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Evaluating antioxidant and anti-inflammatory roles of N acetylcysteine in COVID19 cases: Review

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Abstract
Background: Provide an analytical description of the current evidence regarding the potential anti-inflammatory and antioxidant capabilities N-acetylcysteine and its role in depressing the oxidative and inflammatory processes in COVID-19 cases.
Materials and Methods: Systematic review targeted the antioxidant, anti-inflammatory roles with keywords like "NAC," "COVID-19," "inflammation" "oxidative stress," and "inflammation" to examine recent studies on role of NAC in mitigating oxidative and inflammatory process in somevCOVID-19 cases.
Results: NAC is a molecule of great complexity, possessing a duality in its antioxidant mechanism. It possesses the remarkable ability to counteract the deleterious effects of free radicals, while also acting as a source of cysteine, thereby restoring the body's natural equilibrium of glutathione. Those afflicted with severe cases of COVID-19 often display heightened levels of reactive oxygen species and free radicals, accompanied by a depletion of glutathione, which ultimately triggers a violent cytokine storm. NAC, renowned for its pivotal role as a precursor to GSH within cellular structures, is presently being employed in a myriad of conditions in order to combat the depletion of GSH, and has been duly recognized for its safety. Furthermore, it is worth noting that NAC possesses independent anti-inflammatory properties that are inextricably intertwined with its inherent antioxidant capabilities.
Conclusions: Both clinical and experimental data indicate that NAC is of beneficial to fight the inflammatory, oxidative process and may help reduce prothrombotic state mechanisms observed in severe COVID-19 cases.

Keywords: Antioxidant, COVID-19, NAC

Introduction
The advent of COVID-19 has precipitated a global health emergency of unprecedented scale. This new coronavirus, SARS-CoV-2, was first identified in Wuhan, China in December 2019, and has since taken a devastating toll on populations worldwide **(**Wu *et al*., 2020) [72]. The virus predominantly afflicts the respiratory system during infection, leading to symptoms that can range from mild flu-like signs to severe respiratory complications, and at worst, organ failure **(**Ortiz-Prado *et al*., 2020) [49]. Transmission primarily occurs via respiratory droplets and close proximity to infected individuals. A concerted global effort is underway to find effective treatments that can help combat this pervasive health threat. The tireless efforts of scientists and health professionals around the world give hope in the battle against this pandemic (Jayaweera *et al*., 2020) [77].
Although renowned primarily for its mucolytic properties, N-acetylcysteine (NAC) also boasts formidable antioxidant capabilities. It not only fosters the synthesis of glutathione and facilitates detoxification, but also functions as a direct scavenger of pernicious free radicals (Hasanuzzaman *et al*., 2021) [29]. NAC has also been noted to restore the reactivity of immune cell (Nasi *et al*., 2020) [48], modulate inflammatory responses, counteract thrombotic conditions, and exhibit antiviral prowess
NAC has garnered attention as a potentially effective instrument in the effort against COVID-19, primarily due to its various properties such as its antioxidant effects, anti-inflammatory abilities, and mucolytic properties. By being able to regulate the oxidative state and immune response, NAC could play a crucial role in mitigating the detrimental consequences caused by oxidative stress and inflammation observed in severe cases of COVID-19.

This section will examine the function of NAC in relation to COVID-19, emphasizing its potential as a viable treatment option (Atefi *et al*., 2020) [7].

Furthermore, NAC has been linked to favorable respiratory outcomes and the amelioration of complications pertaining to various bodily organs. Given its pharmacological activities and potential impact on disease progression, NAC emerges as a judicious therapeutic option for COVID-19, (Shi and Puyo, 2020) [60], especially considering the limitations and occasional inefficacy of current treatments. Encouraging preliminary data suggests that NAC enhances clinical outcomes in COVID-19 patients (Shi and Puyo, 2020) [60], thereby warranting its inclusion in their multifaceted management strategies. This paper endeavors to delve into the pathogenic attributes of SARS-CoV-2 and explore the existing understanding of NAC's mechanisms of action throughout the phases of infection.

Additionally, we propose potential NAC dosing strategies for the management of COVID-19 patients across diverse clinical scenarios.

Continuous scientific endeavors are being made to find potential solutions. Of these, N-acetylcysteine (NAC) appears to be a promising candidate. Known for its potent antioxidant and mucolytic attributes, NAC appears to have potential to counteract the effects of this devastating virus (Lana *et al*., 2021; Andreou *et al*., 2020) [38, 4].

This work aims to offer a review of NAC and its potential use in treating COVID-19 the paper will focus on the potential benefits regarding antioxidant and anti-inflammatory action mechanisms of NAC, and how it can be utilized in the context of COVID-19.The foremost aim is to provide an updated, comprehensive resource for healthcare professionals, researchers, and policy makers, facilitating informed decision-making and contributing to global efforts to control the harrowing COVID-19 pandemic.

Review of Literature

Overview of COVID-19

COVID-19, sprung from the novel coronavirus SARS-CoV-2, made its onset in Wuhan, China, in December 2019. It has since spread exponentially worldwide, inconveniencing millions. This contagious respiratory virus has compelled the world to adapt in myriad ways, strained healthcare systems, and led governments to introduce strict measures to attenuate its impact (Kumar *et al*., 2021) [36].

