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The Possibility of Using N-acetylcysteine as a Treatment for COVID-19 Patients

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الملخص:

الخلفية في معظم البلدان، لا تزال جائحة فيروس كورونا 2019 (COVID-19) تشكل خطراً شديداً على الصحة العامة. بالنسبة للأفراد المصابين بفيروس كورونا19-COVID ، يمكن أن يتسبب فيروس كورونا 2 (SARSCoV-2) المسبب لمتلازمة الجهاز التنفسي الحادة الوخيمة في متلازمة الضائقة التنفسية الحادة ويؤدي إلى الوفاة. آليات الاكسدة لا تشارك فقط في الأمراض الانتكاسية المزمنة فحسب، بل تلعب دورًا في الاضطرابات التنفسية الفيروسية المعدية. يتم لعب دور وقائي مركزي ضد المؤكسدات من خلال انخفاض الجلوتاثيون(GSH) ، الذي يتم استنفاذه في عدوى .SARS-CoV-2 مضادات الاكسدة لها قدرة على مواجهة عمل المؤكسدات عن طريق تنظيف أنواع الأكسجين التفاعلية (ROS) وعن طريق تثبيط انزيمات توليد الاكسدة. كعامل مضاد لـــCOVID-19 ، فإن(N-acetylcysteine (NAC ، وهو مقدمة لـــGSH ، له أهمية خاصة كعامل مضاد. علاوة على ذلك، تحتوي NAC ومشتقاته على مجموعة واسعة من الآليات المضادة للأكسدة والمضادة للالتهابات التي يمكن استخدامها للوقاية من COVID-19 وعلاجه. قد يُتوقع أن يؤدي الاستخدام الفموي لـــNAC ، كما هو موضح في تجربة سريرية حديثة للتحقيق في الأنفلونزا والأمراض الشبيهة بالإنفلونزا، إلى تقليل فرصة الإصابة بـــ .COVID-19 أظهرت قدرة NAC على تجديد مستويات GSH مؤخرًا في التجارب السريرية لتعزيز نتائج مرض فيروس كورونا 2019(COVID-19) ، لا سيما في الأشخاص المعرضين لمخاطر عالية. بالنظر إلى الخلفية البيوكيميائية والاستخدام العلاجي الحالي لـــ NAC والأدلة التي تم جمعها حديثًا حول فعاليتها المحتملة ضدCOVID-19 ، فمن المفيد إجراء مزيد من الأبحاث إذا كان يمكن استخدام هذا الدواء كعلاج أو مساعد لـ.COVID-19

الكلمات المفتاحية: الإجهاد التأكسدي. الجلوتاثيون. ان-أسيتيل-سيستين. كوفيد -19.

Abstract

In most countries, the Coronavirus Disease 2019 (COVID-19) pandemic remains a severe public health threat. In COVID-19 individuals, the causative severe acute respiratory syndrome coronavirus 2 (SARSCoV- 2) virus can cause acute respiratory distress syndrome and result in mortality. Not only do oxidative mechanisms play a role in chronic degenerative diseases, but as viral respiratory disorders. Reduced glutathione (GSH), which is decreased in SARS-CoV-2 infection, plays a critical function in protecting against oxidants. Antioxidants work by scavenging reactive oxygen species (ROS) and blocking oxidant-producing enzymes to counteract the effects of oxidants. As an anti-COVID-19 agent, N-acetylcysteine (NAC), a precursor of GSH, is of special relevance. Furthermore, NAC and its derivatives have a wide range of antioxidant and anti-inflammatory mechanisms that could be used to prevent and treat COVID-19. Oral use of NAC, as shown in a recent clinical trial investigating influenza and influenza-like diseases, may be expected to reduce the chance of developing COVID-19. NAC's ability to replenish GSH levels has recently been shown in clinical trials to enhance coronavirus disease 2019 (COVID-19) outcomes, particularly in high-risk people. Given the biochemical background, existing therapeutic usage of NAC, and newly collected evidence on its potential efficacy against COVID-19, it is worthwhile to research further if this medication can be utilized as a treatment or adjuvant for COVID-19.

Keywords: Oxidative stress; Glutathione; N-acetylcysteine; COVID-19; Treatment.

1. INTRODUCTION

Each winter, an increase in the number of infections caused by numerous human respiratory pathogens occurs; however, the timing and extent of the infection vary greatly [1]. Respiratory viruses, such as influenza, Respiratory syncytial virus (RSV), and the two previously known human coronaviruses, have two primary characteristics: seasonality and persistence [1,2]. Coronavirus Disease (COVID-19) is caused by Coronavirus-2 of the Severe Acute Respiratory Syndrome (SARS-COV-2). It was first recognized as pneumonia of unknown reasons on December 31, 2019, in Wuhan, China. The sickness then quickly spread over the globe. The number of cases is rapidly increasing and has spread to many countries throughout the world [3].

The common symptoms of COVID-19 include fever, cough, fatigue, shortness of breath, and muscle aches. Moreover, patients also experience sore throats, nasal congestion, headache, diarrhea, nausea and vomiting, loss of smell (anosmia), or loss of taste (ageusia) [3].

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Patients infected with COVID-19 may experience fever and respiratory symptoms and they are frequently admitted to the hospital as a result of progressive dyspnea and systemic complications that necessitate support measures ranging from supplemental oxygen to mechanical ventilation and intensive care [4].

The board for COVID-19 patients is given non-pharmacological and pharmacological treatment. Pharmacological treatment in asymptomatic COVID-19 patients incorporates directing vitamin C, vitamin D, and medications with antioxidant properties [5,6,7]. Different treatments or extra estimates that can be given to COVID-19 patients are Anti-IL-6 (Tocilizumab), Anti IL-1 (anakinra), stem cells, intravenous immunoglobulin (IVIg), convalescent plasma treatment, vaccination, N-acetylcysteine, colchicine, spironolactone, bronchoscopy, and therapeutic plasma exchange (TPE) [8,9,10].

Most COVID-19 patients had severe pneumonia with excess mucus in the respiratory tract, and because of that, this review focused on N-acetylcysteine NAC as a mucolytic agent. The standard dose of NAC in pneumonia is (3x200 mg) orally,

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utilized as a mucolytic agent. In addition, NAC has antioxidant and anti-inflammatory effects when used in high doses (600 – 2400 mg/day) orally, intravenously, and via inhalation [3,11,12].

