (S) protein, 3-chymotrypsin-like protease, RNA-dependent RNA polymerase (RdRp, nsp12), and main protease (M^{pro}, 3CL^{pro}, nsp5) [20,21]. The mechanisms of antiviral effects of the repurposed drugs for COVID-19 span from the inhibition of virus entry into the host cytoplasm, virus fusion to human cellular receptors such as serine protease (TMPRSS2) inhibitors, and blockade of virus receptors on to the host cell surface (monoclonal antibodies) to the inhibition of virus translation and replication by developing RNA-dependent RNA polymerase inhibitors, protease inhibitors to block polyprotein processing, budding, exocytosis, and virus release inhibitors [22].

4. Pros and Cons of the Use of Anti-Inflammatory Agents

Several clinical studies have established a high recovery rate and reduced mortality of COVID-19 patients managed with several anti-inflammatory agents. However, there are still some drawbacks to the use of some of these agents in patients with other comorbidities. For instance, IFN therapy reduces neutrophil recruitment, which can promote bacterial superinfection. However, these negative effects can be reduced by shortening the treatment period [11]. Prolonged usage of anti-IL-1 β could cause thrombocytopenia, leucopenia, and an increase in hepatic aminotransferases [7]. The main adverse effects of IL-6 blockers are diarrhea, headache, and neutropenia. It is also not recommended for older people or people with medical histories of a compromised immune system, such as tuberculosis (TB) patients [5], and hence there is a need for TB screening before its usage. This limits the usage of IL-6 antagonist in underdeveloped countries lacking in TB screening facilities [7]. The main disadvantage of using some anti-inflammatory targets, such as TNF- α , is the high cost and possibility of reactivation of TB when the intracellular bacteria are not inactivated by the suppressed immune system [5]. Nonspecifically, it may impair its protective functions in cellular homeostasis, as exemplified by a general suppression of innate immunity.

Furthermore, the JAK inhibitors could simultaneously hinder its protective functions in cellular homeostasis [2], leading to the risk of secondary infection as the innate immune system saddled with nonspecific immunity against pathogenic microorganisms will be suppressed [16], in addition to other side effects such as electrolyte imbalance, nausea, diarrhea, and anemia [7]. All these side effects call for caution in the use of these agents for a prolonged period and in people with other comorbidities. Therefore, it is recommended that clinicians closely monitor the clinical and laboratory parameters of patients before starting therapeutic intervention using cytokine inhibitors to ascertain the appropriate cytokine targeting agent and, most importantly, the potential side effects as a result of TB, viral infection, age, and other comorbidities.

5. Conclusions

The high rate of fatality and severe complications associated with COVID-19 has necessitated bedside-to-bench investigations for effective therapeutic options. The upsurge of interest in repurposing anti-inflammatory agents as management/treatment regimens for COVID-19 is due to the reported abrupt deregulation of pro-inflammatory cytokines leading to CS and its associated complications. Hence, early prediction of COVID-19 CS from serum chemistry and hematological indices coupled with an appropriate therapeutic target with anti-inflammatory agents will go a long way in averting the exponential case fatality rate of affected patients.