The effects of COVID-19 on the respiratory system are complex and multifaceted, with symptoms ranging from mild flu-like conditions to severe breathing difficulties and organ failure. Stricken individuals may exhibit persistent cough, breathing troubles, and high fever, usually coupled with varying degrees of exhaustion, aches, and throat soreness. In extreme cases, it evolves into acute respiratory distress syndrome (ARDS), calling for intensive medical attention like ventilation support (Fan *et al*., 2020) [78].

Transmission of SARS-CoV-2

Transmission of SARS-CoV-2 primarily occurs through respiratory droplets expelled by an infected individual when he/she coughs, sneezes, or talks. These minuscule droplets carrying the virus can travel in the air and settle on surfaces. Close contact with the infected, like handshakes or proximity, substantially increases the risk of contracting the disease. Additionally, studies have revealed that the virus can survive for prolonged periods on certain surfaces, facilitating transmission via fomites (Dhand and Li, 2020) [29].

The extremely contagious nature of COVID-19 makes adherence to preventive measures highly critical to curb its spread. Personal hygiene practices like routine hand washing for at least 20 seconds with soap and water, using a hand sanitizer containing a minimum of 60% alcohol can help eliminate the virus from hands. Usage of masks, especially in crowded public settings where social distancing is a challenge, can act as an effective barrier against inhaling or spreading respiratory droplets (Klompas *et al*., 2020) [35].

In occurrences of severe COVID-19 cases, a detrimental phenomenon referred to as a cytokine storm often ensues. This phenomenon entails an overabundant activation of the immune system, leading to escalated inflammation across the entirety of the body, thereby potentially inflicting harm upon numerous organs and tissues, ultimately intensifying the gravity of the ailment. Consequently, the comprehension and proficient handling of this cytokine storm assume a paramount significance in the supervision of severe COVID-19 cases (Bhaskar *et al*., 2020; Fara *et al*., 2020; Tang *et al*., 2020) [9, 23, 65].

Oxidative stress and COVID-19

The likelihood of a severe COVID-19 infection is associated with oxidative stress in multiple ways. Several significant factors have been found as contributing to the severity and fatality rate of COVID-19: being older, being male, having a low socioeconomic status, having hyperglycemia, and being obese; being of Black or South Asian ancestry (Williamson *et al*., 2020) [69]. Accompanying each of these elements is heightened oxidative stress. While there is a link between oxidative stress and the severity of COVID-19, this does not prove a cause-and-effect relationship. One possible explanation for the worsening of COVID-19 symptoms is an increase in oxidative stress, while taking antioxidant supplements may alleviate these symptoms (Delgado-Roche and Mesta, 2020) [18].

To begin, non-structured viral proteins, like the 3a protein of the coronavirus, may set off these responses. NLRP3 inflammasome activation in macrophages is followed by IL-1β activation and an increase in mtROS level, as a result of the

SARS-CoV-1 3a protein (Chen *et al*., 2019) [15]. The SARS-CoV-2 3a protein shows 72% similarity with the SARS-CoV-1 homologue, suggesting that it may have a similar function. Notably, multiple investigations have shown that mtROS are necessary for the NLRP3 inflammasome to activate (Xu *et al*., 2020) [73].

Second, there is experimental proof that macrophages undergo a hyperinflammatory reaction when complexed with IgG antibodies and SARS-CoV-2 S proteins from COVID-19 patients. This immune complex's abnormal glycosylation in the IgG Fc tail is linked to its increased pro-inflammatory activity (Hoepel *et al*., 2020) [30].

Inflammation in COVID-19

There are primarily two stages of the SARS-CoV-2 infection response in humans. The body's natural defense mechanism, the innate immune response, is the initial stage. Here, cytokines and interferons are released by innate immune cells, which set off the adaptive immunological response. Any viral infection, including SARS-CoV-2,

triggers the innate immune response. At this point in the infection process, the sick individual may exhibit signs including lethargy, fever, and muscle pains. The magnitude of the COVID-19 response is influenced, in part, by the individual's unique innate immune response. As an example, when type I interferons are not produced as quickly in elderly people, it might cause an overabundance of inflammation due to the recruitment of inflammatory cells such monocytes, neutrophils, and macrophages. (Mishra *et al*., 2020) [41].