According to De Flora et al [13], oxidative pathways play a significant part in the development of practically all human diseases, and antioxidants therapy shares a wide spectrum of protective actions. It should be noted that, just as exposure to oxidants increases the risk of getting a disease, antioxidants alone are unlikely to totally prevent a pathological condition; rather, they are expected to contribute to lowering its risk and reducing the severity of its consequences. Oxidative stress, like a lack of antioxidant systems, has a role in the aging process, especially when it leads to changes in mitochondrial DNA.

Studies have shown that oxidative stress OxS is a harmful condition caused by excess accumulation of reactive oxygen species and is linked to lung disease [14,15], heart disease [16,17], neurological disorders [18], diabetic complications[19], liver [20] and kidney diseases[21], and the biology of the aging process[22]. Under physiological conditions, OxS is neutralized by antioxidants among which glutathione (GSH) is the most abundant endogenous intracellular antioxidant [23].

Oter [24]suggested that free radicals include reactive oxygen species (ROS), which cause redox-modulated signaling cascades involving the transcription factors AP-1 (activator protein-1), NF- κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and/or Nrf2 (nuclear factor erythroid 2–related factor 2), which can mediate a variety either of physiological functions or macromolecule alterations that lead to pathological conditions. Free radicals, according to De Flora et al [13], can be delivered into the body from external sources or created in the body through biochemical reactions, such as the Fenton reaction and the Haber-Weiss reaction. While the creation of reactive molecules is required for regular physiological and cellular activities, its unregulated or excessive production can result in 'oxidative/nitrosative stress.

According to Alamdari et al [25] and Dominair et al [26], natural scavenging systems, such as the system of decreased GSH, are the principal defensive mechanism against free radical damage. GSH contributes an electron to an unstable molecule, such as ROS, and then becomes reactive and can rapidly bind to another reactive glutathione molecule, forming a glutathione disulfide. This is possible under normal circumstances because of the high concentration of GSH in cells. GSH deficiency, which can occur as a result of COVID-19 or as a result of low levels due to other factors, has been linked to the excessive stress that leads to COVID-19 problems. On the one hand, SARS-CoV-2 infection causes the production of free radicals, which depletes GSH stores. Given that intracellular GSH levels are relatively stable and regulated by many environmental stimuli, such as NF-κB, ROS, and reactive nitrogen species, it is not surprising that less GSH is available for other cellular processes in a COVID-19 patient. Low GSH levels, on the other hand, have been linked to a number of pathologic diseases that are now thought to be risk factors for severe COVID-19, including advanced age, male sex, diabetes mellitus, hypertension, obesity, and even some drugs.

The failure of antiviral and anti-inflammatory agents to exhibit favorable benefits, as well as the thorough investigation of the aforesaid biochemical pathways, has encouraged various researchers to investigate the effects of NAC as an adjuvant treatment in COVID-19 patients.

N-acetylcysteine (NAC) is a drug that was first reported to have clinical benefits in the early 1960s [27]. Acetylcysteine, NAC, and Rmercaptate are just a few of the names for this medication. The organic compounds class is known as N-acyl-alpha-amino acids [28]. Cough, dry eyes, and influenza are just a few of the clinical benefits of NAC. It is also frequently used as an antidote for acetaminophen overdose and to lower nitrate tolerance. NAC is also a common ingredient found in certain cosmetics and vitamin supplements [29]. Also, it is known as an antioxidant that acts directly by increasing intracellular GSH, especially on hepatic tissue [30]. It has an optimal thiol redox state, which is of great importance to optimize the protective ability of the cell to counterbalance oxidative stress (OS) and inflammation [31].

N-acetyl cysteine is an amino acid that contains a thiol group. Cysteine includes sulfanyl (-SH) in its facet chain, which can be beneficial with inside the motion of living cells and ions the aid of using forming channels. The formation of disulfide bonds among cysteine is known to get to the bottom of unique proteins. Cysteine is a product of many occupied and unoccupied orbitals. Its structure can provide an explanation for the feature and medical importance of NAC [26,32,33].

Aldini et al [34] and Dominari et al [26] suggested that NAC has been proposed as a potential prophylactic or adjuvant for coronavirus disease-19 (COVID-19) therapy, a cost-effective alternative for mild to severe cases. Also, it is commonly used in the prevention and adjuvant treatment in conditions with thick and tenacious mucus production, such as pneumonia, cystic fibrosis, chronic bronchitis, and postoperative pulmonary complications. NAC contains unbound sulfhydryl groups that break disulfide bonds of the glycoprotein matrix within the mucus, which helps dissolve the mucus, making NAC a potent mucolytic. On the other hand, NAC is not only responsible for managing the redox state by replenishing the thiol stores, but it is also a cysteine precursor, making it a durable antioxidant.

According to de Andrade et al [35] by extracellular deacetylation of NAC, cysteine is released and introduced into cells via amino acid transporters. The hypothesis is that free cysteine is required for the synthesis of GSH.

The ways to provide NAC are oral and intravenous. The administration of NAC orally is preferred, despite some clinical situations that require intravenous administration [35]. It is a safe and inexpensive medication and has been commercially accessible for some time [36].

NAC consumed orally is absorbed in the stomach, and intestine and is delivered to the liver via the portal vein. In the liver, NAC, quickly, integrates peptides for the generation of proteins and a diversity of metabolites [37,38]. NAC in plasma can be found in various oxidized forms and in a reduced form. Also, it oxidized to a disulphide, diacetylcystine, and it may react with other low molecular mass thiols, such as cysteine and glutathione, forming mixed disulfides. In addition, NAC can suffer redox reactions with thiol groups of the plasma proteins and become oxidized [39].

Rushworth and Megson [36] proposed that NAC crosses the intact cell membrane before suffering hydrolysis to cysteine within the cell with the action of *N*-deacetylases. The rate-limiting step of the synthesis involves the conjugation of Cys with L-glutamate (glutamate–cysteine ligase; GCL), while L-glycine is added in a subsequent synthetic step involving GSH synthase.

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The ability of an N-acetylcysteine to act as an antioxidant in a biologically relevant situation is a highly complex concept, but one that is central to understanding the mode of action of NAC in many of its potential therapeutic uses. In addition, the location of ROS generation, the ROS species generated, the relative abundance of endogenous antioxidants in the locality, and the rate constants of endogenous antioxidants for the ROS generated, together with their relative concentrations, will all be vital determinants of the success or failure of an administered antioxidant in helping to prevent cellular damage [36].

