CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187
https://zenodo.org/records/10700717

https://www.iajps.com/volumes/volume11-february-2024/03-issue-02-february-24/

Available online at: http://www.iajps.com *Review Article*

TARGETING HEMOSTASIS DYSFUNCTION AND INFLAMMATION IN COVID-19 PATIENTS: POTENTIAL THERAPEUTICS AVENUES THROUGH VIRAL AND HOST MOLECULES

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Abstract:
The COVID-19 pandemic has presented magnitude of challenges for global health authorities and researchers alike. The World Health Organization (WHO) is overseeing innumerable clinical studies aimed at determining the potency of existing drug against the virus. Concurrently, scientists worldwide are analysing into the cellular and molecular mechanisms underlying SARS-CoV-2 infection. Studies indicate that assorted factors such as blood haemostasis dysfunction, hypoxia, venous thrombotic and inflammation events play crucial roles in the evolution of COVID-19, from its early stage to several expressions. Understanding how the virus instigates these detrimental cellular and biochemical processes is predominant. This mini review explores budding trends in the pathophysiology of COVID-19 and discusses therapeutic perspectives. Researchers are striving to untwist how SARS-CoV-2 triggers adverse cellular and biochemical reactions in infected individuals, offering hope for the progression of effective treatments.
Key-Words: *Hemostasis, COVID-19, SARS-CoV-1, Inflammation, Host Cells, Cytokines*

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Please cite this article in press Shweta Manoj Dhule et al., ***Targeting Hemostasis Dysfunction And Inflammation In Covid-19 Patients: Potential Therapeutics Avenues Through Viral And Host Molecules*** *, Indo Am. J. P. Sci, 2024; 11 (02).*

1.INTRODUCTION

The COVID-19 pandemic, caused by the SARS-CoV-2 virus, began erstwhile, following the diagnosis of Acute Respiratory Syndrome Disease (ASRD) in Wuhan, China. Researchers quickly depicted the molecular structure of the virus and identified its target receptor as the membrane angiotensin-converting enzyme-2(ACE-2).This detection provided crucial insights into how the viral infects cells and tiled the way for developing potential treatments and vaccines[1,2].Attempts to find effective drug therapies for COVID-19 were initiated through clinical studies such as the solidarity Trial and the Discovery Trial in Europe. These trials investigate a large assortment of medications, including traditional antiviral and antiretroviral drugs, anti-malaria medications, antibodies, cytokines, and derive from Chinese plants. The goal is to identify treatments that can effectively battle the virus and improve outcomes for patients affected by COVID-19[3,4,5]. Recent clinical studies have revealed that COVID-19 patients are sensitive to hypoxia [6], characterized by risk of low levels in the body. Additionally, there's a risk of pulmonary venous thromboembolism [7], where blood clots form in the lung's vein, probably leading to severe respiratory complications. Furthermore, gut dysbiosis [8-10] imbalance in the gut's microbial community, has been observed in COVID-19 cases, bestowing to gastrointestinal symptoms and impacting overall immune health. These findings highlight the multifaceted nature of COVID-19's effects on the body, necessitating comprehensive medical management and ongoing research efforts.

2.PHYSIOPATHOLOGY ASSOCIATED WITH SARS-COV-2 INFECTION

2.1 Inflammation

When doctors analyse the blood of the patient, they've observed something called a "cytokine storm". This term refers to a situation where the body's immune system becomes overly active and releases a large number of cytokines, which are signalling molecules that help regulate immune responses. However, in a cytokine storm, this response becomes uncontrolled and can lead to serious inflammation throughout the body. This excessive inflammation can cause damage to tissues and organs and is associated with severe conditions such as sepsis or certain autoimmune disorders. Essentially, it's like the immune system is going into OneDrive, which can be very harmful to the patient's health [11,12]. During Viral infections like COVID-19, the body's immune response kicks into gear, releasing a plethora of pro-inflammatory cytokines. These are signalling molecules produced by specialized immune cells, and their excessive release can worse a patient's health condition. In COVID-19 patients, various blood types of blood cells, such as platelets, monocytes, and neutrophils, become activated. Additionally, resident cells in tissue like the lungs (alveolar macrophages), kidneys (mesangial cells), and brain (glial cells) may not become activated. Alongside cytokines, lipid inflammatory mediators [13] like prostaglandins and leukotrienes, as well as molecules associated with swelling (histamine, serotonin, and bradykinin), contribute to the inflammatory process seen in COVID-19. This heightened immune response can lead to significant tissue damage and complications for the patient. Macrophages and neutrophils, when activated during SARS-CoV-2 infection, release oxygen free radicals through a process dependent on NADPH oxidase. This oxidative stress adds another layer of burden to the physiological effects of the virus. These free radicals can cause damage to tissues and exacerbate inflammation, contributing to the severity of the infection and potential complications for patients[14].Recent studies, including a meta – analysis investigation, have revealed that intravenous corticosteroid treatment, known for its anti-inflammatory properties, is linked to improved outcomes in severe cases of COVID-19.This suggests that reducing inflammation with corticosteroids may be beneficial in managing the severity of the disease and enhancing patient recovery[15].