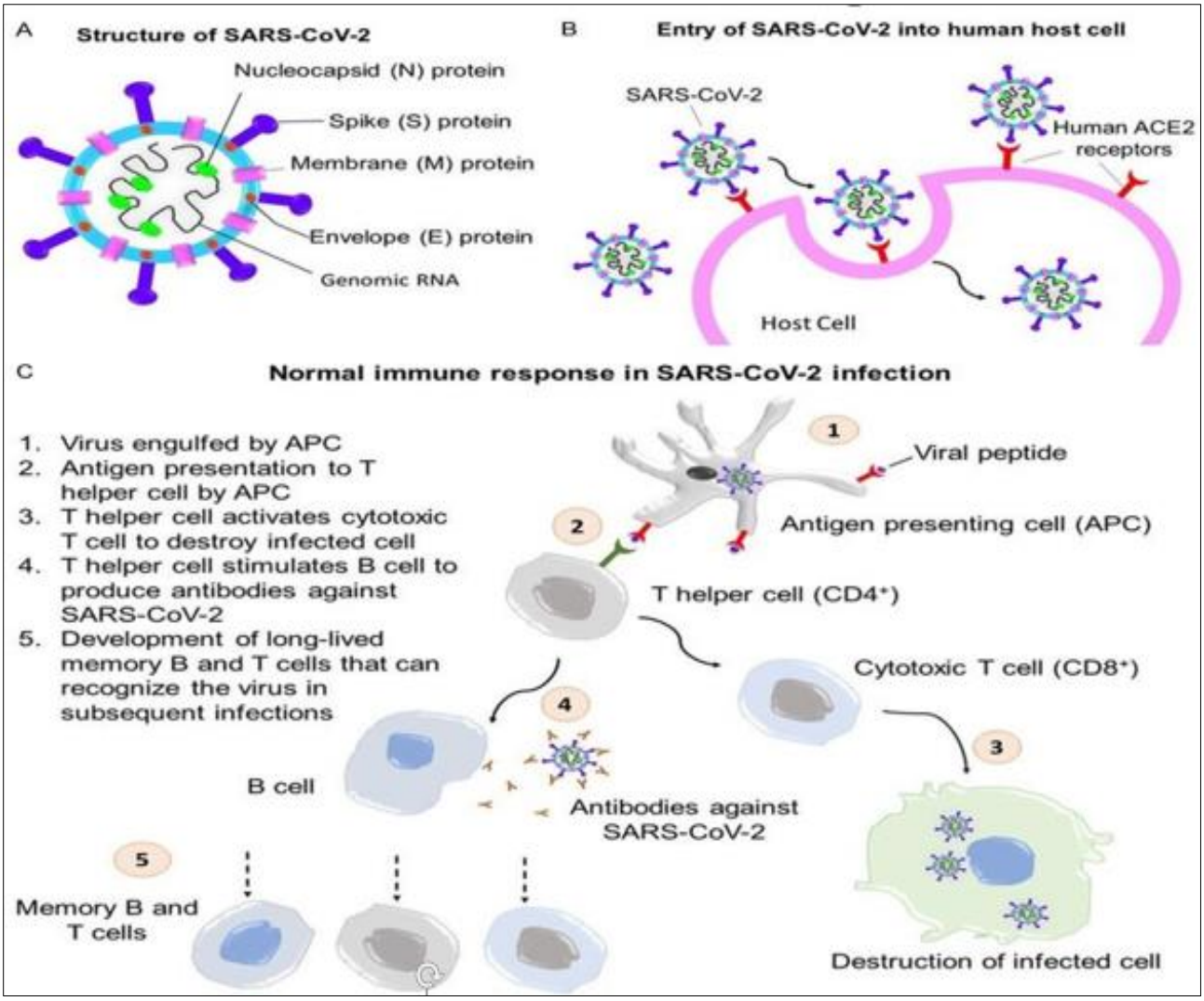

Fig 1: A) the architecture of SARS- CoV-2 B) how the virus enters human host cells, and (C) how the immune system normally responds to an infection with SARS CoV-2

Patients with severe COVID-19 are more likely to exhibit alterations in immune cell numbers and a substantial rise in proinflammatory markers. A decrease in B cells, T cells, and natural killer (NK) cells was shown by Qin *et al*. in COVID-19 patients (Qin *et al*., 2020) [56]. The severe group appeared to have an even smaller amount of these cells compared to the non-severe group. In contrast, the former showed a smaller percentage of basophils, eosinophils, and monocytes, as well as a higher neutrophil lymphocyte ratio (NLR), leukocyte count, and neutrophil count. There was an impact on both regulatory and effector T cells in the immune system. In severe cases of COVID-19, a number of infection-related and inflammatory markers, such as procalcitonin and C-reactive protein (CRP), serum ferritin, interleukin (IL)2R, IL-6, IL-8, tumor necrosis factor (TNF)-α (Qin *et al*., 2020) [56].

Another study by Tan *et al*. found similar results: severe COVID-19 cases had significantly higher levels of IL-6, IL-10, and CRP, as well as a generally reduced number of B cells, NK cells, and T cells (CD4+ and CD8+ cells) (Tan *et al*., 2020) [64].

N-acetylcysteine

N-acetylcysteine (NAC) is a compound evolved from an essential amino acid known as L-cysteine. NAC is extraordinary substance acts as a catalyst for the synthesis of glutathione, a critical antioxidant that plays a crucial part in safeguarding our cellular structures from harmful effects of oxidative stress, a key factor in many health issues, including aging (Silvagno *et al*., 2020) [61].

With its immense versatility and profound impact, N-acetylcysteine has emerged as a groundbreaking solution for promoting overall well-being and maintaining optimal health. By providing essential support to our cellular defense mechanisms, it empowers our bodies to combat the detrimental effects of free radicals and restore balance within (Schwalfenberg, 2021) [59]. Furthermore, NAC's remarkable ability to enhance glutathione production not only aids in the neutralization of toxins but also aids in the

regulation of immune function, making it an invaluable asset in the prevention and management of various health conditions. Through its potent antioxidant properties, N-acetylcysteine exhibits a remarkable ability to combat inflammation, support detoxification, and optimize cellular function (De Flora *et al*., 2020; Poe and Corn, 2020) [17, 53].