N-acetylcysteine has been used for the treatment of paracetamol toxicity [40]. Also, it has been used as a beneficial drug treatment for some disorders such as polycystic ovary syndrome, Alzheimer's and Parkinson's diseases and in some cases, such as improving pregnancy rate [33]. It has beneficial effects in other chronic clinical conditions, such as inflammatory bowel disease, obstructive pulmonary disease, systemic sclerosis, cystic fibrosis, human immunodeficiency virus (HIV) infection, septic shock and diabetes along with hepatic injuries [41,42].

In viral infections, NAC has been investigated since the early 1990s. In 1992, Roederer et al [43] showed that NAC inhibited inflammatory stimulation *in vivo*, including that caused by HIV replication. On the other hand, Geiler et al [44] investigated that NAC inhibited H5N1 replication and H5N1-induced production of pro-inflammatory molecules. Molteni et al [45] showed that these findings are mostly explained by the effect of NAC on reactive oxygen species (ROS). During viral infections, ROS is produced *via* multiple pathways, including mitochondrial reactions, degradation of lipids and proteins, and importantly from respiratory burst reactions in phagocytes. Also, several viruses such as HIV-1, Respiratory Syncytial Viral, and H5N1 have been shown to increase oxidative stress in the host by dysregulating the oxidative stress pathways and causing an escalation of ROS synthesis. On the other hand, high levels of ROS help in the phagocytosis and apoptosis of infectious organisms, while low levels promote viral replication and mutations resulting in the development of resistant strains. As a result of that, ROS causes significant host cell damage and lysis.

According to Sun [46] NAC scavenges ROS directly through direct interaction with target proteins containing a cysteine residue or thiol group, and indirectly by increasing the synthesis of GSH. The potent antioxidant catalyzes the reduction of hydrogen peroxide to water and oxygen and the reduction of peroxide radicals to alcohols and oxygen. In addition, NAC protects cells from apoptosis by chemically forming inactive adducts or complexes.

SARS-CoV-2 infection is associated with an imbalance of oxidants and antioxidants, resulting in inflammation and tissue damage [47]. Glutathione is an antioxidant widely found in the body and plays a role in protecting cells from oxidative stress [10]. Giving NAC as a "glutathione-boosting treatment" can reduce pro-inflammatory cytokines to reduce the risk of the severity of COVID-19 caused by cytokine storms in the body [48,49,50].

Gordon et al [51] suggested that NAC regulates pro-inflammatory kinases, such as nuclear factor kappa B (NF-kB) through activation of GSH and the direct antioxidant effect of its free thiol group. Increased ROS levels activate NF-KB, a redox-sensitive transcription factor that regulates the expression of pro-inflammatory cytokines, like IL-1, IL-6, and tumor necrosis factor-alpha, as well as genes associated with apoptosis. NAC, a glutathione precursor, inhibits NF-kB, preventing tumor necrosis factor (TNF alpha) activation and nuclear translocation of NF-kB. The latter leads to a decrease in the production of inflammatory cytokines.

COVID-19 and N-acetylcysteine NAC Data from studies

Nencini et al [52] indicated that oxidative stress is an imbalance between the production and scavenging of reactive oxygen and nitrogen species (ROS and RNS) and free radicals that can induce lipid peroxidation, DNA fragmentation, and protein oxidation. These damages result in the loss of membrane integrity, structural and functional changes in proteins, and gene mutations [53].

Studies by [54,55,56] proved that the affected cells are trying to neutralise reactive molecules by deploying their anti-oxidative defense. Enzymatic antioxidants and non-enzymatic antioxidants under physiological conditions are essential for cellular response to deal with oxidative stress. They are affected and used as indexes to evaluate the level of oxidative stress.

Oter et al [24] and De flora et al [13] suggested that NAC direct scavenge free radicals, and the constant reaction rate with ROS is smaller than that concerning antioxidant enzymes such as catalase and superoxide dismutase. Consequently, the direct elimination of radicals is not as significant as its antioxidant activity. Also, it is a strong antioxidant and a potential therapy option for diseases characterized by the generation of free oxygen radicals.

Amin et al [57] and Elgindy et al [58] indicated that NAC increases intracellular levels of glutathione and decreases mitochondrial membrane depolarization by preventing apoptosis and oxygen-related genotoxicity in endothelial cells. The antioxidant effectiveness comes from its position as a precursor to glutathione, one of the most powerful naturally occurring antioxidants.

Kumar et al [59] have studied GSH deficiency and oxidative stress OxS in older humans, immunocompromised HIV patients and diabetic patients and have reported that adjusting these defects with GlyNAC (a mix of GSH precursor amino acids glycine, and cysteine given as N-acetylcysteine) significantly improves multiple additional defects and boosts health. Although GSH shortage is thought to be the most common cause of significant symptoms and death in COVID-19 patients, nothing is known about GSH adequacy, OxS, or oxidant damage in COVID-19 patients.

Orally administered NAC at a dose of 1200mg each day in hospitalised patients with moderate or serious COVID-19 pneumonia, prevents their clinical deterioration to severe respiratory failure requiring invasive or non-invasive mechanical ventilation and reduces 14- and 28-day mortality. Only serious disease and standard-of-care therapy (without NAC) were related to increased mortality. NAC survival benefit was mainly attributed to essentially reduced mortality in patients with serious 19 pneumonia. As per the introduced outcomes, NAC administration improved oxygenation over time, and reduced leukocytes, CRP and d-dimers levels, which is suggestive of its anti-inflammatory action [60].

A recent study by Zhang et al [61], showed that the addition of 1200 mg/d of NAC to conventional treatment reduced oxidative stress and the inflammatory response. NAC has been shown to prevent the development of ventilator-associated pneumonia in

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intubated patients, leading to a shorter duration of hospital and intensive care unit (ICU) stays.

Oral administration of NAC is expected to reduce the chance of developing COVID-19, as it has been previously demonstrated for influenza and influenza-like diseases, based on a broad range of antioxidant and anti-inflammatory mechanisms. Furthermore, high-dose intravenous NAC could be used as an adjuvant in the treatment of severe COVID-19 patients and in the control of its lethal complications, such as pulmonary and cardiovascular adverse events [62].

Clinical trials have recently shown that the ability of NAC to replenish glutathione stores may altogether improve coronavirus disease 2019 results, particularly in high-risk individuals. A similar study by Dominari et al [26] has concluded that NAC's capacity to mitigate the effect of the cytokine storm and prevent elevation of liver enzymes, C-reactive protein, and ferritin is related to higher achievement rates weaning from the ventilator and return to typical function in COVID-19 patients.