2.2 Haemostasis Dysfunction

Numerous clinical and laboratory findings across various countries have identified several key molecular and cellular mechanisms that could play a pivotal role in the pathophysiology induced by SARS-CoV-2[16,17]. Observations in COVID-19 patients reveal both hypoxia and dysfunction in haemoglobin oxygen transport. Additionally venous thromboembolism has been identified as a potential contributor to tissue damage in various organs including the lung, brain, heart and kidney. The severity of COVID-19 appears to be linked to thrombogenic blood parameters, with reports indicating blood coagulation dysfunction [18,19] and thrombocytopenia [20] among affected individuals. In COVID-19 patients, there can be issues with blood clotting and low platelet counts. Blood clots can form in various organs, and severe cases often show high levels of substances like plasmin [21] and D-dimers [22], indicating increased clot breakdown. Tissue factor is thought to play a significant role in causing these clotting problems in COVID-19 patients [23,24]. The Intricate processes of blood coagulation and fibrinolysis in humans rely on numerous serine

protease enzymes. These enzymes, like thrombin and plasmin, play pivotal roles in regulating clot formation and dissolution. Alongside a multitude of other blood proteins with enzymatic activities, they meticulously control these processes, ensuring proper blood flow balance and preventing excessive clotting or bleeding. Haemostasis, the regulation of blood clotting. It is a focal point in numerous infectious diseases and health conditions like envenomation. For instance, snake venom-induced blood clotting involves several serine protease enzymes present in the venom [25]. The blood clotting and fibrinolysis processes in COVID-19 patients may be influenced if the viral proteases are released into the bloodstream. These proteases would potentially interact with the human blood clotting and fibrinolysis cascade, similar to the dysfunctions observed in snake venom-induced haemostasis [26]. Numerous venom enzymes contribute to the toxicity of snake venom, including phospholipases, proteases, and other toxins. Similarly, in SARS-CoV-2, proteins like the papain-like protease and 3-chymotrypsin-like protease play crucial roles in viral replication and infectivity [27,28,29].

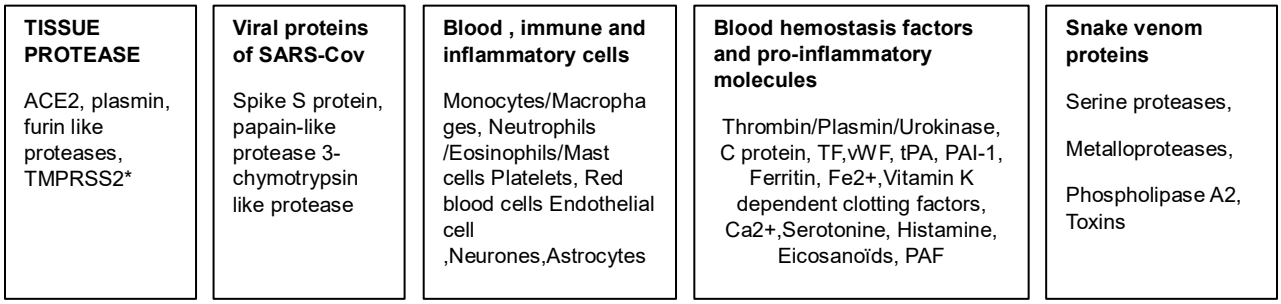

Fig 1. This figure encloses the list of cells and molecules which could have close enzymatic and various pharmacological interactions.