Its multifaceted benefits extend beyond oxidative stress protection, encompassing cognitive health, respiratory support, liver function optimization, and even mental well-being. By offering a comprehensive approach to holistic health, NAC stands as a testament to the remarkable potential of natural compounds in promoting longevity, vitality, and overall wellness. In a world that often relies on artificial solutions, N-acetylcysteine serves as a beacon of hope, providing a safe and effective means of fortifying our bodies against the ravages of time and environmental stressors. As scientific research continues to uncover the magnitude of its impact, N-acetylcysteine is destined to revolutionize the field of health and wellness, offering a promising future filled with optimal vitality and well-being for all (Pedre *et al*., 2021) [50]

The potential benefits of NAC extend far beyond its conventional role as a mucolytic agent used to treat respiratory disorders such as chronic obstructive pulmonary disease (COPD) and cystic fibrosis. While it is impressive that NAC can dismantle disulfide bonds within mucus, aiding airway clearance, its range of abilities extends even further. Recent research has highlighted its unique capacity to bolster cellular protection, manage inflammation, and tune the immune response, potentially making it a powerful weapon in the global fight against COVID-19 (Bourgonje *et al*., 2021) [10].

Anti -inflammatory effects of N-acetylcysteine

NAC plays a protective role, guarding our cells from the harmful effects of free radicals, N-acetylcysteine (NAC) possesses direct and indirect antioxidant properties (Tieu *et al*., 2023) [68]. The free thiol group of NAC can directly interact with ROS to form NAC disulphide. However, as a glutathione precursor, NAC can exert an indirect antioxidant effect (Tenório *et al*., 2021) [66]. These highly reactive molecules can harm our cellular structures, leading to the onset of various diseases and disorders. The antioxidant properties of NAC neutralize these free radicals, mitigating their destructive impact, thereby enhancing cellular health. Both *in vitro* and *in vivo* studies have confirmed the protection of the alveolar epithelium from oxygen radical toxicity by treatment with NAC (Pisoschi *et al*., 2021) [52].

NAC has shown amazing anti-inflammatory abilities, making it a powerful player in managing the harmful outcomes of chronic inflammation. By limiting the in-body inflammatory reactions, it can help ease symptoms associated with a variety of inflammatory conditions, including respiratory, gastrointestinal, and even neurological diseases (Tenório *et al*., 2021) [66].

NAC displays a unique capacity to modulate immune responses, making it powerful in the fight against infectious diseases. By adjusting and optimizing the function of our immune system, NAC aids in fortifying our body's innate defenses, providing the tools needed to effectively combat pathogens and viruses (Poe and Corn, 2020) [53].

Fig.1.2 illustrates the impressive anti-inflammatory effects of reduced glutathione (GSH) can be explained by its capacity to hinder ACE activity, restrain the generation of reactive oxygen species (ROS), and diminish NF-kB activation (Highlighted in red) (Silvagno *et al*., 2020) [61].

However, it is important to acknowledge that the equilibrium between ACE and ACE2 is greatly distorted in favor of ACE due to the presence of the oxidized form of glutathione (GSSG), renin (As indicated by the upward-pointing circled arrows representing ACE induction), and viral infections (As depicted by the downward-pointing circled arrow illustrating ACE2 downregulation (Silvagno *et al*., 2020) [61].