Subsequently, the discoveries of the study by Kumar et al [59] showed that COVID-19 is related to excessively raised OxS and proof of oxidant harm is important, as it could contribute to COVID-19-related injury and mortality. Focusing on OxS and oxidant harm actually could be key in further developing health and survival in COVID-19-infected patients. OxS begins from the accumulation of excess reactive oxygen species which are formed in mitochondria during the process of energy generation. Cells usually depend on antioxidants for protection from OxS and oxidant harm, and GSH is the most abundant intracellular antioxidant. Along these lines, GSH lack can amplify the destructive potential of OxS because of compromised antioxidant defenses. In uninfected people, OxS tends to occur mainly in older humans (>60 years of age) and not in younger age groups. To be sure, the 'free radical theory of aging' was proposed in 1956 to suggest that elevated OxS in older humans could be responsible for the aging process. Thusly, the observation in this study that COVID-19-infected patients in the young (21–40 years) and middle-aged (41–60 years) groups have seriously raised OxS and oxidant harm is significant, as it could assist in explaining the health deterioration related to COVID-19 resulting in hospitalization and death**.**

In published clinical trials by Kumar et al [59] on older adults OA, HIV-infected patients, and diabetic patients, it was reported that GlyNAC supplementation for 2 weeks rapidly improves GSH deficiency, OxS, and damage caused by OxS [63,64], and longer durations of supplementation correct these defects [4,65]**.** A computational analysis of therapeutic targets and the discovery of potential drugs against SARS-Cov-2 identified GSH as a key potential candidate [66]**.** GSH has been reported to inhibit replication of the influenza virus (which causes viral respiratory pneumonia with a high annual mortality rate in OA) [67], and the study speculated that if boosting GSH can inhibit replication of the SARS-Cov-2 virus which causes COVID-19, this could be a game changer in the global fight against the COVID-19 pandemic. A small case study reported that increasing GSH levels improved dyspnea in 2 patients infected with COVID-19 **[68]**, and NAC supplementation is reported to have a beneficial impact in ventilated COVID-19 patients [69]. However, antioxidant supplements should be taken with caution in COVID-19 due to the risk of generating reductive stress, a situation in which excessive reductions in reactive oxygen species can be harmful. Multiple clinical trials, [70] have shown that GlyNAC successfully lowers OxS, without triggering reductive stress. Additional advantages of GlyNAC supplementation come from its capacity to provide the vitally important amino acids glycine and cysteine. Glycine is a 1-carbon metabolite and a methyl-group donor which is essential for DNA synthesis, cellular reactions, brain, cartilage and cellular health.

De flora et al [13] and several other authors [71,72,73] have proposed the use of NAC in the prevention and/or treatment of COVID-19. Because of its low toxicity profiles, the 60-year-experience of clinical use and the way that NAC is supported by the FDA under various formulations and is well known as a health supplement, this drug might be repurposed as an anti-COVID-19 agent.

Two strategies, in particular, can be considered. The first one is the oral administration of NAC, at the dose of 600 mg twice daily to reduce the risk of developing COVID-19 and to lessen its severity, especially during epidemic periods and in high-risk individuals due to age and/or concomitant pathological conditions or contact with infected SARS-CoV-2 carriers. Interestingly, because this protocol has previously been shown to reduce the incidence and severity of influenza and influenza-like illnesses [74], the hypothesis that NAC administration can provide broad protection against a variety of respiratory viral diseases is mechanistically sound. Oral NAC (600 mg/twice daily) was also found to be safe and beneficial in preventing and delaying ventilator-associated pneumonia, as well as improving the complete recovery rate in a high-risk (intensive care unit) ICU group [62]. A cross-sectional study of 164 COVID-19 patients in Kolkata (India) indicated that moderate-severe patients who got NAC along with standard medication had a variety of clinical advantages [75]**.**

In the case of apparent COVID-19 forms, the second option is to employ NAC as an adjuvant therapy, maybe in combination with other medications, at the high intravenous doses similar to those used as an antidote to paracetamol overdose. It is worth noting that paracetamol, which is the chosen medicine for symptomatic and domiciliary therapy of COVID-19 in its early stages, can deplete GSH, especially in persons with greater COVID-19 risk, raising the chance of severe COVID-19 forms [76]. As a result, the use of paracetamol as a safer alternative to nonsteroidal anti-inflammatory drugs (NSAIDs) in COVID-19 should be carefully reconsidered and it would be important to further investigate whether NAC supplementation should be used in cases of prolonged administration of high doses of this antipyretic and analgesic compound, regardless of COVID-19 [76]. The intravenous use of NAC improves a case of severe COVID-19 infection treated with hydroxychloroquine in a patient lacking in glucose 6-phosphate dehydrogenase (G6PD), which enhances human coronavirus infection due to GSH depletion [71]. In contrast, a double-blind, randomized, placebo-controlled trial in Sao Paulo, Brazil, involving 135 individuals with severe COVID-19 (confirmed or suspected) found no benefit from a 20-hour intravenous injection of 21 g NAC (approximately 300 mg/kg) in terms of the need for endotracheal intubation and mechanical ventilation [77].

2. DISCUSSION

Several in vitro and in vivo research have looked at the probable mechanisms of NAC beneficial actions. Beyond its well-known role as a precursor of glutathione, NAC has been shown to have a variety of antioxidant and anti-inflammatory properties, including (i) downregulation of the inflammasome NLRP3,

which reduces pro-inflammatory cytokine expression and release from activated mononuclear phagocytes [78], (ii) inhibition of endotoxin-induced release of IL-1b, IL-8, and TNF-a [79], (iii) improves gut barrier dysfunction, preventing systemic endotoxemia and inflammatory response, while previous studies have linked COVID-19 to gut barrier dysfunction and systemic endotoxemia [80,81]. (iv) downregulates programmed cell death protein 1 expression in (T helpers cells) CD4 and (T suppressor cells) CD8 lymphocytes [82]. NAC may also have a direct antiviral effect against SARS-CoV-2.

Previous case studies and series of patients with COVID-19 have shown that NAC administered at 1200 mg/d created a positive clinical impact [60,68,71].

Early NAC withdrawal in COVID-19 has been linked to a return of laboratory indices of inflammation, according to earlier research [71]. Clinically, very high doses of intravenous NAC (200 mg/kg/d) have been used to treat (acute respiratory distress syndrome) ARDS. However, sector found no evidence of a survival benefit from high NAC dose administration, despite the fact the length of ICU stay was reduced [83]. It should not be forgotten that large doses of other free radical scavengers including beta-carotene, vitamin E, and vitamin C have been linked to increased oxidative stress in the past [84].