2.3 Serine Protease-Mediated Virus approach into Host Cells

The process of SARS-CoV-2 entering host cells relies on the activation of the virus's S spike protein by a specific serine protease present in the host cells. Therefore, host cell surface proteases play a crucial role in virus infectivity. In the case of SARS-CoV-2, the human serine protease TMPRSS2 primes the virus's S protein [30], facilitating its binding to its receptor, Angiotensin Converting Enzyme 2 (ACE2). Additionally, other host proteases might also be involved in priming the S spike protein [31]. Studies investigating the molecular sequence of SARS-CoV-2 RNA and its spike glycoprotein have identified additional host cell serine protease enzymes that may be involved in priming the S protein on host cells [32,33]. Research findings indicate that unlike previous coronaviruses, the genomic sequence of SARS-CoV-2 RNA contains 12 bases that encode a peptide sequence of a few amino acids. This sequence serves as a cleavage site for various serine proteases distributed throughout the human body. The sequence of the SARS-CoV-2 S glycoprotein elucidates why the virus can infect a wide range of organs, contributing to its heightened virulence and its extensive impact on the bloodstream, lungs, and other organs. The structure of the SARS-CoV-2 S glycoprotein explains how the virus can invade various organs, leading to its increased ability to cause severe illness [21] and affecting multiple systems such as the bloodstream, lungs, and other organs.

2.4 Objectivity in therapeutic targeting of SAR-COV-2 associated pathology

Recent advancements in our understanding of COVID-19's biology and how it affects the body have greatly improved how we treat the disease, particularly in severe cases. While we still don't have a specific antiviral medication targeting the SARS-CoV-2 virus itself, other drugs have shown promise in managing the illness.

When COVID-19 becomes severe, it can lead to complications beyond just the viral infection itself. For example, it can make patients more susceptible to bacterial infections or cause dangerous blood clots to form. To address these issues, doctors have been using certain medications:

- **Anti-bacterials**: These drugs help fight bacterial infections that can arise as a secondary complication of COVID-19. While they don't directly target the virus, they can prevent or treat bacterial infections that might worsen a patient's condition.
- **Blood Thinners (Anticoagulants)**: COVID-19 can increase the risk of blood clotting, which can lead to serious complications like strokes or lung problems. Blood thinners help prevent these clots from forming, reducing the risk of these severe outcomes.

- **Corticoids**: These are a type of steroid medication that helps reduce inflammation in the body. In severe cases of COVID-19, where the immune system's response is overly aggressive and causing harm, corticoids can help calm this response down, potentially improving outcomes.

While these treatments have provided some hope in managing severe cases of COVID-19, it's important to note that they are not universally effective for all patients. Treatment decisions should be made on a case-by-case basis, considering the patient's specific condition and needs. Additionally, ongoing research is continually improving our understanding of the disease and identifying new treatment strategies.

Given the physiological process linked to SARS-COV-2 infection, it is clear that targeting various protease activity is crucial. These protease plays a key role in multiple stages of virus life cycle, from priming viral S spike protein facilitating virus replication and assembly. Thus, inhibiting these protease activities in both host cells and viral enzymatic machinery is essential. Protease inhibition has been successful therapeutic strategy for numerous viral infections, including HIV [34].

Molecular modelling has recently proposed repurposing certain existing certain protease inhibitors for COVID-19 therapy [35]. This paper will focus on discussing therapeutic strategies involving protease inhibitors, while treatments utilizing nucleotide and nucleoside drugs to disrupt viral replication will be addressed elsewhere [36].

Emerging therapeutic approaches for COVID-19 include exploring lactoferrin milk enzyme [37-40] and oligosaccharides [41-44] as potential antiviral treatments in human infectious diseases. Laboratory experiments have demonstrated the antiviral properties of these substances. Notably, a recent clinical trial conducted in Italy [39] investigated the use of lactoferrin in treating mild-to-moderate and asymptomatic COVID-19 patients with the aim of preventing disease progression.

According to the study findings, lactoferrin was associated with prompt viral clearance and rapid improvement in clinical symptoms. Additionally, there was a noteworthy decrease in D-Dimer, Interleukin-6, and ferritin levels in the blood, all indicating positive therapeutic effects. Consequently, lactoferrin emerges as a genuinely promising therapeutic agent, whether utilized as a purified active compound or as an integral component of a natural product.