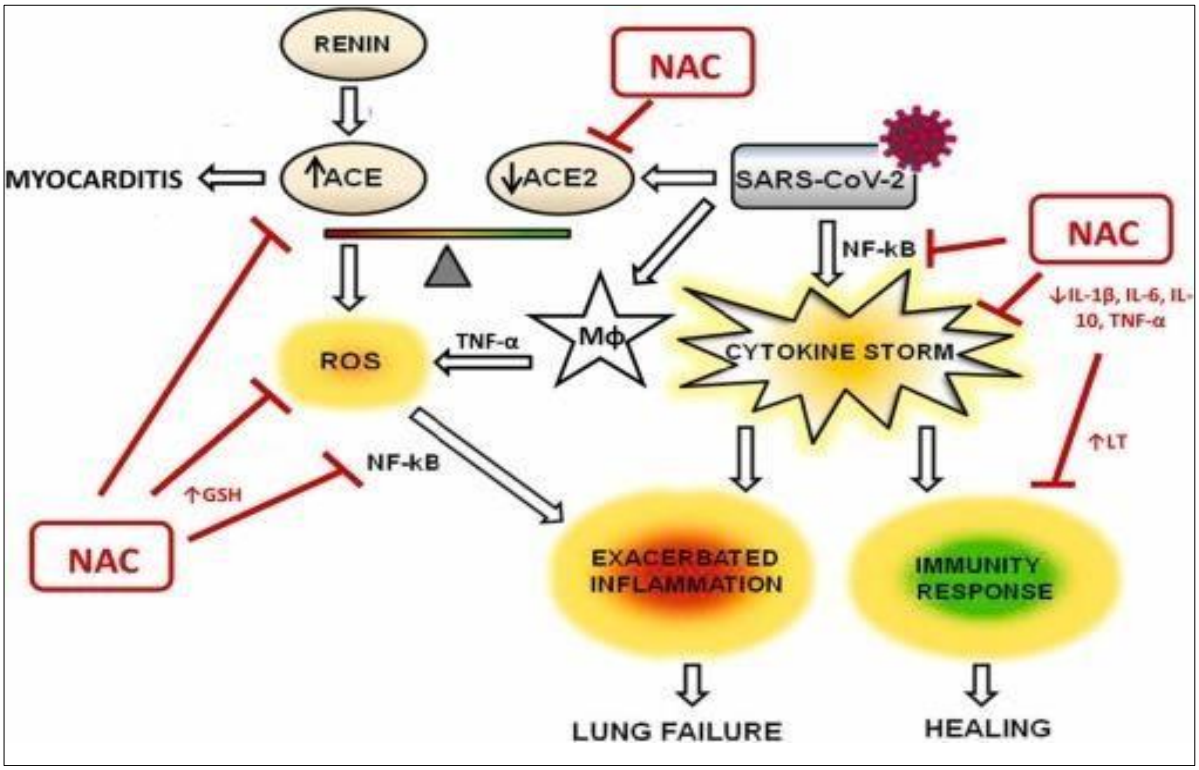

Fig 2: anti-inflammatory effects of reduced glutathione (GSH) can be explained by its capacity to hinder ACE activity

Antioxidant properties of NAC

NAC show antioxidant properties, thereby turning it into an appealing option for COVID-19 treatment. It acts as a building block to glutathione, a vital antioxidant, aiding in boosting its intra-cellular production. Through restoration of glutathione levels, NAC aids in mitigating the oxidative stress and negates the damage instigated by reactive oxygen species (ROS) in COVID-19 patients. This section will focus on the antioxidant workings of NAC and its impact on the redox equilibrium in relation to COVID-19 (Shi and Puyo, 2020) [60].

NAC, a membrane-permeable cysteine precursor, is used as a reactive oxygen species (ROS) scavenger and a potent antioxidant (Pedre *et al*., 2021) [50].

Potential of N-acetylcysteine (NAC) in reducing immune activation

N-acetyl cysteine has been used as an antioxidant in clinical practice for decades, but its uses are mostly off-label. However, there is ample evidence in preclinical and clinical studies that it can attenuate immune activation and prevent cytokine release (Poe amd Corn, 2020) [53]

It significantly decreased the activation and cytokine production by neutrophils (Mo *et al*., 2020) [43]. In another study, NAC significantly decreased the mortality in influenza affected mice by decreasing the production of ROS and cytokines like TNF and IL-6. Similarly (Wong *et al*., 2021) [70].

Potential antioxidant benefits of NAC in COVID-19 treatment

The prospective advantages of N-acetylcysteine (NAC) in treating COVID-19 are diverse and significant. Firstly, NAC's impressive antioxidant properties enable it to counteract reactive oxygen species (ROS) and prevent them from causing oxidative harm in the lungs, which are particularly vulnerable in COVID-19 patients. This in turn aids in the preservation of lung function and obstructs the progression of the disease. Secondly, NAC exhibits potent anti-inflammatory properties which can help dampen the overreactive immune response instigated by the virus, thereby decreasing the chances of a cytokine storm and related organ damage. Through immune response modulation, NAC unveils its potential for therapeutic usage in COVID-19 patients (De Flora *et al*., 2020) [17].

Apart from its noted antioxidant, anti-inflammatory and antiviral properties, NAC also displays immunomodulatory effects. This implies that it has the capability to oversee and balance the immune response to construct a more coordinated and effective defense against the virus. This capacity to regulate the immune system pronounces NAC as a valuable adjunctive therapy for COVID-19 management, particularly for cases where an unchecked immune response is evident (De Flora *et al*., 2020) [17].

Moreover, NAC boasts a proven safety profile and has been broadly utilized for various medical conditions. Its well-recognized tolerability and minimal side-effects render it a viable option for COVID-19 treatment, both for patients in hospitals and those with milder cases where early intervention is key. The ability to administer NAC orally or intravenously adds another layer of versatility and practicality in a clinical setting (Andreou *et al*., 2020) [38].

Reducing oxidative stress and restoring the endothelium in endotheliitis instances, NAC can effectively manage ROS. This prevents activation of platelets and NET formation because it restricts vWF release from the sub-endothelium. To reduce the risk of COVID-19 infection and vascular thrombosis, NAC is essential (Alam *et al*., 2023) [3].

Mechanisms of action of NAC in COVID-19

The effects of N-acetylcysteine (NAC) in COVID-19 have intricate and diverse mechanisms. NAC has a significant role in regulating the immune response by carefully managing the production of vital pro-inflammatory cytokines like interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β) (De Flora *et al*., 2020) [17].

Further, this remarkable compound significantly impacts the redox state of cells, adeptly enhancing the production of glutathione while also showing the extraordinary ability to directly scavenge reactive oxygen species (ROS). This collective action, along with its inherent mucolytic properties, results in a comprehensive therapeutic strategy aimed at mitigating inflammation, oxidative stress, and excessive mucus production within the complex respiratory system of COVID-19 patients. As a result, it is necessary to undertake an exhaustive and meticulous analysis of the multiferous mechanisms through which NAC exerts its broad-reaching effects within the framework of COVID-19 management and treatment (Silvagno *et al*., 2020) [61].