Previous in vitro and experimental animal studies have investigated that higher doses of NAC may have a pro-oxidant effect, depending on the nature of the radicals generated by the biological system. In particular, high NAC doses have been demonstrated to promote (ferrous) Fe2 / (hydrogen peroxide) H2O2-dependent oxidative stress and superoxide radical production [85,86].

A study by S.F . Assimakopoulos et al [60] provides evidence that 1200 mg/d of oral NAC administration in patients with COVID-19 pneumonia prevents the development of severe respiratory failure and improves survival.

According to human clinical trials, Kumar et al [4] GlyNAC supplementation improves inflammation, mitochondrial dysfunction, endothelial vascular dysfunction, insulin resistance, genotoxicity, autophagy/mitophagy and muscle strength, in addition to GSH shortage and OxS [87]. This is significant because patients with COVID-19 have similar problems. Overall, the findings of this study, as well as previous clinical trials observations on the potentially beneficial role of GlyNAC supplementation in COVID-19-infected patients, indicate the need for more research to determine the impact of GlyNAC supplementation in COVID-19-infected patients [88,89].

NAC may be advocated in the prevention and treatment of COVID-19. Especially in the elderly and people with chronic conditions that predispose them to these diseases and make them worse. Individuals who have been in close vicinity to SARS-CoV-2 carriers, especially those identified by smartphone contact tracing apps, may be an additional target for oral NAC to reduce the chance of getting COVID-19 [74]. NAC administration has been proposed as one of the viable methods for preserving endothelial function and reducing microthrombosis in COVID-19 severe variants [90].

Intravenously administered NAC at the high doses commonly used in cases of paracetamol intoxication, given at the first onset of chest symptoms, would be expected to play an adjuvant therapeutic role in combination with antivirals or other drugs in case of severe COVID-19 forms with pulmonary and/or systemic symptoms.

Because the redox environment of the ACE2 receptor of SARS-CoV-2 spikes is regulated by the thiol-disulfide balance in the extracellular region, and because replenishment of depleted GSH stores by NAC exerts formidable antioxidant and anti-inflammatory effects, NAC has been proposed as anti-SARS-CoV-2 agents. These effects may be useful in controlling the cytokine storm that is a characteristic of COVID-19 [13]. The angiotensin-converting enzyme 2 (ACE2) receptor binds to SARS-CoV-2 spike proteins, which initiates the viral replication cycle in cells [91].

Many cell types carry angiotensin-converting enzyme (ACE) and ACE2 proteases on their surfaces, which have the same substrates, angiotensin I and angiotensin II, but the opposite actions [25]. SARS-CoV-2 reduces ACE2 availability and promotes ACE activity by binding it when it enters human cells [92]. In patients who have an inherent tendency to have larger levels of ACE the imbalance between ACE and ACE2 can be much more noticeable. It is well known that ACE/ACE2 ratios can differ among individuals and ACE-predominant people are more prone to excessive inflammation [25].

3. CONCLUSION

In the treatment of several viral infections, NAC has shown encouraging benefits. It inhibits viral replication and lowers viral load by boosting GSH levels. Several studies have recently sought to investigate the effects of NAC in severe COVID-19 patients, with mixed findings. Although it appears that the capacity of NAC to reduce pro-inflammatory cytokines production and moderate the impact of cytokine storms could contribute to better outcomes in COVID-19 patients, there is currently little evidence to support this. Based on the information presented above, this paper's author suggests that using NAC will improve outcomes in COVID-19 patients. Furthermore, due to the high safety profile and inexpensive cost of oral NAC, its use as an adjuvant therapy in COVID-19 could be beneficial. According to recent studies, NAC efficacy and prognosis are based on the dose and duration of NAC administration. As a result, more in vivo and in vitro experiments are needed to determine the proper NAC doses in cases with COVID-19 infection. Furthermore, the best timing to start NAC treatment initiation (e.g. just after symptoms appear or later in the disease course) has yet to be determined.

4. REFERENCES

1. Dowell F & Ho S. Seasonality of infectious diseases and severe acute respiratory syndrome–what we don't know can hurt us. The lancet infectious diseases.2004; 4 (11): 704–708.
2. Grant B, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nutrients.2020; 12 (4): 988.
3. Puri S.H, Qory H. The Effectiveness of High-dose N-acetylcysteine in Severe COVID-19 Patients, KELUWIH: Jurnal Kesehatan dan Kedokteran. 2021;Vol.3(1): 22-34.

 ISSN:Online 2790-1637, Print 2790-1629; National Library of Libya, Legal number : 154/2018

4. Kumar P, Liu C, Suliburk J.W, Minard C.G, Muthupillai R, Chacko S et al. Supplementing Glycine and N-acetylcysteine (GlyNAC) in Aging HIV Patients Improves Oxidative Stress, Mitochondrial Dysfunction, Inflammation, Endothelial Dysfunction, Insulin Resistance, Genotoxicity, Strength, and Cognition: Results of an Open-Label Clinical Trial. Biomedicines.2020; 8: 390.

5. Vivianni A & Farhanah N. Faktor Â Faktor Prediktor Mortalitas Sepsis Dan Syok Sepsis Di Icu Rsup Dr Kariadi. Diponegoro Med. J. (Jurnal Kedokt. Diponegoro).2016;5: 504–517.

6. Rusdi M.S. Mini Review: Farmakologi pada Corona Virus Disease (Covid-19). Lumbung Farm. J. Ilmu Kefarmasian.2021; 54–61.

7. Sujana K.S & Maulida M. Efektivitas N-Acetylsistein pada Pasien COVID-19.2021;48: 416–418.

8. Mazzaro E, Bortolotti U, Milano A, Thiene G, Casarotto D. Long term survival without anticoagulation after aortic valve replacement with a Lillehei-Kaster prosthesis. A case report. J. Heart Valve Dis.1993; 2: 1–8.

9. Sari E.F, Rumende C.M, Harimurti K. Faktor–Faktor yang Berhubungan dengan Diagnosis Pneumonia pada Pasien Usia Lanjut. J. Penyakit Dalam Indones.2017; 3: 183.

10. Burhan E, Susanto D, Isbaniah F, Nasution A, Ginanjar E, Pitoyo W, et al. Pedoman Tatalaksana COVID-19. Edisi Ke-3. Jakarta : Perhimpunan Dokter Paru Indonesia (PDPI), Perhimpunan Dokter Spesialis Kardiovaskular Indonesia (PERKI), Perhimpunan Dokter Spesialis Penyakit Dalam Indonesia (PAPDI), Perhimpunan Dokter Anestesiol. Cell Mol Life Sci. 2020; 60: 6-20.