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References

1. Mortus, J.R.; Manek, S.E.; Brubaker, L.S.; Loor, M.; Cruz, M.A.; Trautner, B.W.; Rosengart, T.K. Thromboelastographic Results and Hypercoagulability Syndrome in Patients with Coronavirus Disease 2019 Who Are Critically Ill. *JAMA Netw. Open* **2020**, *3*, 2020–2023. [[CrossRef](#)]
2. Yang, L.; Xie, X.; Tu, Z.; Fu, J.; Xu, D.; Zhou, Y. The signal pathways and treatment of cytokine storm in COVID-19. *Signal Transduct. Target. Ther.* **2021**, *6*, 255. [[CrossRef](#)]
3. Li, X.; Geng, M.; Peng, Y.; Meng, L.; Lu, S. Molecular immune pathogenesis and diagnosis of COVID-19. *J. Pharm. Anal.* **2020**, *10*, 102–108. [[CrossRef](#)]
4. Tay, M.Z.; Poh, C.M.; Renia, L.; MacAry, P.A.; Ng, L.F.P. The trinity of COVID-19: Immunity, inflammation and intervention. *Nat. Rev. Immunol.* **2020**, *20*, 363–374. [[CrossRef](#)]
5. Chukwuma, I.F.; Apeh, V.O.; Nwodo, O.F.C. Mechanisms and potential therapeutic targets of hyperinflammatory responses in SARS-CoV-2. *Acta Virol.* **2021**, *65*. [[CrossRef](#)]
6. Chukwuma, I.F.; Apeh, V.O.; Emaimo, J. Cross talk on SARS-CoV-2 and human immunity. *Niger. J. Pharm. Res.* **2020**, *16*, 51–59. [[CrossRef](#)]
7. de Mélo Silva Júnior, M.L.; de Souza, L.M.A.; Dutra, R.E.M.C.; Valente, R.G.D.M.; Melo, T.S. Review on therapeutic targets for COVID-19: Insights from cytokine storm. *Postgrad. Med. J.* **2021**, *97*, 391–398. [[CrossRef](#)]
8. Rowaiye, A.B.; Okpalefe, O.A.; Adejoke, O.O.; Ogidigo, J.O.; Oladipo, O.H.; Ogu, A.C.; Oli, A.N.; Olofinase, S.; Onyekwere, O.; Abubakar, A.R.; et al. Attenuating the Effects of Novel COVID-19 (SARS-CoV-2) Infection-Induced Cytokine Storm and the Implications. *J. Inflamm.* **2021**, *14*, 1487–1510. [[CrossRef](#)]
9. Ahmad, R.; Haque, M. Surviving the Storm: Cytokine Biosignature in SARS-CoV-2 Severity Prediction. *Vaccines* **2022**, *10*, 614. [[CrossRef](#)]
10. Sapra, L.; Bhardwaj, A.; Azam, Z.; Madhry, D.; Verma, B.; Rathore, S.; Srivastava, R.K. Phytotherapy for treatment of cytokine storm in COVID-19. *Front. Biosci.-Landmark* **2021**, *5*, 51–75. [[CrossRef](#)]
11. Rabaan, A.A.; Al-Ahmed, S.H.; Muhammad, J.; Khan, A.; Sule, A.A.; Tirupathi, R.; Mutair, A.A.; Alhumaid, S.; Al-Omari, A.; Dhawan, M.; et al. Role of inflammatory cytokines in COVID-19 patients: A review on molecular mechanisms, immune functions, immunopathology and immunomodulatory drugs to counter cytokine storm. *Vaccines* **2021**, *9*, 436. [[CrossRef](#)]
12. Skevaki, C.; Fragkou, P.C.; Cheng, C.; Xie, M.; Renz, H. Laboratory characteristics of patients infected with the novel SARS-CoV-2 virus. *J. Infect.* **2020**, *81*, 205–212. [[CrossRef](#)]
13. Almayahi, Z.K.; Raveendran, A.V.; Al Malki, R.; Safwat, A.; Al Baloshi, M.; Abbas, A.; Al Salami, A.S.; Al Mujaini, S.M.; Al Dhuhli, K.; Al Mandhari, S. Clinical features, laboratory characteristics and risk factors for mortality of COVID-19 patients in a secondary hospital in Oman during the first wave of the SARS-CoV-2 pandemic. *Bull. Natl. Res. Cent.* **2022**, *46*, 139–150. [[CrossRef](#)]
14. Hannawi, S.; Hannawi, H.; Naeem, K.B.; Elemam, N.M.; Hachim, M.Y.; Hachim, I.Y.; Darwish, A.S.; Al Salmi, I. Clinical and Laboratory Profile of Hospitalized Symptomatic COVID-19 Patients: Case Series Study from the First COVID-19 Center in the UAE. *Front. Cell. Infect. Microbiol.* **2021**, *11*, 632965. [[CrossRef](#)]
15. Rezabakhsh, A.; Sadat-Ebrahimi, S.R.; Ala, A.; Nabavi, S.M.; Banach, M.; Ghaffari, S. A close-up view of dynamic biomarkers in the setting of COVID-19: Striking focus on cardiovascular system. *J. Cell. Mol. Med.* **2022**, *26*, 274–286. [[CrossRef](#)]
16. Kim, J.S.; Lee, J.Y.; Yang, J.W.; Lee, K.H.; Effenberger, M.; Szpirt, W.; Kronbichler, A.; Shin, J. II Immunopathogenesis and treatment of cytokine storm in COVID-19. *Theranostics* **2021**, *11*, 316–329. [[CrossRef](#)]
17. Iannaccone, G.; Scacciavillani, R.; Del Buono, M.G.; Camilli, M.; Ronco, C.; Lavie, C.J.; Abbate, A.; Crea, F.; Massetti, M.; Aspromonte, N. Weathering the Cytokine Storm in COVID-19: Therapeutic Implications. *CardioRenal Med.* **2020**, *10*, 277–287. [[CrossRef](#)]
18. Llivisaca-Contreras, S.A.; Naranjo-mor, J.; Pino-acosta, A.; Pieters, L.; Berghe, W.V.; Manzano, P.; Vargas-p, J.; Le, F.; Cevallos-cesvallos, J.M. Plants and Natural Products with Activity against Various Types of Coronaviruses: A Review with Focus on SARS-CoV-2. *Molecules* **2021**, *26*, 4099. [[CrossRef](#)]
19. Mishra, S.K.; Tripathi, T. One year update on the COVID-19 pandemic: Where are we now? *Acta Trop.* **2021**, *214*, 105778. [[CrossRef](#)]
20. Adegboyega, A.E.; Johnson, T.O.; Omale, S. Computational modeling of the pharmacological actions of some antiviral agents against SARS-CoV-2. In *Data Science for COVID-19*; Academic Press: Cambridge, MA, USA, 2021; pp. 467–482.

21. Johnson, T.O.; Adegboyega, A.E.; Ojo, O.A.; Yusuf, A.J.; Iwaloye, O.; Ugwah-Oguejiofor, C.J.; Asomadu, R.O.; Chukwuma, I.F.; Ejembi, S.A.; Ugwuja, E.I.; et al. A Computational Approach to Elucidate the Interactions of Chemicals from *Artemisia annua* Targeted Toward SARS-CoV-2 Main Protease Inhibition for COVID-19 Treatment. *Front. Med.* **2022**, *9*, 907583. [[CrossRef](#)]
22. Khan, S.A.; Al-Balushi, K. Combating COVID-19: The role of drug repurposing and medicinal plants. *J. Infect. Public Health* **2021**, *14*, 495–503. [[CrossRef](#)]