This thorough investigation into the complex mechanisms of action allows for a deeper understanding of NAC's operation within the intricate framework of COVID19. The multifaceted nature of NAC's impact underscores its importance in regulating the immune response, as evidenced by its measured control over the production of vital pro-inflammatory cytokines, such as IL-6, TNF-α, and IL-1β (Mohanty *et al*., 2021) [45].

Besides regulating the immune response, NAC also has a profound influence on the redox state of cells. It has the capacity to boost the production of glutathione, a vital antioxidant, while also serving as a direct scavenger of reactive oxygen species (ROS). This bifunctional role allows NAC to effectively combat oxidative stress in COVID-19 patients **(**Shi and Puyo, 2020) [60].

Moreover, NAC demonstrates inherent mucolytic properties, enhancing its comprehensive therapeutic approach. By targeting excessive mucus secretion in the respiratory system, it helps mitigate symptoms associated with COVID-19, such as coughing and difficulty in breathing.

The significance of this function of NAC is evident as it actively addresses one of the most noticeable manifestations of the disease (De Flora *et al*., 2020) [17].

NAC has been utilized often in medical procedures for a long time since it is readily available, cheap, and safe. Using NAC as soon as symptoms of COVID-19 appear, whether orally or intravenously, can reduce the replication of SARS-CoV-2 and improve outcomes (Corn, 2020) [53]. A moderate form of COVID-19 can be prevented by taking NAC orally as a preventative strategy, while serious complications, intensive care unit hospitalization, and death can be avoided by giving the virus intravenously while in the hospital. Table 1.1 details the correct oral and intravenous dosages of NAC for the treatment and prevention of COVID-19 infection. It is possible to significantly decrease hospitalization, mechanical ventilation, and mortality by administering NAC in conjunction with another antiviral

medication (Shi and Puyo, 2020) [60]. Also, when used in conjunction with NAC, copper has potent antiviral properties that can be used to lower the viral load during the initial phases of COVID-19 (Andreou *et al*., 2020) [38].

Table 1: Summary of recommended doses of NAC for prevention and treatment of COVID-19 (Alam *et al*., 2023) [3]

Clinical signs and symptom	Doses	Route of administration
Prevention		
Very mild	2 times daily, 600 mg	Oral
Treatment		
Very mild	3 times daily, 600 mg	Oral
Mild	3 times daily, 300 mg	IV
Moderate	3 times daily, 300 mg	IV

Antioxidant and anti-inflammatory properties of NAC in COVID-19

It is widely postulated that N-acetylcysteine (NAC), a powerful antioxidant and potent anti-inflammatory agent, could potentially have a fundemental role in both the prevention and therapeutic management of the ongoing infection pandemic. Numerous studies, including the research conducted by Elhidsi *et al*. in 2021 [21], have provided compelling evidence supporting the potential efficacy of NAC in combating the detrimental effects of this viral infection. By harnessing its antioxidant properties, NAC aids in neutralizing harmful free radicals and reducing oxidative stress, thus safeguarding the cells and tissues from damage (Pedre *et al*., 2021) [50]. Additionally, NAC's remarkable anti-inflammatory capabilities help dampen the excessive immune response triggered by the virus, thereby alleviating the degree of infection symptoms and preventing the development of complications (Andreou *et al*., 2020) [38].

The remarkable anti-inflammatory properties of reduced glutathione (GSH) can be attributed to its ability to inhibit ACE activity, suppress the production of reactive oxygen species (ROS), and reduce NF-kB activation (marked in red). However, it is crucial to note that the balance between ACE and ACE2 is significantly skewed towards ACE due to the oxidative form of glutathione (GSSG), renin (As indicated by the upward-pointing circled arrows symbolizing ACE induction), and viral infections (As shown by the downward-pointing circled arrow indicating ACE2 down regulation (Silvagno *et al*., 2020) [61].

NAC effect on prothrombotic state observed in severe COVID-19

Experimental evidence suggests that NAC has the potential to affect the mechanisms that lead to the prothrombotic state observed in severe COVID-19 (Di *et al*., 2022) [20]. NAC enhances the effects of endothelial nitric oxide, which acts as a vasodilator and prevents platelet aggregation (Mahmoudinezhad *et al*., 2023) [40].

This mechanism is thought to be related to NAC's ability to counteract the deficiency of glutathione peroxidase 3, an extracellular antioxidant enzyme that generates bioactive nitric oxide and plays a part in its synthesis. The breakdown of arterial clots refractory to conventional methods may be accelerated by intravenous NAC, according to studies. The primary target of NAC's antithrombotic activity appears to be Von Willebrand Factor (VWF), a protein that contributes to the formation of arterial clots by binding platelets together (Prasannan and Scully, 2021) [55].

Additionally, NAC has been found to decrease soluble VWF levels in plasma, break down large VWF multimers released from activated endothelial cells, and inhibit VWF-dependent platelet aggregation and binding to collagen. In animal experiments, NAC injections successfully resolved thrombi caused by ionophore treatment and reduced plasma VWF multimer levels (Di *et al*., 2022) [20].

Discussion

Researchers looked examined how well NAC worked as a treatment for COVID19 in terms of C-reactive protein, D-dimer, ferritin, PaO2/FiO2, length of time in the hospital or intensive care unit, and death. The findings showed that NAC might potentially lessen the severity of the disease and death rates in COVID-19 patients (Assimakopoulos *et al*., 2021) [6], But in the latest meta-analysis by Paraskevas *et al*., there was a lot of variation among trials (I2 = 59%-90%).In patients treated with NAC, the pooled impact was beneficial in lowering severity and death.