11. De Flora S, Balansky R, La Maestra S. Rationale for the use of N-acetylcysteine in both prevention and adjuvant therapy of COVID-19. FASEB J. 2020;34: 13185–13193.

12. Djalante R, Lassa J, Setiamarga D, Sudjatma A, Indrawan M, Haryanto B, et al. Review and analysis of current responses to COVID-19 in Indonesia. Prog. Disaster Sci. 2020; 6: 100091.

13. De Flora S, Balansky R, La Maestra S. Antioxidants and COVID-19. J Prev Med Hyg.2021;62(Suppl. 1):E34-E45.

14. Kirkham P.A, Barnes P.J. Oxidative stress in COPD. Chest.2013; 144: 266–273.

15. Van der Vliet A, Janssen-Heininger Y.M.W, Anathy V. Oxidative stress in chronic lung disease: From mitochondrial dysfunction to dysregulated redox signaling. Mol. Asp. Med.2018; 63:59–69.

16. Kibel A, Lukinac A.M, Dambic V, Juric I, Selthofer-Relatic K. Oxidative Stress in Ischemic Heart Disease. Oxid. Med. Cell Longev. 2020; 6627144.

17. Peoples J.N, Saraf A, Ghazal N, Pham T.T, Kwong J.Q. Mitochondrial dysfunction and oxidative stress in heart disease. Exp. Mol. Med.2019; 51: 1–13.

18. Jiang T,Sun Q, Chen S. Oxidative stress: A major pathogenesis and potential therapeutic target of antioxidative agents in Parkinson's disease and Alzheimer's disease. Prog. Neurobiol.2016; 147: 1–19.

19. Giacco F & Brownlee M. Oxidative stress and diabetic complications. Circ Res.2010;107: 1058–1070.

20. Ashraf U & Sheikh A. Endoplasmic reticulum stress and Oxidative stress in the pathogenesis of Non-alcoholic fatty liver disease. Free Radic. Res.2015;49: 1405–1418.

21. Daenen K, Andries A, Mekahli D, Van Schepdael A, Jouret F, Bammens B. Oxidative stress in chronic kidney disease. Pediatr. Nephrol.2019;34: 975–991.

22. Luo J, Mills K, Le Cessie S, Noordam R, van Heemst D. Ageing, age-related diseases and oxidative stress: What to do next? Ageing Res Rev.2020; 57: 100982.

23. Teskey G, Abrahem R, Cao R, Gyurjian K, Islamoglu H, Lucero M et al. Glutathione as a Marker for Human Disease. Adv. Clin. Chem.2018; 87: 141–159.

24. Oter S, Jin S, Cucullo L, Dorman HJ. Oxidants and antioxidants: friends or foes? Oxid Antioxid Med Sci.2012;1:1-4.

25. Alamdari DH, Moghaddam AB, Amini S, Keramati MR, Zarmehri AM, Alamdari AH, et al. Application of methylene blue -vitamin C -N-acetyl cysteine for treatment of critically ill COVID-19 patients, report of a phase-I clinical trial. Eur J Pharmacol.2020; 885:173494.

26. Dominari A, Hathaway III D, Kapasi A, Paul T, Makkar SS, Castaneda V, et al. Bottom-up analysis of emergent properties of N-acetylcysteine as an adjuvant therapy for COVID-19. World J Virol.2021;10(2): 34-52.

27. Larsson S. C, Håkansson N, & Wolk A. Dietary cysteine and other amino acids and stroke incidence in women. Stroke.2015; 46(4): 922-926.

28. Zafarullah M, Li WQ, Sylvester J, Ahmad M. 2003.Molecular mechanisms of N-acetylcysteine actions

29. Šalamon Š, Kramar B, Marolt TP, Poljšak B, Milisav I. Medical and Dietary Uses of NAcetylcysteine.2019.

30. Ribeiro G, Roehrs M, Bairros A, Moro A, Charão M, Araújo F & Leal M . N acetylcysteine on oxidative damage in diabetic rats. Drug and chemical toxicology.2011; 34(4); 467-474.

31. Kerksick C, & Willoughby D. The antioxidant role of glutathione and N-acetyl-cysteine supplements and exercise-induced oxidative stress. Journal of the International Society of Sports Nutrition.2005; 2(2): 38.

32. Wang Q, Hou Y, Yi D, Wang L, Ding B, Chen X & Wu G. Protective effects of N-acetylcysteine on acetic acid-induced colitis in a porcine model. BMC gastroenterology.2013; 13(1): 133.

33. Mokhtari V, Afsharian P, Shahhoseini M, Kalantar S. M, & Moini A. A Review on Various Uses of N-Acetyl Cysteine. Cell Journal (Yakhteh).2017; 19(1): 11.

34. Aldini G, Altomare A, Baron G, Vistoli G, Carini M, Borsani L, et al. N-Acetylcysteine as an antioxidant and disulphide breaking agent: the reasons why. Free Radic Res. 2018;52: 751-762.

35. de Andrade Q, Moura A, dos Santos M, de Araújo P, de Farias Santos C & Goulart F. Oxidative stress and inflammation in hepatic diseases: therapeutic possibilities of N-acetylcysteine. International journal of molecular sciences.2015;16(12): 30269-30308.

36. Rushworth G. F, & Megson I. L. Existing and potential therapeutic uses for N-acetylcysteine: the need for conversion to intracellular glutathione for antioxidant benefits. Pharmacology & therapeutics.2014; 141(2): 150-159.

37. Noszál B, Visky D, & Kraszni M. Population, acid-base, and redox properties of N-acetylcysteine conformers. Journal of medicinal chemistry.2000; 43(11):2176-2182.

38. Lasram M, Dhouib I.B, Annabi A, El Fazaa S, & Gharbi N. A review on the possible molecular mechanism of action of N-acetylcysteine against insulin resistance and type-2 diabetes development. Clinical biochemistry.2015;48(16-17):1200-1208.

39. Dodd S, Dean O, Copolov L, Malhi S & Berk M. N-acetylcysteine for antioxidant therapy: pharmacology and clinical utility. Expert opinion on biological therapy.2008; 8(12): 1955-1962.