Within the realm of traditional medicine, certain natural food and plant extracts renowned for their antiviral, antioxidant, anti-inflammatory, and anticancer attributes have recently garnered attention as potential therapeutic options for addressing COVID-19. Considered as potential therapeutic candidates, camel milk stands out as a traditional food in numerous countries across Asia and Africa, valued for both nutritional and healing purposes. Extensive reviews [45-47] have documented the health benefits and therapeutic attributes associated with camel milk. Notably, lactoferrin, a prominent component of camel milk, has been the subject of extensive research due to its recognized antiviral, antibacterial, [35, 48, 49] and immune-modulatory properties [50]. Furthermore, lactoferrin's serine protease activity has been investigated for its potential relevance in antiviral mechanisms [36], while its anti-plasminogen activity suggests a possible role in regulating blood clotting and fibrinolysis [37].

The antiviral properties of milk oligosaccharides stem from their ability to bind to viral glycoproteins via carbohydrate interactions [45-47,51,52]. Camel milk contains both oligosaccharides and lactoferrin, with the latter being proposed as a beneficial dietary component for managing COVID-19[53]. However, the ingestion of whole camel milk for its antiviral and antibacterial effects may entail the involvement of additional molecules beyond just oligosaccharides and lactoferrin.

Plant and seaweed-derived lectins are recognized for their ability to interact with the carbohydrate components of glycoproteins and to engage with viruses [54]. Previous studies have demonstrated that many lectins have the capacity to bind to the S glycoprotein of coronaviruses [55], yielding encouraging outcomes in laboratory experiments aimed at combating viral infections [56].

Recent laboratory experiments have revealed that a lectin derived from edible hyacinth beans effectively inhibits the infections of both Influenza and SARS-CoV-2, both in vitro and in vivo [57]. Numerous studies have demonstrated [62, 63] the binding and antiviral capabilities of various types of lectins, prompting researchers to consider lectins as a potential therapeutic approach against COVID-19 [53,57]. However, the clinical application of lectins may pose challenges due to their high molecular weight. Issues such as determining the appropriate route of administration, ensuring the bioavailability of administered lectins, and addressing potential concerns

related to their antigenic and mitogenic properties would need to be carefully addressed in clinical trials. Given the pathophysiology associated with COVID-19, which involves inflammatory responses and compromised antioxidant levels in patients, various natural substances have been proposed for managing the disease. One such substance is thymoquinone, the primary active component found in extracts of Nigella sativa [60]. Extensive research has explored the therapeutic potential of Nigella sativa extracts and thymoquinone, both of which exhibit intriguing pharmacological properties [61] including anti-inflammatory, anti-cancer, and antioxidant effects. Recently, there has been a suggestion to consider the use of thymoquinone in COVID-19 patients, with discussions on potential routes of administration and pharmaceutical formulations that may hold promise for clinical application [63,64].

Magnesium plays a vital role in numerous biochemical processes enclosed by the human body. Deficiency in magnesium can lead to various health issues, including cardiac, neurological, and metabolic disorders. Interestingly, some of the physiological elements observed in COVID-19 patients, such as perturbation in blood haemostasis, endothelial dysfunction, inflammation, and oxidative stress [65], analogous to those associated with magnesium deficiency. Therefore, supplementing magnesium, as contemplated by some experts, may assist COVID-19 patients in managing certain pathophysiological events of the disease [66-68].

CONCLUSION:

In the absence of an effective vaccine against SARS-CoV-2, critical cases of COVID-19 are managed using various therapeutic protocols involving antibiotics, blood clotting/fibrinolysis drugs, glucocorticoids, antimalarial agents, and certain antivirals [69]. Chloroquine and hydroxychloroquine, traditionally antimalarial drugs [70], have been included in many treatment regimens across different countries, although their efficacy remains a subject of debate within the scientific community. Despite exhibiting effective antiviral properties in laboratory settings and boasting a long history of use as antimalarial medications, their true effectiveness against COVID-19 is still uncertain.

Additionally, adjunct treatments for COVID-19 include vitamins such as vitamin C and B1, as well as prebiotics, probiotics, and magnesium. Furthermore, health-promoting foods like olive oil [71] and argan oil [72, 73] hold significant potential for nutritional interventions in COVID-19 patients due to their rich composition of vitamins and antioxidants, including polyphenols, phytosterols, vitamin E, carotenoids, oleic acid, and other essential fatty acids.

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