Consistent with our findings, another meta-analysis examined the therapeutic effectiveness of NAC in patients with ARDS due to non-COVID-19 diseases and found that it decreased the length of time patients spent in the hospital and intensive care unit; (Taher *et al*., 2021) [63], yet it failed to make a significant dent in death rates. The therapeutic practice of ROS scavenging by antioxidants has been supported by its criteria and reasoning; NAC is one such antioxidant that has seen extensive application (Tenório *et al*., 2021) [66].

The disparity in fatality rates between our research and Zhang *et al*. might be explained by this. The discrepancies between our research and the one by Zhang *et al*. might be explained by variations in the underlying comorbidities, sample size, and agents causally involved.

In contrast, our results demonstrated that NAC improved oxygenation (PaO2/FiO2 ratio) and decreased levels of inflammatory markers such as the Ddimer and CRP, suggesting that NAC may mitigate the severity of COVID-19 (Chen *et al*., 2023) [14].

An earlier section discussed the idea of administering NAC to high-risk persons with severe COVID-19 as oxidative stress is a key component of the disease's pathogenesis, severity, and death (Fernandes *et al*., 2020) [24].

Ibrahim *et al*.'s observational research provided the initial detailed proof of NAC effectiveness in COVID-19 clinical patients. Patients over the age of 40 on mechanical ventilation with COVID-19 demonstrated clinical improvement after intravenous NAC treatment, mostly due to substantial decreases in ferritin and Creative protein (Alam *et al*., 2023) [3].

Patients with COVID-19 who took 2 grammes of oral IVGSH-a drug that is a forerunner to NAC therapy-reduced their dyspnea significantly (De Flora *et al*., 2020) [17]. Afterwards, mortality was considerably decreased in a large cohort trial of 19,208 COVID-19 patients hospitalized; 2, 071 of these patients received medication with 600 mg/kg daily NAC (Alam *et al*., 2023) [3]. Treatment with NAC considerably reduced CRP levels and duration of hospital stay while increasing blood oxygenation (Alam *et al*., 2023) [3].

Considering that NAC displays antioxidant properties both directly and indirectly. It interacts with a free thiol, functioning as a direct antioxidant, to scavenge ROS. Indirectly aiding in ROS detoxification, GSH, as a precursor

to NAC, takes part in redox processes that give electrons (Mohanty *et al*., 2021) [45]. A higher viral load promotes oxidative damage to important organs including the heart and lungs, while reduced amounts of GSH and thiols boost SARS-CoV-2 viral replication. Furthermore, lymphopenia, caused by an apoptotic cascade in lymphocytes brought on by GSH depletion, is intricately linked to severe illness and high mortality, especially in COVID-19 patients (Bartolini *et al*., 2021) [8].

An increased vulnerability to COVID-19 infection may be caused by higher levels of IL 1β, IL6, TNF-α, CRP, and D-dimer, according to a recent research that linked GSH shortage (Horowitz *et al*., 2020) [31], particularly in the elderly who also suffer from other health conditions including diabetes, high blood pressure, and obesity. On the flip side, research has shown that GSH therapy may lessen the spread of viral infections and viral load, suppress the production of pro-inflammatory cytokines (Such as IL6, IL8, and TNFα), minimize oxidative stress and thrombosis, and perhaps improve immunological function (Guloyan *et al*., 2020) [28]. Additionally, research has shown that GSH supplementation may improve innate and adaptive response against SARS-CoV-2 infection by modulating immune cells (Forcados *et al*., 2021) [25], evidence that GSH-enhancing treatment might play a pivotal role in mitigating the impact of COVID-19 and its potentially lethal consequences. When looking at the biochemical relationship between COVID-19/RTI and GSH shortage, Table 2 shows the overall picture.

Table 2: Biochemical associations between COVID-19 and GSH deficiency. Data compiled from (Polonikov, 2020; Calzetta *et al*., 2018; Labarrere and Kassab, 2022) [54, 12, 37].

Parameters	COVID-19/ respiratory infection	GSH deficiency
Ang II	Increased	Increased
'Ang' 1,7	Decreased	Decreased
'IL 1β, IL6'	Increased	Increased
'TNF-α'	Increased	Increased
'NF-κβ activation'	Increased	Increased
'CRP'	Increased	Increased
'D-dimer'	Increased	Increased
'Oxidative stress/ROS'	Increased	Increased
'Cytokine storm'	Increased	Increased
'Coagulability'	Increased	Increased
'Innate and adaptive immunity'	Decreased	Decreased

In pulmonary syncytial and influenza viral infections, NAC has been seen to block NF-κβ activation. In COVID-19 infection, NF-κβ activation is linked to the increased production of inflammatory cytokines such IL-1β, IL-6, L-17, CRP, Ddimer, and TNFα (Alam *et al*., 2023) [3]. In addition to its antiviral effects, NAC has been discovered to restore the immunological response, reduce inflammation, and protect against thrombotic disorders. By blocking ACE2, an experimental investigation shown that NAC mitigates the harmful effects of Ang II (De Flora *et al*., 2020) [17].