40. Harada M, Kishimoto K, Furuhashi T, Naito K, Nakashima Y, Kawaguchi Y ,et al. Infertility observed in reproductive toxicity study of N-acetyl-L-cysteine in rats. Biology of reproduction.2003; 69(1): 242-247.

41. Li J, Zhang S, Wu Y, Guo W, Zhang Y, & Zhai W. Protective effects of N-acetylcysteine on the liver of brain-dead Ba-Ma mini pig. In Transplantation proceedings.2010, January; 42(1):195-199.

42. Moura F. A, de Andrade K. Q, dos Santos J. C. F, Araújo O. R. P, & Goulart M. O. F. Antioxidant therapy for treatment of inflammatory bowel disease: Does it work?. Redox biology.2015; 6: 617-639.

43. Roederer M, Ela SW, Staal FJ, Herzenberg LA. N-acetylcysteine: a new approach to anti-HIV therapy. AIDS Res Hum Retroviruses.1992;8: 209-217.

44. Geiler J, Michaelis M, Naczk P, Leutz A, Langer K, Doerr HW, et al. N-acetyl-L-cysteine (NAC) inhibits virus replication and expression of pro-inflammatory molecules in A549 cells infected with highly pathogenic H5N1 influenza A virus. Biochem Pharmacol.2010;79: 413-420.

45. Molteni CG, Principi N, Esposito S. Reactive oxygen and nitrogen species during viral infections. Free Radic Res. 2014;48: 1163-1169

46. Sun SY. N-acetylcysteine, reactive oxygen species and beyond. Cancer Biol Ther.2010; 9: 109-110.

47. Damayanti K & Ryusuke O. Pneuminia, Fakultas Kedokteran Universitas Udayana.2017.

48. Medicine J.H. 2020.Coronavirus COVID-19(SARSCoV-2).

49. Nasi A, McArdle S, Gaudernack G, Westman G, Melief C, Rockberg J et al. Reactive oxygen species as an initiator of toxic innate immune responses in retort to SARS-CoV-2 in an aging population, consider N-acetylcysteine as early therapeutic intervention. Toxicol. Reports.2020; 7:768–771.

50. Spearow J.L, Copeland L. 2020.Review: Improving Therapeutics for COVID-19 with Glutathione-boosting Treatments that Improve Immune Responses and Reduce the Severity of Viral Infections.

https://doi.org/10.31219/osf.io/y7wc2

51. Gordon JW, Shaw JA, Kirshenbaum LA. Multiple facets of NF-κB in the heart: to be or not to NF- κB. Circ Res.2011;108: 1122-1132.

52. Nencini C, Giorgi G, & Micheli L. Protective effect of silymarin on oxidative stress in rat brain. Phytomedicine.2007; 14(2-3): 129-135.

53. Reddy B. V, Sundari J. S, Balamurugan E, & Menon V. P. Prevention of nicotine and streptozotocin treatment induced circulatory oxidative stress by bis-1, 7-(2-hydroxyphenyl)-hepta-1, 6-diene-3, 5-dione in diabetic rats. Molecular and cellular biochemistry.2009; 331(1-2): 127.

54. Medina J & Moreno-Otero R. Pathophysiological basis for antioxidant therapy in chronic liver disease. Drugs.2005; 65(17): 2445-2461.

55. Mallikarjuna K, Shanmugam K. R, Nishanth K, Wu M. C, Hou C. W, Kuo C. H, et al. Alcohol-induced deterioration in primary antioxidant and glutathione family enzymes reversed by exercise training in the liver of old rats. Alcohol.2010; 44(6): 523-529.

56. Dey A & Lakshmanan J. The role of antioxidants and other agents in alleviating hyperglycemia-mediated oxidative stress and injury in liver. Food & function.2013; 4(8): 1148-1184.

57. Amin F, Shaaban M, Bediawy A. N-acetyl cysteine for treatment of recurrent unexplained pregnancy loss. Reproductive biomedicine online.2008;17(5): 722-726.

58. Elgindy A, El-Huseiny M, Mostafa I, Gaballah M, & Ahmed A. N-acetyl cysteine: could it be an effective adjuvant therapy in ICSI cycles? A preliminary study. Reproductive biomedicine online.2010; 20(6): 789-796.

59. Kumar P, Osahon O, Vides D.B, Hanania N, Minard C.G, Sekhar R.V. Severe Glutathione Deficiency, Oxidative Stress and Oxidant Damage in Adults Hospitalized with COVID-19: Implications for GlyNAC (Glycine and N-Acetylcysteine) Supplementation. Antioxidants.2022; 11:50.

60. ASSIMAKOPOULOS S.F et al. N-acetyl-cysteine reduces the risk for mechanical ventilation and mortality in patients with COVID-19 pneumonia: a two-center retrospective cohort study. INFECTIOUS DISEASES. 2021; VOL. 0 (NO. 0): 1–8.

61. Zhang Q, Ju Y, Ma Y et al. N-acetylcysteine improves oxidative stress and inflammatory response in patients with community-acquired pneumonia: a randomized controlled trial. Medicine (Baltimore).2018;97(45):e13087.

62. Sharafkhah M, Abdolrazaghnejad A, Zarinfar N et al. Safety and efficacy of N-acetyl-cysteine for prophylaxis of ventilator- associated pneumonia: a randomized, double-blind, placebo- controlled clinical trial. Med Gas Res.2018;8(1):19–23.

63. Sekhar R.V, Patel S.G, Guthikonda A.P, Reid M, Balasubramanyam A, Taffet G.E et al. Deficient synthesis of glutathione underlies oxidative stress in aging and can be corrected by dietary cysteine and glycine supplementation. Am. J. Clin. Nutr.2011; 94: 847–853.

64. Nguyen D, Hsu J.W, Jahoor F, Sekhar R.V. Effect of increasing glutathione with cysteine and glycine supplementation on mitochondrial fuel oxidation, insulin sensitivity, and body composition in older HIV-infected patients. J. Clin. Endocrinol. Metab.2014; 99: 169–177.

65. Kumar P, Liu C, Hsu J.W, Chacko S, Minard C, Jahoor, F et al. Glycine and N-acetylcysteine (GlyNAC) supplementation in older adults improves glutathione deficiency, oxidative stress, mitochondrial dysfunction, inflammation, insulin resistance, endothelial dysfunction, genotoxicity, muscle strength, and cognition: Results of a pilot clinical trial. Clin. Transl. Med.2021; 11: e372.

66. Wu C, Liu Y, Yang Y, Zhang P, Zhong W, Wang Y et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. Acta Pharm. Sin. B.2020;10: 766–788.

