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Title: Repositioning anti-inflammatory agents as drug targets for COVID-19: A prospect for circumventing SARS-CoV-2 induced fatality.

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Abstract: The re-emergence of severe acute respiratory syndrome coronavirus (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 anti-viral agents targeting receptors and proteins involved in the pathophysiology of SARS-CoV-2., such as spike (S) proteins, papain-like protease (PLpro), replicase polyproteins 1a, main protease, RNA dependent RNA polymerase (RDRP), RNA binding protein of NSP9, and 3-chymotrypsin- However, the upsurge of interest in repositioning anti-inflammatory agents was borne out of the reported risks played by cytokine storm in the COVID-19 fatality. Hypercytokinemia 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 death of the patient. The overwhelming evidence has shown that early prediction of cytokine storm with serum chemistry and hematological markers (D-dimer, ferritin, cytokine, lactate dehydrogenase, C-Reactive proteins, alanine aminotransferase, neutrophil/lymphocyte ratio, and erythrocyte sedimentation rate) and the use of appropriate anti-inflammatory agents (synthetic drugs and herbal products) will nip cytokine storm. A wide array of targets will nip cytokine storm in the bud, such as

the use of inhibitors of interleukin-1, interferons (IFNs), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6). Janus kinase (JAKs) as well as cyclooxygenase-2 (COX-2). This review critically used information retrieved from PubMed, China National Knowledge Infrastructure, Embase, Medline, and Google Scholar to elaborate laboratory features of COVID-19 patents, therapeutic interventions for COVID-19, 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.

Introduction

Severe acute respiratory 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 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 which develops into acute respiratory distress syndrome (ARS), shock, multiple organ failure, and ultimately death [4,5].

The intensified search for a vaccine and anti-viral 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 [6], which adds a lot of clauses to the use of vaccines as a prophylactic option, while anti-viral agents alone may not prove beneficial, as clinical and autopsy results from patients have revealed the presence of cytokine storm, coagulopathy, and thrombosis, which are indexes of hyper-inflammation and the major causes of disease severity and death [7]. This drew the attention of clinicians to the need to combine anti-viral agents with anti-inflammatory agents to avert cytokine syndrome mediated death in COVID-19.

CYTOKINE STORM IN COVID-19.

As part of innate immunity against SARS-CoV-2, recognition of the virus by pattern recognition receptors (PRRs) attracts leukocytes and increases diapedesis, leading to local inflammation. This activates the release of several cytokines, ranging from interleukins (IL-1, IL-6, and IL-8), chemokines (CCL2, CCL3, CCL5, CXCL10), granulocyte-macrophage colony-stimulating factor (GM-CSF), and granulocyte colony-

stimulating factor (G-CSF) [8]. These cytokines further aggravate the inflammatory response by attracting T-cells involved in the production of TNF-α, and IFNs, which will, in turn, activate dendritic and endothelial cells, thereby inducing more cytokine production, leading to hypercytokinemia [8].

Hypercytokinemia culminates in dysregulation of concentrations 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 **Figure 1** [9]. The hallmark of which is fibrin deposition, induction of cell apoptosis and necrosis, diffuse alveolar lesion, and the SARS syndrome, which causes multiple organ failure and death of patients. 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- (TNF-α), Interleukin (IL-1 and IL-6), lymphopenia as well as chemokines ligand-2, CCL-3, and CXCL10 [8]. Thus, COVID-19 abrogates the host immune aimed at combatting SARS-CoV-2 to an uncontrolled inflammatory response [2].