Besides its antioxidant effects, NAC also prevents blood clots and has a thrombolytic impact by decreasing the amount of bonds of disulfide (-S-S-) to sulfhydryl (-SH) groups in vWF polymers. This causes vWF to break apart and platelets to dissociate (De Flora *et al*., 2020) [17].

Reducing oxidative stress and restoring the endothelium in endotheliitis instances, NAC may effectively manage ROS. This prevents activation of platelets and NET formation because it restricts vWF release from the sub-endothelium. To reduce the severity of COVID-19 infection and vascular thrombosis, NAC is essential (Alam *et al*., 2023) [3].

Each author separately assessed the included studies' quality using the following criteria outlined in the Newcastle-Ottawa Scale (NOS) general specification: 1) Case definition; 2) Control definition; 3) Control selection; 4) Case repetitiveness; 5) Case and control comparability; 6) NAC exposure ascertainment; 7) Case and control ascertainment using the same approach; and 8) Non-response rate (Peterson *et al*., 2011). If a study dealt with quality aspects 1-4 or 6-7, it was given a score of 1; otherwise, it was given a score of 0 (0). Still, studies were given a 2 for feature 5 if they accounted for both age and confounders; a 1 for studies that only accounted for age or confounders; and a 0 for studies that did not account for either. So, if a research satisfies all of the NOS's quality requirements (Table 3.), it may get a maximum score of 9.

Table 3: A table summarizing NAC-treated studies determining study location, design, sample size, NOS score, and The 'COVID-19' severity index and death rate (Alam *et al*., 2023) [3].

Study no.	Authors	Study country	Sample size		COVID-19 mortality and severity index	Study design	NOS score
			NAC	CONT			
1	'de Alencar *et al*.	Brazil	67,	68,	Mortality, CRP, D-dimer, Hospital stay, ICU stay, PaO_2/FiO_2 ratio	RC trial	9
2	'Izquierdo *et al*.	Spain	2,071	17,137	Mortality	Retros pective cohort study	8
3	'Assimakopoulos *et al*.	Greece	42,	40,	Mortality, CRP, D-dimer, Ferritin, PaO_2/FiO_2 ratio	Retros pective cohort study	9
4	'Taher *et al*.	Iran	47,	45,	Mortality, Hospital stay, ICU stay, PaO_2/FiO_2 ratio	Pilot study	8
5	'Chen *et al*.	USA	7,	9,	CRP, Ferritin, PaO_2/FiO_2 ratio	Retros pective cohort study	7
6	'Ibrahim *et al*.	USA	9,	9,	CRP, Ferritin	Observ ational study	7
7	'Avdeev *et al*.	Russia	24,	22,	Mortality, CRP, D-dimer, PaO_2/FiO_2 ratio	Casecontrol study	8
8	'Faverio *et al*.	Italy	585,	321,	Mortality	RC trial	8

Both the severity and the outcome of an illness are correlated with severe inflammation. The three inflammatory markers ferritin (95.45% sensitivity; 86.57% specificity), lactate dehydrogenase (LDH) (90.91% sensitivity; 80.56% specificity), and serum C-reactive protein (86.36% sensitivity; 88.89% specificity) were found to be useful in predicting mortality in a study involving 283 patients with RT-PCR confirmed COVID-19 (Arshad *et al*., 2020) [5]. A number of inflammatory markers, including serum soluble IL-2 receptor, IL-6, IL-8, IL-10, TNF-α, procalcitonin, ferritin, LDH, high-sensitivity CRP, and the ratio of high-sensitivity CRP to lymphocytes, were all found to be higher in severely sick COVID-19 patients, according to Zeng *et al*. An early decrease in inflammatory markers was associated with improved outcomes, but IL-6 and LDH were distinct indicators of disease severity. There was no discernible decrease in inflammatory mediators and markers among the severely sick and dying individuals as the illness progressed (Zeng *et al*., 2020) [74].

Conclusion and recommendation

The new coronavirus infection and its pathogenesis Research on COVID-19 infection is ongoing on a global scale. The intricate illness known as COVID-19, which is caused by the SARS-CoV-2 virus, involves the interplay between the virus's interactions with specific cells, the immune system's actions, and the body's overall reaction to these events.

But whether COVID-19 causes oxidative stress in airway epithelium is still a mystery. Respiratory discomfort due to oxygen treatment for patients with moderate to severe COVID-19 is common, and it may lead to oxidative stress and acute respiratory distress syndrome (ARDS).

Several experimental and clinical data suggest a possible role of NAC as adjuvant therapy in the prevention or treatment of COVID-19. This well-known molecule, with a good safety profile, with a well-established role in treating liver failure due to GSH depletion induced by acetaminophen intoxication, is a good candidate to take into consideration also in the treatment of viral infections. Improvement of cell-mediated immunity, replenishment of GSH activity in cells, antioxidant and anti-inflammatory effects were the basis for better outcomes in patients with a viral infection, namely, COVID-19. The final demonstration of its efficacy requires clinical studies enrolling high numbers of patients, as COVID-19 is a little-known, multifactorial disease. The statistical significance level of results is not obtained by small samples. It would be important to optimize NAC's use in different settings by identifying eligible conditions and defining a long-term protocol, which could completely elicit the antioxidant efficacy of NAC.

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