67. Amatore D, Celestino I, Brundu S, Galluzzi L, Coluccio P, Checconi P, et al. Glutathione increase by the n-butanoyl glutathione derivative (GSH-C4) inhibits viral replication and induces a predominant Th1 immune profile in old mice infected with influenza virus. FASEB Bioadv.2019;1: 296–305.

68. Horowitz I, Freeman R, Bruzzese J. Efficacy of glutathione therapy in relieving dyspnea associated with COVID-19 pneumonia: A report of 2 cases. Respir. Med. Case Rep.2020;30: 101063.

69. Assimakopoulos F, Aretha D, Komninos D, Dimitropoulou D, Lagadinou M, Leonidou L, et al. N-acetyl-cysteine reduces the risk for mechanical ventilation and mortality in patients with COVID-19 pneumonia: A two-center retrospective cohort study. Infect. Dis. Lond.2021;53: 847–854.

70. McCaddon A, Regland B. COVID-19: A methyl-group assault? Med. Hypotheses.2021; 149: 110543.

71. Ibrahim H, Perl A, Smith D, Lewis T, Kon Z, Goldenberg R, et al.Therapeutic blockade of inflammation in severe COVID-19 infection with intravenous N-acetylcysteine. Clin Immunol.2020;219:108544.

72. Andreou A, Trantza S, Filippou D, Sipsas N, Tsiodras S. COVID-19: The potential role copper and N-acetylcysteine (NAC) in a combination of candidate antiviral treatments against SARSCoV- 2. In Vivo.2020;34:1567-88.

73. Al-Horani RA & Kar S. Potential anti-SARS-CoV-2 therapeutics that target the post-entry stages of the viral life cycle: a comprehensive review. Viruses, 2020;12:E1092.

74. De Flora S, Grassi C, Carati L. Attenuation of influenza-like symptomatology and improvement of cell-mediated immunity with long-term N-acetylcysteine treatment. Eur Respir J.1997;10(15):35-41.

75. Bhattacharya R, Mondal M, Naiya SB, Lyngdoh L, Mukherjee R, Singh PK. The beneficial role of N-acetylcysteine as an adjunctive drug in treatment of COVID-19 patients in a tertiary care hospital in India: an observational study. Int J Res Med Sci. 2020;8(35):18-22.

76. Sestili P, Fimognari C. Paracetamol-induced glutathione consumption: is there a link with severe COVID-19 illness? Front Pharmacol.

https://doi.org/https://doi.org/10.3389/ fphar.2020.579944.

77. de Alencar JCG, de Lucena Moreira C, Dudy Müller A, Chaves CE, Akemi Fukuhara M, et al. Covid Register Group. Double-blind, randomized, placebo-controlled trial with N-acetylcysteine for treatment of severe acute respiratory syndrome caused by COVID-19. Clin Inf Dis. 2020;72:e736-e741.

78. Liu Y, Yao W, Xu J et al. The anti-inflammatory effects of acetaminophen and N-acetylcysteine through suppression of the NLRP3 inflammasome pathway in LPS-challenged piglet mononuclear phagocytes. Innate Immun.2015;21(6): 587–597.

79. Lee SI, Kang KS. N-acetylcysteine modulates lipopolysaccharide- induced intestinal dysfunction. Sci Rep.2019;9(1): 1004.

80. Assimakopoulos F, Maroulis I, Patsoukis N, et al. Effect of antioxidant treatments on the gut-liver axis oxidative status and function in bile duct-ligated rats. World J Surg. 2007;31(10):2023–2032.

81. Sirivongrangson P, Kulvichit W, Payungporn S, et al. Endotoxemia and circulating bacteriome in severe COVID-19 patients. Intensive Care Med Exp.2020;8(1):72.

82. Scheffel MJ, Scurti G, Wyatt MM et al. N-acetyl cysteine protects anti-melanoma cytotoxic T cells from exhaustion induced by rapid expansion via the downmodulation of Foxo1 in an Akt-dependent manner. Cancer Immunol Immunother.2018;67(4):691–702.

83. Zhang Y, Ding S, Li C et al. Effects of N-acetylcysteine treatment in acute respiratory distress syndrome: A meta-analysis. Exp Ther Med.2017;14(4):2863–2868.

84. Sotler R, Poljsak B, Dahmane R et al. Prooxidant Activities of Antioxidants and Their Impact on Health. Acta Clin Croat.2019;58(4):726–736.

85. Sagrista ML, Garcia AE, Africa De Madariaga M et al. Antioxidant and pro-oxidant effect of the thiolic compounds N-acetyl-L-cysteine and glutathione against free radical-induced lipid peroxidation. Free Radic Res.2002; 36(3):329–340.

86. Harvey BH, Joubert C, Du Preez JL, et al. Effect of chronic N-acetyl cysteine administration on oxidative status in the presence and absence of induced oxidative stress in rat striatum. Neurochem Res.2008;33(3):508–517.

 ISSN:Online 2790-1637, Print 2790-1629; National Library of Libya, Legal number : 154/2018

87. Sekhar R.V. GlyNAC Supplementation Improves Glutathione Deficiency, Oxidative Stress, Mitochondrial Dysfunction, Inflammation, Aging Hallmarks, Metabolic Defects, Muscle Strength, Cognitive Decline, and Body Composition: Implications for Healthy Aging. J. Nutr.2021; 29: nxab309.

88. Pedersen S.F, Ho Y.C. SARS-CoV-2: A storm is raging. J. Clin. Investig.2020; 130: 2202–2205.

89. Chen M, Zheng Y, Yu Y, Wang Y, Huang Q, et al. Blood molecular markers associated with COVID-19 immunopathology and multi-organ damage. EMBO J. 2020;39: e105896.

90. Guglielmetti G, Quaglia M, Sainaghi PP, et al. "War to the knife" against thromboinflammation to protect endothelial function of COVID-19 patients. Crit Care. Published 2020 Jun 19;24:365.

91. Hati S & Bhattacharyya S. Impact of thiol-disulfide balance on the binding of Covid-19 spike protein with Angiotensin Converting Enzyme 2 receptor.2020.

https://doi. org/10.1101/2020.05.07.083147

92. Liu Y, Wang M, Luo G, Qian X, Wu C, Zhang Y et al. Experience of Nacetylcysteine airway management in the successful treatment of one case of critical condition with COVID-19: A case report. Medicine (Baltimore).2020;99: e22577.

 ISSN:Online 2790-1637, Print 2790-1629; National Library of Libya, Legal number : 154/2018