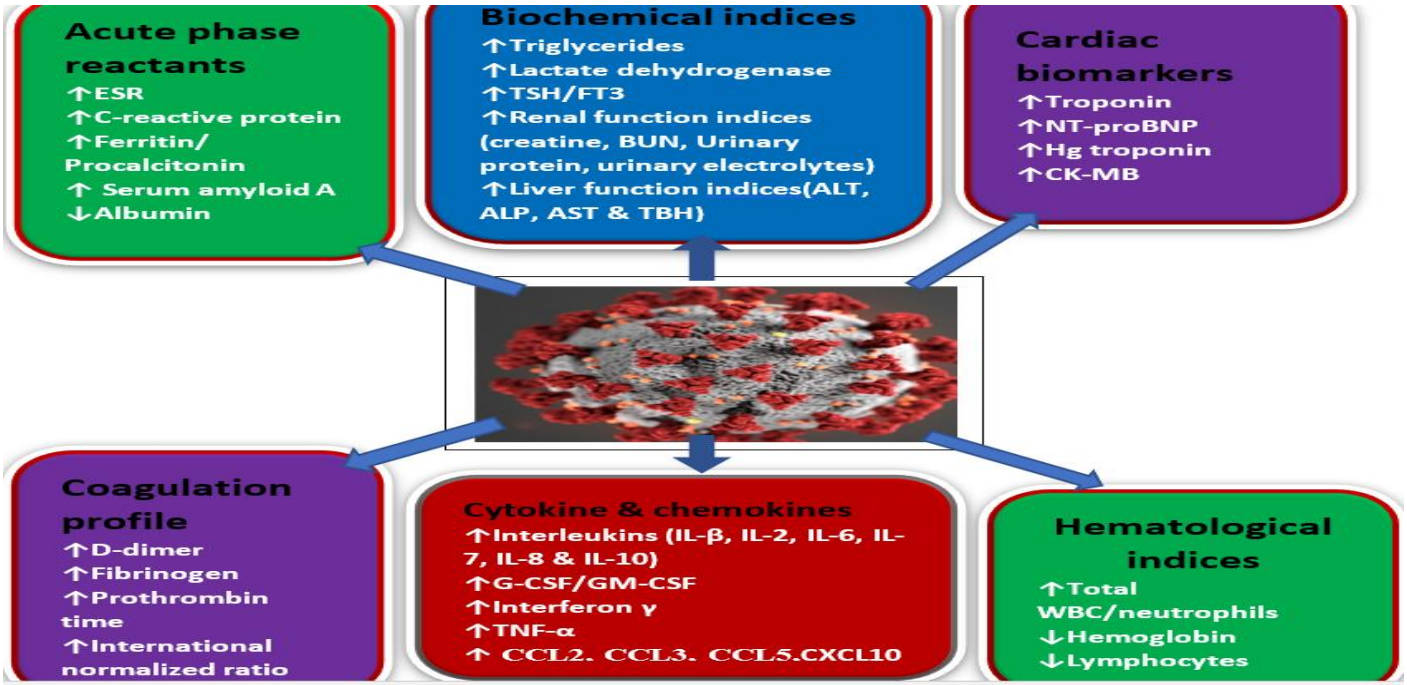

Figure1: Changes in laboratory characteristics during a cytokine storm.

Immunity to SARS-CoV-2 induces a hyperinflammatory response which leads to deregulation of body chemistry.

Early identification of biochemical markers of cytokine storm from serum chemistry and hematological indices will facilitate the use of an optimal drug for management and treatment of COVID-19 severity, thereby avoiding cytokine storm induced mortality. Cytokine storm could be predicted from abnormal levels of serum

chemistry and hematological indices including D-dimer (≥1000ng/ml), ferritin (≥ 400 μg/L), C-reactive protein (≥ 20 mg/dL), lactate dehydrogenase (≥ 450 u/L), TNF-α (< 35pg/mL), IL-6 (< 25 pg/mL), alanine transaminase (> IU/L) as well erythrocyte sedimentation sediment (> 100 mm/hr. and neutrophil/lymphocyte ratio (2.1-11.1) [10].

Anti-inflammatory options for management and treatment of cytokine storm

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 A wide array of synthetic drugs ranging from those targeted at inhibiting specific proteins involved in the inflammatory response, receptors as well as signaling pathways. Some of the commonly used drugs and their pharmaceutical actions are presented in **Table 1**[9-11]**.**

Table 1: Synthetic therapeutic options for COVID-19 induced cytokine storm

Targeted inhibitors	**Available drugs**	**Mechanisms of action**
IL-1β	Anakinra, canakinumab	Bind at the same binding receptor for IL-1β thereby preventing IL-1β 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, infiximab	Block TNFRI receptors thereby controlling TNF-dependent cytokine cascade
IL-6	Tocilizumab, clazakizumab, sarilumab, situximab, and levilimab.	Inhibits binding of IL-6 which prevents transcriptional induction via JAK/STAT and increase pulmonary capillary permeability
GM-CSF	Mavrillmumab, lenzilumab, sargramostim, gimsilumab**.**	Inhibits signaling pathways that produce macrophages and granulocytes
JAK	Baricitinib, tofacitinib, ruxolitinib	Limits amplification of immune response via JAK/START, entry of virus and also inhibits cytokine signaling

Natural products: Currently, a plethora of herbal remedies employed as phytopharmaceuticals for management and treatment of COVID-19 are undergoing various stages of clinical trials, such as artemisinin,

Azadiracha indica (neem), *Nigella sativa* (black seed), and traditional Chinese Medicine while other natural products are also repositioned as therapeutic targets for cytokine storm based on their already established anti-inflammatory potential [8]. Some of these remedies are presented in **Table 2.**

Table 2: Natural products with potential cytokine

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

These herbal remedies have active ingredients that could be repositioned as COVID-19 CS targets

Conclusion: Hyperinflammatory response has been identified as the major inducer of immunological derangement and ultimately cytokine storm. Early prediction of COVID-19 CS from serum chemistry and hematological indices coupled with an appropriate therapeutic target of COVID-CS with anti-inflammatory compounds will go a long way in averting the exponential case fatality rate of affected patients.

Conflict of interest: There is no conflict of interest to declare

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